Manufacturers & Exporters of Antiretroviral Drugs

www.mcneilargusindia.com

MCNEIL & ARGUS PHARMACEUTICALS LTD.

Manufacturers & Exporters of Pharmaceutical Formulations Since 1979
(WHO GMP & ISO 9001:2008 Certified Unit)

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From The Chairman's Desk :

I feel immense pride and honour to welcome you in the family of **MCNEIL & ARGUS PHARMACEUTICALS LIMITED** - A trusted name for unwavering Devotion, Dedication, Achievements and Service to mankind. The company started its manufacturing of Pharmaceutical Formulations in the year 1979. The company has crossed many mile stones during its long journey of 34 years in Manufacturing, Marketing and Exports of Medicines. The Company was a leading and Trusted Supplier of Medicines to Central Government Health Scheme, Directorate General of Health Services, Ministry of Health & Family Welfare and many other Ministries & Autonomous Bodies of Government of India. The company achieved glory of paramount importance when it was awarded licence to Manufacture, Market and Export of Antiretroviral drugs for the treatment of HIV+ve & AIDS cases. The company believes that it owes a great deal to the society. The comparative low cost treatment of its Antiretroviral drugs has covered more number of ailing people and helped them to get rid of this dreaded disease. During this period the Company's Antiretroviral Drugs have been registered in a number of countries like Malaysia, Myanmar, Nepal, Nigeria, Zambia & Papua New Guinea etc. The Company has exported its Antiretroviral Drugs successfully to a number of countries apart from the above mentioned earlier. Some of the prominent countries where its products have been well accepted are Bangladesh, Congo Brazzaville, Mauritania, Fiji, Burundi, and Equatorial Guinea etc. The Company has exported Lopinavir 80mg & Ritonavir 20mg per ml Oral Solution to Bangladesh on the special request from Bangladesh. It is a drug of choice for infants and new borns. We are sure that with your active participation in the eradication of HIV+ve and AIDS cases, the Company will always be there to help in every possible way and means.

I once again thank all of you in helping the Company show a positive growth in the field of rare molecules of Antiretroviral Drugs.

Wish you a very bright future with our organization.

With profound regards & best wishes !

BHAI G.D. CHHIBBER
Chairman
MCNEIL & ARGUS PHARMACEUTICALS LIMITED

MCNEIL & ARGUS PHARMACEUTICALS LTD.

ARGA - L Tablets
Lopinavir 200mg
Ritonavir 50mg

ARGA - LR Tablets
Lopinavir 133.3mg
Ritonavir 33.3mg

ARGA - LP Tablets
Lopinavir 100mg
Ritonavir 25mg

ARGAVIR Tablets
Ritonavir 100mg

D SINE Tablets
Didanosine 25/50/100/200/
250/400 mg

E.F. Tablets
Efavirenz 200/600mg

LAMI Tablets
Lamivudine 100/150/300/mg

MATVIR Tablets
Atazanavir 150/200/300mg

MCABAVIR Tablets
Abacavir 300mg

MCABAVIR Plus Tablets
Abacavir Sulphate
Equivalent to Abacavir 300mg
Lamivudine 150mg

MCLAMI-Plus Tablets
Lamivudine 150mg
Zidovudine 300mg
Nevirapine 200mg

MCABAVIR Comp Tablets
Abacavir 300mg
Lamivudine 150mg
Zidovudine 300mg

MCNAVIR Tablets
Saquinavir 500mg

NEL - 250 Tablets
Nelfinavir 250mg

NEV - 200 Tablets
Nevirapine 200mg

ZVD Tablets
Zidovudine 100/300 mg

STV COMP. 30 Tablets
Stavudine 30mg
Lamivudine 150mg
Nevirapine 200mg

STV COMP. Tablets
Stavudine 40mg
Lamivudine 150mg
Nevirapine 200mg

STV PLUS 30 Tablets
Stavudine 30mg
Lamivudine 150mg

STV PLUS Tablets
Stavudine 40mg
Lamivudine 150mg

ZVD PLUS Tablets
Zidovudine 300mg
Lamivudine 150mg

MCNEIL & ARGUS PHARMACEUTICALS LTD.

TENMAC-LM Tablets
Tenofovir Disoproxil Fumarate 300mg
Lamivudine 300mg

TENMAC-EF Tablets
Tenofovir Disoproxil Fumarate 300mg
Emtricitabine 200mg
Efavirenz 600mg

Tenmac-LEF
Tenofovir Disoproxil Fumarate 300mg
Lamivudine 300mg
Efavirenz 600mg

TENMAC Tablets
Tenofovir Disoproxil Fumarate 300mg

TENMAC-EM Tablets
Tenofovir Disoproxil Fumarate 300mg
Emtricitabine 200mg

INDA-400 Capsules
Indinavir 400mg

MCOSVIR Capsules
Oseltamivir 75mg

STV - 40 Capsules
Stavudine 40mg

E.F. Capsules
Efavirenz 200/600 mg

Lamivudine, Nevirapine Stavudine Tablets
Lamivudine 60mg &
Nevirapine100mg
Stavudine12mg

Lopinavir & Ritonavir Tablets
Lopinavir 100mg
Ritonavir 25mg

Lamivudine Nevirapine & Stavudine Tablets
Lamivudine 30mg
Nevirapine 50mg
Stavudine 6mg

KIT
Part 'A'
Lamivudine (Two Tablets) 150mg
Zidovudine (OneTablet)300mg
Part 'B'
Efavirenz (One Tablet) 600mg

Efavirenz Capsules
Efavirenz 50mg

Stavudine 30mg Capsules
Stavudine 30mg

Lamivudine Oral Solution
Lamivudine50mg/5ml

Lopinavir & Ritonavir Oral Solution
Lopinavir 80mg,
Ritonavir20mg/ml

Mcabavir Oral Solution
Abacavir 20mg/ml

Stavudine for Oral Solution
Stavudine1mg/ml

Zidovudine Oral Solution
Zidovudine 50mg/5ml

Nevirapine Oral Suspension
Nevirapine50mg/5ml

WHO GMP & ISO Certified Company

MCNEIL & ARGUS PHARMACEUTICALS LTD.

Organisational Profile

Mcneil & Argus Pharmaceuticals Ltd. 100 Rampur Sarsehri Road, Ambala Cantt is engaged in the Manufacturing, Marketing & Exports of Pharmaceutical Specialities including Antiretroviral Drugs since 1979 – A Land Mark of touching 34th milestone of quality production.

It has an established ultra modern facility as per WHO GMP Standards to Manufacture, Tablets, Capsules, & Liquids. The unit is managed by experienced technical staff for production & quality control along with a team of expert technicians who have the experience of more than 30 years in quality production.

The company has a Pharmaceuticals Formulation Plant located on a 25000 sq. meters plot situated at 100, Rampur Sarsehri Road, Ambala Cantt (India) connected by Air from Chandigarh Airport, which is 45km from the factory location and from New Delhi International Airport which is at a distance of 200km.. The covered area is approximately 60000 Sq. Feet The factory is located in a calm, green serene atmosphere, away from any factory producing obnoxious odour or pollutants suited to manufacture rare molecules like Antiretroviral Drugs.

PLANT I

This plant is fully equipped for the manufacturing of Antiretroviral Drugs for the treatment of HIV+ve and AIDS cases.

Total Quality Management is achieved by:

Confirming to WHO GMP Standards.

All the job functions of the company are in time with its Quality policy. Total Quality Management of the firm is looked after by a Quality Assurance Executives. All department heads upto the Managers, maintain and follow Quality Management System, are guided and coordinated by the Quality Assurance Executives.

The Quality Management Assurance with the help of any other personnel has the responsibility to see that all procedures are as per the standard operating procedures are followed. Personnel competence is also assessed by the Quality Assurance Executive. The total Quality Management System is designed for 'Zero Defect Product' for which the Quality Assurance Executive is responsible.

All evaluation of procedures and validations are done by the Quality Assurance Department.

The factory is having its own fully equipped laboratory with all the In-House testing facilities of the products being manufactured.

It is also having adequate, competent Technical Staff to carry out the Manufacturing Operations Analysis.

The Quality Assurance Department is responsible for:

Preparing, issuing and updating Quality Assurance Policy. Maintaining and controlling all documentation related to technology transfer.

Each process operation has it own air handling system and has temperature & humidity controls. The corridors are also environmentally controlled and are at positive pressure as compared to the individual rooms to prevent any mixing of air / powder from each room to the corridors. Pressure balancing of each air handling system has been done to avoid any cross contamination.

Each Core Process Room is supplied with controlled air passed through pre filters having efficiency of 99% down to 5 µ followed by microvee filters having efficiency of 99% down to 3 µ and finally through H.E.P.A. filters having efficiency of 99.97% down to 0.3 µ. Separate return air ducts are provided in each room. Efficiency of 0.3 µ H.E.P.A. filters are determined by checking the velocity, pressure gradient of individual areas and based on the result, decision for filter changing is taken. Any major change in the design of air handling system calls for revalidations. The individual process area is designed to have a temperature varying from 210 C to 250 C are maintained. The corridors are kept at positive pressure with respect to the process cubicles 10% of fresh air taken in each re-circulation cycle of returned air.

The AHU's are designed to have air changes depending upon the process requirement.

PLANT II

This section is fully equipped to manufacture Beta Lactum range of drugs ie Ampicillin and other Penicilli derivatives. The Beta Lactum section is separate and independent . The Air Handling Units with Hepa Filters and Thermostatically controller Humidity and Atmosphere temperature are installed here.

PLANT III

This section is fully equipped to manufacture Non Beta Lactum Group of Tablets, Capsules and Liquids. Modern and latest Machines are installed to give the best quality of Pharmaceutical Formulations produced here.

Description of HIV

Human immunodeficiency virus infection / acquired immunodeficiency syndrome (HIV/AIDS) is a disease of the human immune system caused by infection with human immunodeficiency virus (HIV). During the initial infection, a person may experience a brief period of influenza-like illness. This is typically followed by a prolonged period without symptoms. As the illness progresses, it interferes more and more with the immune system, making the person much more likely to get infections, including opportunistic infections and tumors that do not usually affect people who have working immune systems.

Description of AIDS

Acquired immunodeficiency syndrome (AIDS) is defined in terms of either a CD4+ T cell count below 200 cells per µL or the occurrence of specific diseases in association with an HIV infection. In the absence of specific treatment, around half the people infected with HIV develop AIDS within ten years. The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia (40%), cachexia in the form of HIV wasting syndrome (20%) and esophageal candidiasis. Other common signs include recurring respiratory tract infections.

Opportunistic infections may be caused by bacteria, viruses, fungi and parasites that are normally controlled by the immune system. Which infections occur partly depends on what organisms are common in the person's environment. These infections may affect nearly every organ system. People with AIDS have an increased risk of developing various viral induced cancers

Origination of HIV

Genetic research indicates that HIV originated in west-central Africa during the early twentieth century. AIDS was first recognized by the Centers for Disease Control and Prevention (CDC) in 1981 and its cause—HIV infection—was identified in the early part of the decade.[5] Since its discovery, AIDS has caused nearly 30 million deaths (as of 2009). As of 2010, approximately 34 million people are living with HIV globally. AIDS is considered a pandemic—a disease outbreak which is present over a large area and is actively spreading.

Effect of HIV on the immunity system

Pathophysiology

After the virus enters the body there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood. This response is accompanied by a marked drop in the number of circulating CD4+ T cells. The acute viremia is almost invariably associated with activation of CD8+ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. The CD8+ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4+ T cell counts recover. A good CD8+ T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus.

Spreading of HIV

HIV is transmitted by three main routes: sexual contact, exposure to infected body fluids or tissues, and from mother to child during pregnancy, delivery, or breastfeeding (known as vertical transmission). There is no risk of acquiring HIV if exposed to feces, nasal secretions, saliva, sputum, sweat, tears, urine, or vomit unless these are contaminated with blood. It is possible to be co-infected by more than one strain of HIV—a condition known as HIV superinfection

Symptoms of AIDS

Additionally, people with AIDS frequently have systemic symptoms such as prolonged fevers, sweats (particularly at night), swollen lymph nodes, chills, weakness, and weight loss. Diarrhea is another common symptom present in about 90% of people with AIDS.

Testing

Most people infected with HIV develop specific antibodies (i.e. seroconvert) within three to twelve weeks of the initial infection. Diagnosis of primary HIV before seroconversion is done by measuring HIV-RNA or p24 antigen. Positive results obtained by antibody or PCR testing are confirmed either by a different antibody or by PCR.
Antibody tests in children younger than 18 months are typically inaccurate due to the continued presence of maternal antibodies. Thus HIV infection can only be diagnosed by PCR testing for HIV RNA or DNA, or via testing for the p24 antigen.

Need for Medication

If HIV is allowed to reproduce, or "replicate," inside the body, it will cause damage to the immune system. Ultimately, the immune system becomes so weak that the body becomes vulnerable to other diseases. This is the point at which a person is usually diagnosed with full-blown AIDS, which can result in death due to other opportunistic infections like Tuberculosis, etc

Anti-HIV drugs can help HIV-infected people live longer. Treatment, therefore, is a very important option, and people living with HIV should consider starting treatment before the virus has had a chance to do serious damage to the immune system.

Antiretroviral drugs

The management of HIV/AIDS normally includes the use of multiple antiretroviral drugs in an attempt to control HIV infection. There are several classes of antiretroviral agents that act on different stages of the HIV life-cycle. it can take 10-15 years for an HIV-infected person to develop AIDS; antiretroviral drugs can slow down the process even further.
Antiretroviral (ARV) drugs are classified by the phase of the retrovirus life-cycle that the drug inhibits.

There are currently 5 major classes of antiretroviral drugs :
Binding and Fusion inhibitors
Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTI)
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

MCNEIL & ARGUS PHARMACEUTICALS LTD.

ARGA-L

(Lopinavir & Ritonavir Tablets)

COMPOSITION:

Each tablet contains:

Lopinavir	200mg
Ritonavir	50mg

DESCRIPTION:

Lopinavir/ritonavir has demonstrated antiviral activity in the HIV-infected adult.

PHARMACOLOGY:

Lopinavir, an inhibitor of the HIV protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Ritonavir was originally developed as an inhibitor of HIV protease. It is now rarely used for its own antiviral activity, but remains widely used as a booster of other protease inhibitors. More specifically, ritonavir is used to inhibit a particular liver enzyme that normally metabolizes protease inhibitors, cytochrome P450-3A4 (CYP3A4). The drug's molecular structure inhibits CYP3A4, so a low dose can be used to enhance other protease inhibitors.

PHARMACOKINETICS :

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of ARGA-L 400/100 mg BID yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg BID. The in vitro antiviral EC50 of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of ARGA-L is due to lopinavir.

Absorption

In a pharmacokinetic study in HIV-positive subjects (n=19), multiple dosing with 400/100 mg ARGA-LBID with food for 3 weeks produced a mean ± SD lopinavir peak plasma concentration (Cmax) of 9.8 ± 3.7 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 µg/mL and minimum concentration within a dosing interval was 5.5 ± 2.7 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 µg· h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of ARGA-Lco-formulated capsules and liquid. When administered under fasting conditions, both the mean AUC and Cmax of lopinavir were 22% lower for the ARGA-Lliquid relative to the capsule formulation.

Distribution

At steady state, lopinavir is approximately 98-99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg ARGA-LBID, and is similar between healthy volunteers and HIV-positive patients.

Elimination

Following a 400/100 mg 14C-ARGA-L Ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of 14C-lopinavir can be accounted for in urine and feces, respectively, after 8 days. Unchanged Lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The apparent oral clearance (CL/F) of lopinavir is 5.98 +/- 5.75 L/hr (mean +/- SD, N=19)

INDICATIONS:

ARGA-L is indicated in combination with other antiretroviral agents for the treatment of HIV-infection. This indication is based on analyses of plasma HIV RNA levels and CD4 cell counts in controlled studies of ARGA-L of 48 weeks duration and in smaller uncontrolled dose-ranging studies of ARGA-L of 72 weeks duration.

DOSAGE AND ADMINISTRATION:

Adults

The recommended dosage of ARGA-Lis 400/100 mg twice daily taken with food.

Concomitant therapy: Efavirenz, nevirapine, amprenavir or nelfinavir: A dose increase of ARGA-L to 533/133 mg twice daily taken with food is recommended when used in combination with efavirenz, nevirapine, amprenavir or nelfinavir.

CONTRAINDICATIONS:

ARGA-L is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir.

Co-administration of ARGA-L is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table.Table : Drugs That Are Contraindicated With ARGA-LDrug Class Drugs Within Class That Are Contraindicated With ARGA-LAntihistamines Astemizole, Terfenadine Ergot Derivatives Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine GI motility agent Cisapride Neuroleptic Pimozide Sedative/hypnotics Midazolam, Triazolam

PRECAUTIONS:

Hepatic Impairment and Toxicity

ARGA-L is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decomposition. There have been post marketing reports of hepatic dysfunction, including some fatalities.

Resistance/Cross-resistance

Various degrees of cross-resistance among protease inhibitors have been observed. The effect of ARGA-L therapy on the efficacy of subsequently administered protease inhibitors is under investigation.

Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

Fat Redistribution

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

Lipid Elevations

Treatment with ARGA-L has resulted in large increases in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing should be performed prior to initiating ARGA-L therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. Established and Other Potentially Significant Drug Interactions for additional information on potential drug interactions with ARGA-Land HMG-CoA reductase inhibitors.

Pregnancy

No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). There are, however, no adequate and well-controlled studies in pregnant women.

Nursing Mothers
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving ARGA-L.

ADVERSE EFFECTS:
Immune reconstitution syndrome (IRS) has been reported in patients treated with combination antiretroviral therapy (ART), including ARGA-L. During the initial phase of combination ART, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis carinii pneumonia, or tuberculosis) which may necessitate further evaluation and treatment.
Pancreatitis has been observed in patients receiving ARGA-L, including those who developed marked triglyceride elevations; in some cases, fatalities have occurred. Although a causal relationship with ARGA-L has not been established, marked triglyceride elevation is a risk factor in the development of pancreatitis.
Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during ARGA-L therapy. Pancreatitis should be considered if clinical symptoms suggestive of pancreatitis occur, including nausea, vomiting, abdominal pain, or abnormal laboratory values such as increased serum lipase or amylase. Patients who exhibit these signs or symptoms should be evaluated and ARGA-Lor other antiretroviral therapy should be suspended.

DRUG INTERACTIONS:
ARGA-L can be administered with or without food. ARGA-L induces glucuronidation and has the potential to reduce plasma concentrations of zidovudine or abacavir concentrations if these drugs are taken concurrently. Concentrations of antiarrhythmic drugs (amiodarone, bepridil, lidocaine, and quinidine) may be increased if taken concurrently with ARGA-L; therapeutic monitoring of antiarrhythmic concentration may be necessary.
Concomitant use of ARGA-L with lipid lowering agents will result in an increase of concentrations of these agents. Levels of atorvastatin or cerivastatin should be lowered to the lowest possible level when used in combination with ARGA-L. Pravastatin or fluvastatin should be considered as substitutes for atorvastatin or cerivastatin.
Concomitant use of lovastatin or simvastatin with ARGA-Lis not recommended, as serious reactions such as myopathy, including rhabdomyolysis, may occur.
Concurrent use of carbamazepine, dexamethasone, phenobarbital or phenytoin with ARGA-Lmay decrease concentrations of lopinavir and lead to decreased effectiveness of lopinavir.
Serum concentrations of clarithromycin may increase if administered concomitantly with ARGA-L. In patients concurrently taking clarithromycin, doses of ARGA-Lshould be decreased as necessary in patients with renal impairment.
Concentrations of cyclosporine, sirolimus, and tacrolimus may increase if administered concomitantly with ARGA-L. Therapeutic monitoring is recommended for patients taking any of these immunosuppressants concurrently with ARGA-L.

STORAGE CONDITIONS:
Store in a cool & dry place, protected from light.
Keep out of reach of children.

PRESENTATION:
1x60's in HDPE containers.
1x120's in HDPE containers.

ARGAVIR

Ritonavir Tablets

COMPOSITION:
Each tablet contains:
Ritonavir 100mg

DESCRIPTION:
Ritonavir inhibits HIV protease and renders the enzyme incapable of processing of polyprotein precursor which leads to production of noninfectious immature HIV particles.

PHARMACOLOGICAL:
Ritonavir was originally developed as an inhibitor of HIV protease. It is now rarely used for its own antiviral activity, but remains widely used as a booster of other protease inhibitors. More specifically, ritonavir is used to inhibit a particular liver enzyme that normally metabolizes protease inhibitors, cytochrome P450-3A4 (CYP3A4). The drug's molecular structure inhibits CYP3A4, so a low dose can be used to enhance other protease inhibitors.

PHARMACOKINETICS:
The pharmacokinetics of ritonavir have been studied in healthy volunteers and HIV-infected patients (CD4 ≥ 50 cells/μL)..

Absorption
The absolute bioavailability of ritonavir has not been determined. After a 600 mg dose of oral solution, peak concentrations of ritonavir were achieved approximately 2 hours and 4 hours after dosing under fasting and non-fasting (514 KCal; 9% fat, 12% protein, and 79% carbohydrate) conditions, respectively.

Effect of Food on Oral Absorption
When the oral solution was given under non-fasting conditions, peak ritonavir concentrations decreased 23% and the extent of absorption decreased 7% relative to fasting conditions. Dilution of the oral solution, within one hour of administration, with 240 mL of chocolate milk, Advera® or Ensure® did not significantly affect the extent and rate of ritonavir absorption. After a single 600 mg dose under non-fasting conditions, in two separate studies, the soft gelatin capsule (n = 57) and oral solution (n = 18) formulations yielded mean ± SD areas under the plasma concentration-time curve (AUCs) of 121.7 ± 53.8 and 129.0 ± 39.3 μg.h/mL, respectively. Relative to fasting conditions, the extent of absorption of ritonavir from the soft gelatin capsule formulation was 13% higher when administered with a meal (615 KCal; 14.5% fat, 9% protein, and 76% carbohydrate).

Metabolism
Nearly all of the plasma radioactivity after a single oral 600 mg dose of 14C-ritonavir oral solution (n = 5) was attributed to unchanged ritonavir. Five ritonavir metabolites have been identified in human urine and feces. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug; however, the concentrations of this metabolite in plasma are low. In vitro studies utilizing human liver microsomes have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of M-2.

Elimination
In a study of five subjects receiving a 600 mg dose of 14C-ritonavir oral solution, 11.3 ± 2.8% of the dose was excreted into the urine, with 3.5 ± 1.8% of the dose excreted as unchanged parent drug. In that study, 86.4 ± 2.9% of the dose was excreted in the feces with 33.8 ± 10.8% of the dose excreted as unchanged parent drug. Upon multiple dosing, ritonavir accumulation is less than predicted from a single dose possibly due to a time and dose-related increase in clearance.

INDICATIONS:
Treatment of HIV infection; should always be used as part of a multidrug regimen (at least three antiretroviral agents).

DOSAGE AND ADMINISTRATION:
Ritonavir is used for the treatment of HIV infection.
The recommended dose for adults is 600 mg twice daily. To reduce the occurrence of side effects, ritonavir should be started at 300 mg twice daily and increased every 2-3 days by 100 mg twice daily.
The recommended dose for children is 400 mg/m2 two times a day and should not exceed 600 mg two times daily. Treatment should be started at 250 mg/m2 and increased every 2-3 days by 50 mg/m2 two times daily.
Ritonavir should be administered with meals.

CONTRAINDICATIONS:
Hypersensitivity to ritonavir or any component of the formulation; concurrent amiodarone, bepridil, cisapride, dihydroergotamine, ergonovine, ergotamine, flecainide, lovastatin, methylergonovine, midazolam, pimozide, propafenone, quinidine, simvastatin, St John's wort, triazolam, and voriconazole

WARNINGS AND PRECAUTIONS:
Use caution in patients with hepatic insufficiency; safety and efficacy have not been established in children <2 years of age; use caution with benzodiazepines, rifabutin, sildenafil, and certain analgesics (meperidine, piroxicam, propoxyphene). Selected HMG-CoA reductase inhibitors are contraindicated; atorvastatin should be used at the lowest possible dose, while fluvastatin or pravastatin may be safer alternatives. Ritonavir may interact with many medications. Careful review is required. Dosage adjustment is required for combination therapy with amprenavir and ritonavir; in addition, the risk of hyperlipidemia may be increased during concurrent therapy. Warn patients that redistribution of fat may occur.
PREGNANCY: Use of ritonavir during pregnancy has not been adequately evaluated.
NURSING MOTHERS: It is not known whether ritonavir is secreted in breast milk. Nevertheless, HIV-infected mothers should not breast-feed because of the potential risk of transmitting HIV to an infant that is not infected.

SIDE EFFECTS:
The most serious side effects are liver failure, and failure of the pancreas (pancreatitis). Ritonavir also may elevate blood glucose, triglyceride and cholesterol levels.
Common symptomatic side effects of ritonavir include weakness, diarrhea, abdominal discomfort, and nausea. Less frequent effects include numbness around the mouth or in the extremities, and abnormal taste sensation.

DRUG INTERACTIONS:
Ritonavir interacts with many drugs. Some of the important interactions are mentioned below. Viewers should consult their healthcare provider before combining any drugs with ritonavir.
Ritonavir should not be used together with amiodarone, quinidine, triazolam, midazolam, pimozide, propafenone and flecainide because ritonavir increases the blood levels of these drugs and may lead to serious side effects.
Ritonavir also increases the concentrations in blood of rifabutin and sildenafil. Therefore, the doses of rifabutin and sildenafil should be reduced. The blood concentrations of oral contraceptives, methadone and theophylline are reduced by ritonavir, and this could reduce the effectiveness of these drugs. Ritonavir decreases the concentration of meperidine and increases the buildup of meperidine's toxic breakdown product in the body. Therefore, ritonavir reduces the beneficial effect of meperidine while increasing its side effects.
Ritonavir may increase the blood concentration of lovastatin, simvastatin, atorvastatin and cerivastatin. This may result in increased occurrence of myopathy (muscle pain) or rhabdomyolysis (muscle breakdown).
St. John's wort and rifampin decrease the concentration of ritonavir in the body and this could reduce the effectiveness of ritonavir.
Clarithromycin, ketoconazole, fluconazole and fluoxetine may increase blood concentrations of ritonavir and result in increased side effects from ritonavir.

OVERDOSAGE:
Human experience is limited; there is no specific antidote for overdose with ritonavir. Dialysis is unlikely to be beneficial in significant removal of the drug. Charcoal or gastric lavage may be useful to remove unabsorbed drug.

STORAGE CONDITIONS:
Store in a cool & dry place, protected from light.
Keep out of reach of children.

PRESENTATION:
1x60's in HDPE containers.
1x84's in HDPE containers.

LAMIVUDINE

Lamivudine 10 mg/ML Solution

COMPOSITION:

Each ml contains:
Lamivudine 10 mg

PHARMACOLOGICALACTION:

Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication in vitro, including zidovudine-resistant clinical isolates of the human immunodeficiency virus (HIV). Lamivudine is metabolised intracellularly to the active 5'-triphosphate which inhibits the RNA-and DNA-dependant activities of HIV reverse transcriptase by termination of the viral DNA chain. Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content. In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells. In vitro, lamivudine therefore has a high therapeutic index. Reduced in-vitro sensitivity to lamivudine has been reported for HIV isolated from patients who have received lamivudine therapy before.

Pharmacokinetics:

Pharmacokinetics in adults:
Following oral administration, lamivudine is well absorbed with bioavailability of approximately 80%. The mean time (Tmax) to maximum serum concentration (Cmax) is about an hour. At therapeutic dose levels of 4 mg/kg/day (as two 12-hourly doses), Cmaxis in the order of 1-1.5 micrograms/mL.
The mean volume of distribution from intravenous studies has been reported as 1.3 L/kg and the mean terminal half-life of elimination as 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 L/kg/h, with predominantly renal clearance of more than 70% via active tubular secretion, but little hepatic metabolism, at less than 10 L. The intracellular half-life of the lamivudine triphosphate active metabolite is prolonged, averaging over 10 hours in peripheral blood lymphocytes. A delay in Tmax, and reduction in Cmax have been observed when co-administered with food, but no dose adjustment is needed, as lamivudine bioavailability is not altered. Lamivudine displays limited binding to albumin and exhibits linear pharmacokinetics over the therapeutic dose range. Co-administration of zidovudine results in a 13% increase in zidovudine exposure and a 28% increase in peak plasma levels. No dosage adjustments are necessary, as this is not considered to be of significance to patient safety. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The true extent of penetration or relationship with any clinical efficacy is unknown.
Pharmacokinetics in children:
In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability is reduced to approximately 65%, in paediatric patients, with an increased clearance of 0.52 L/kg/hr.
There are limited pharmacokinetic data for patients <3 months of age.

INDICATIONS

LAMIVUDINE is indicated as part of antiretroviral combination therapy for treatment of HIV infected adults and children.

CONTRA-INDICATIONS

Hypersensitivity to any of the ingredients.

WARNINGS

Patients receiving LAMIVUDINE and other antiretroviral agents may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases.
Current antiretroviral therapy, including LAMIVUDINE, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, in the treatment of HIV infection.

INTERACTIONS

Zidovudine plasma levels are not significantly altered when co-administered with LAMIVUDINE (see Pharmacokinetics).
An interaction with trimethoprim, a constituent of co-trimoxazole. causes a 40% increase in lamivudine plasma concentrations at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment.
Administration of co-trimoxazole with the LAMIVUDINE/zidovudine combinations in patients with renal impairment should be carefully assessed. LAMIVUDINE may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. LAMIVUDINE is therefore not recommended to be used in combination with zalcitabine.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Adults and adolescents more than 12 years of age:
The recommended dose of LAMIVUDINE is 300 mg daily. This may be administered as either 300 mg once daily or 150 mg twice daily.
The package insert for zidovudine must be consulted for information on its dosage and administration.
For patients with low body weights (less than 50 kg), the recommended oral dose of LAMIVUDINE is 2 mg/kg twice daily.
Children >3 months to 12 years of age:
The recommended dose is 4 mg/kg twice daily up to a maximum of 300 mg daily.
Children <3 months of age:
There are limited data to propose specific dosage recommendations (see Pharmacokinetics).
LAMIVUDINE can be taken with or without food.
Renal and Hepatic Impairment:
Renal impairment, whether disease- or age-related, affects lamivudine elimination. For recommended dosage regimens in patients with a creatinine clearance below 50 mL/min see table below.

Adults and adolescents >12 years of age:

Creatinine Clearance (mL/min)	Recommended dose of LAMIVUDINE
>50	150 mg twice daily
30-49	150 mg once daily
15-29	150 mg first dose, then 100 mg once daily
5-14	150 mg first dose, then 50 mg once daily
<5	50 mg first dose, then 25 mg once daily

Children > 3 months to 12 years:

Creatinine Clearance (mL/min)	Recommended dose of LAMIVUDINE
>50	4 mg/kg first dose, then 4 mg/kg twice daily
30-49	4 mg/kg first dose; then 4 mg/kg once daily
15-29	4 mg/kg first dose. then 2.6 mg/kg once daily
5-14	4 mg/kg first dose, then 1.3 mg/kg once daily
<5	1.3 mg/kg first dose, then 0.7 mg/kg once daily

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Gastro-intestinal disorders:
Pancreatitis, upper abdominal pain, nausea; vomiting and diarrhoea have been reported.
Blood and lymphatic system disorders:
Neutropenia, thrombocytopenia and anaemia have occurred.
Skin and appendages disorders:
Alopecia has been reported.
Central and Peripheral Nervous system disorders:
Peripheral neuropathy, paraesthesia, and headache have been reported.

Musculo-skeletal system disorders:
Arthralgia, muscle disorders including less frequently, rhabdomyolysis have been reported.
Body as a whole:
Malaise, fatigue and fever have occurred.
Hypersensitivity reactions:
Skin rash.
Changes in laboratory test parameters:
Transient rises in serum liver enzymes (AST; ALT) and rises in serum amylase have been reported.
Special precautions:
LAMIVUDINE should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection, as there is a small risk of rebound hepatitis post treatment.
Pancreatitis:
Pancreatitis has been observed in some patients receiving LAMIVUDINE. However it is unclear whether this is due to LAMIVUDINE or to underlying HIV disease.
Lactic acidosis/severe hepatomegaly with steatosis:
Long-term use of LAMIVUDINE can result in potentially fatal lactic acidosis. Symptomatic hyperlactacaemia and lactic acidosis are uncommon. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.
In patients with suspicious symptoms or biochemistry. measure the venous lactate level (normal <2 mmol/L), and respond as follows:

Lactate 2 - 5 mmol/L: monitor regularly, and be alert for clinical signs.
Lactate 5 - 10 mmol/L without symptoms: monitor closely.
Lactate 5 - 10 mmol/L with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia. diabetic ketoacidosis, thyrotoxicosis, lymphoma).
Lactate 5 - 10 mmol/L: STOP all therapy (80% mortality in case studies).

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of LAMIVUDINE alone or in combination, in the treatment of HIV infection. Most cases were women.
Caution should be exercised when administering LAMIVUDINE to patients with known risk factors for liver disease (see WARNINGS).
Treatment with LAMIVUDINE should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.
Opportunistic infections:
Patients receiving LAMIVUDINE may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by medical practitioners experienced in the treatment of patients with associated HIV disease (see WARNINGS).
The risk of HIV transmission to others:
Patients should be advised that current antiretroviral therapy, including LAMIVUDINE, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.
Patients with moderate to severe renal impairment:
In patients with moderate to severe renal impairment, the terminal half-life of lamivudine is increased due to decreased clearance. The dose should therefore be adjusted (see DOSAGE AND DIRECTIONS FOR TREATMENT).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Treatment is symptomatic and supportive.

IDENTIFICATION:
Clear colourless to light pale yellow syrupy liquid contained in an amber PET bottle

PRESENTATION:
Amber PET bottle (100 ml or 240 ml):
Amber color, plastic (PET) bottle with a screw on cap, contained in a carton.

STORAGE INSTRUCTIONS:
Store below 30ºC. Protect from light.
KEEP OUT OF REACH OF CHILDREN.

LOPINAVIR & RITONAVIR ORAL SOLUTION

Lopinavir 80mg & Ritonavir 20mg Solution

COMPOSITION

Each ml contains:

Lopinavir	80mg
Ritonavir	20mg
Alcohol IP	42.4%v/v

PHARMACEUTICAL FORM

Oral Solution (Syrup)

CLINICAL PARTICULARS

Antiretroviral drugs

Therapeutic Indications

Lopinavir/Ritonavir oral solution is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children above the age of 2 years.
The choice of Lopinavir/Ritonavir oral solution to treat protease inhibitor experienced HIV-1 infected patients should be based on individual viral resistance testing and treatment history of patients.

Method of administration

Adult and adolescent use: the recommended dosage of Lopinavir/Ritonavir oral solution is 5 ml of oral solution (400/100 mg) twice daily taken with food.
Paediatric use (2 years of age and above): the recommended dosage of Lopinavir/Ritonavir oral solution is 230/57.5 mg/m2 twice daily taken with food, up to a maximum dose of 400/100 mg twice daily. The 230/57.5 mg/m2 dosage might be insufficient in some children when co-administered with nevirapine or efavirenz. An increase of the dose of Lopinavir/Ritonavir oral solution to 300/75 mg/m2 should be considered in these patients. Dose should be administered using a calibrated oral dosing syringe.
The oral solution is the recommended option for the most accurate dosing in children based on body surface area.

Paediatric dosing guidelines for the dose 230/57.5 mg/m2

Body Surface Area* (m2)	Twice daily oral solution dose (dose in mg)
0.25	0.7 ml (57.5/14.4 mg)
0.40	1.2 ml (96/24 mg)
0.50	1.4 ml (115/28.8 mg)
0.75	2.2 ml (172.5/43.1 mg)
0.80	2.3 ml (184/46 mg)
1.00	2.9 ml (230/57.5 mg)
1.25	3.6 ml (287.5/71.9 mg)
1.3	3.7 ml (299/74.8 mg)
1.4	4.0 ml (322/80.5 mg)
1.5	4.3 ml (345/86.3 mg)
1.7	5 ml (402.5/100.6 mg)

* Body surface area can be calculated with the following equation
BSA (m2) = √ (Height (cm) X Weight (kg) / 3600)

Children less than 2 years of age: the safety and efficacy of Lopinavir/Ritonavir oral solution in children aged less than 2 years have not yet been established. Total amounts of alcohol and propylene glycol from all medicines, including Lopinavir/Ritonavir oral solution, that are to be given to infants should be taken into account in order to avoid toxicity from these excipients.

Hepatic impairment: In HIV-infected patients with mild to moderate hepatic impairment, an increase of approximately 30% in lopinavir exposure has been observed but is not expected to be of clinical relevance. No data are available in patients with severe hepatic impairment. Lopinavir/Ritonavir oral solution must not be given to these patients.

Renal impairment: since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because lopinavir and ritonavir are highly protein bound, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

Contraindications

Hypersensitivity to the active substances or to any of the excipients.
Severe hepatic insufficiency.
Special warning and special precautions for use
Patients with coexisting conditions
Hepatic impairment: the safety and efficacy of Lopinavir & Ritonavir Oral Solution has not been established in patients with significant underlying liver disorders. Lopinavir & Ritonavir Oral Solution is contraindicated in patients with severe liver impairment. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

Renal impairment: since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. Because lopinavir and ritonavir are highly protein bound, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

Haemophilia: there have been reports of increased bleeding, including spontaneous skin haematomas and haemarthrosis in patients with haemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued.
Lipid elevations
Treatment with Lopinavir & Ritonavir Oral Solution has resulted in increases, sometimes marked, in the concentration of total cholesterol and triglycerides. Triglyceride and cholesterol testing is to be performed prior to initiating Lopinavir & Ritonavir Oral Solution therapy and at periodic intervals during therapy.
Pancreatitis
Cases of pancreatitis have been reported in patients receiving Lopinavir & Ritonavir Oral Solution, including those who developed hypertriglyceridaemia. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis.

Hyperglycaemia

New onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving protease inhibitors. In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis.
Fat redistribution & metabolic disorders
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances.
Immune Reactivation Syndrome
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART.

Interaction with other medicaments and other forms of interaction

Lopinavir & Ritonavir Oral Solution contains lopinavir and ritonavir, both of which are inhibitors of the P450 isoform CYP3A. Lopinavir & Ritonavir Oral Solution is likely to increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. These increases of plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events.
Concomitant administration with colchicine, notably in patients with renal or hepatic impairment, should be avoided.The combination of Lopinavir & Ritonavir Oral Solution with:
- tadalafil, indicated for the treatment of pulmonary arterial hypertension, is not recommended
- fusidic acid in osteo-articular infections is not recommended
- salmeterol is not recommended.
- rivaroxaban is not recommended.

Pregnancy
As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the foetus.

Breastfeeding
Studies in rats revealed that lopinavir is excreted in the milk. It is not known whether this medicinal product is excreted in human milk. HIV-infected women must not breast-feed their infants under any circumstances to avoid transmission of HIV.
Fertility
Animal studies have shown no effects on fertility. No human data on the effect of Lopinavir/Ritonavir on fertility are available.

Undesirable effects
The safety of Lopinavir & Ritonavir Oral Solution has been investigated in over 2600 patients in Phase II-IV clinical trials, of which over 700 have received a dose of 800/200 mg once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some studies, Lopinavir & Ritonavir Oral Solution was used in combination with efavirenz or nevirapine.
The most common adverse reactions related to Lopinavir & Ritonavir Oral Solution therapy during clinical trials were diarrhoea, nausea, vomiting, hypertriglyceridaemia and hypercholesterolemia. The risk of diarrhoea may be greater with once daily dosing of Lopinavir & Ritonavir Oral Solution. Diarrhoea, nausea and vomiting may occur at the beginning of the treatment while hypertriglyceridaemia and hypercholesterolemia may occur later.
Cushing's syndrome has been reported in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate; this could also occur with other corticosteroids metabolised via the P450 3A pathway e.g. budesonide.
Increased creatine phosphokinase (CPK), myalgia, myositis, and rarely, rhabdomyolysis have been reported with protease inhibitors, particularly in combination with nucleoside reverse transcriptase inhibitors.
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).
Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).
In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown.

Overdose and Treatment
To date, there is limited human experience of acute overdose with Lopinavir & Ritonavir Oral Solution.
Overdoses with Lopinavir & Ritonavir Oral Solution oral solution have been reported (including fatal outcome). The following events have been reported in association with unintended overdoses in preterm neonates: complete atrioventricular block, cardiomyopathy, lactic acidosis, and acute renal failure.
The adverse clinical signs observed in dogs included salivation, emesis and diarrhoea/abnormal stool. The signs of toxicity observed in mice, rats or dogs included decreased activity, ataxia, emaciation, dehydration and tremors.
There is no specific antidote for overdose with Lopinavir & Ritonavir Oral Solution.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Mechanism of action: Lopinavir provides the antiviral activity of Lopinavir & Ritonavir Oral Solution. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus.

Effects on the electrocardiogram: QTcF interval was evaluated in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 39 healthy adults, with 10 measurements over 12 hours on Day 3. The maximum mean (95% upper confidence bound) differences in QTcF from placebo were 3.6 (6.3) and 13.1(15.8) for 400/100 mg twice daily and supratherapeutic 800/200 mg twice daily LPV/r, respectively. The induced QRS interval prolongation from 6 ms to 9.5 ms with high dose Lopinavir/Ritonavir (800/200 mg twice daily) contributes to QT

prolongation. The two regimens resulted in exposures on Day 3 which were approximately 1.5 and 3-fold higher than those observed with recommended once daily or twice daily LPV/r doses at steady state. No subject experienced an increase in QTcF of ≥ 60 msec from baseline or a QTcF interval exceeding the potentially clinically relevant threshold of 500 msec.

Pharmacokinetic Properties

Absorption: multiple dosing with 400/100 mg Lopinavir & Ritonavir Oral Solution twice daily for 2 weeks and without meal restriction produced a mean ± SD lopinavir peak plasma concentration (Cmax) of 12.3 ± 5.4 µg/ml, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 8.1 ± 5.7 µg/ml. Lopinavir AUC over a 12 hour dosing interval averaged 113.2 ± 60.5 µg•h/ml. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established.

Effects of food on oral absorption: Lopinavir & Ritonavir Oral Solution soft capsules and liquid have been shown to be bioequivalent under nonfasting conditions (moderate fat meal). Administration of a single 400/100 mg dose of Lopinavir & Ritonavir Oral Solution soft capsules with a moderate fat meal (500 – 682 kcal, 22.7 –25.1% from fat) was associated with a mean increase of 48% and 23% in lopinavir AUC and Cmax, respectively, relative to fasting. For Lopinavir & Ritonavir Oral Solution oral solution, the corresponding increases in lopinavir AUC and Cmax were 80% and 54%, respectively.

Administration of Lopinavir & Ritonavir Oral Solution with a high fat meal (872 kcal, 55.8% from fat) increased lopinavir AUC and Cmax by 96% and 43%, respectively, for soft capsules, and 130% and 56%, respectively, for oral solution. To enhance bioavailability and minimise variability Lopinavir & Ritonavir Oral Solution is to be taken with food.

Distribution: at steady state, lopinavir is approximately 98 – 99% bound to serum proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin, however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg Lopinavir & Ritonavir Oral Solution twice daily, and is similar between healthy volunteers and HIV-positive patients.

Biotransformation: in vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolised by the hepatic cytochrome P450 system, almost exclusively by isozyme CYP3A. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir and therefore, increases plasma levels of lopinavir. A 14C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg Lopinavir & Ritonavir Oral Solution dose was due to parent active substance. At least 13 lopinavir oxidative metabolites have been identified in man. The 4-oxo and 4-hydroxymetabolite epimeric pair are the major metabolites with antiviral activity, but comprise only minute amounts of total plasma radioactivity. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism, and likely the induction of lopinavir metabolism. Pre-dose lopinavir concentrations decline with time during multiple dosing, stabilising after approximately 10 days to 2 weeks.

Elimination: after a 400/100 mg 14C-Lopinavir/Ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of 14C-lopinavir can be accounted for in urine and faeces, respectively. Unchanged lopinavir accounted for approximately 2.2% and 19.8% of the administered dose in urine and faeces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The effective (peak to trough) half-life of lopinavir over a 12 hour dosing interval averaged 5 – 6 hours, and the apparent oral clearance (CL/F) of lopinavir is 6 to 7 l/h.

Paediatrics:

There are limited pharmacokinetic data in children below 2 years of age. The pharmacokinetics of Lopinavir & Ritonavir Oral Solution 300/75 mg/m2 twice daily and 230/57.5 mg/m2 twice daily have been studied in a total of 53 paediatric patients, ranging in age from 6 months to 12 years. The lopinavir mean steady-state AUC, Cmax, and Cmin were 72.6 ± 31.1 µg•h/ml, 8.2 ± 2.9 µg/ml and 3.4 ± 2.1 µg/ml, respectively after Lopinavir & Ritonavir Oral Solution 230/57.5 mg/m2 twice daily without nevirapine (n=12), and were 85.8 ± 36.9 µg•h/ml, 10.0 ± 3.3 µg/ml and 3.6 ± 3.5 µg/ml, respectively after 300/75 mg/m2 twice daily with nevirapine (n=12). The 230/57.5 mg/m2 twice daily regimen without nevirapine and the 300/75 mg/m2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen without nevirapine.

31.1 µg•h/ml, 8.2 ± 2.9 µg/ml and 3.4 ± 2.1 µg/ml, respectively after Lopinavir & Ritonavir Oral Solution 230/57.5 mg/m2 twice daily without nevirapine (n=12), and were 85.8 ± 36.9 µg•h/ml, 10.0 ± 3.3 µg/ml and 3.6 ± 3.5 µg/ml, respectively after 300/75 mg/m2 twice daily with nevirapine (n=12). The 230/57.5 mg/m2 twice daily regimen without nevirapine and the 300/75 mg/m2 twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen without nevirapine.

Gender, Race and Age:

Lopinavir & Ritonavir Oral Solution pharmacokinetics have not been studied in the elderly. No age or gender related pharmacokinetic differences have been observed in adult patients. Pharmacokinetic differences due to race have not been identified.

Renal Insufficiency:

Lopinavir & Ritonavir Oral Solution pharmacokinetics have not been studied in patients with renal insufficiency; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal insufficiency.

Hepatic Insufficiency:

The steady state pharmacokinetic parameters of lopinavir in HIV-infected patients with mild to moderate hepatic impairment were compared with those of HIV-infected patients with normal hepatic function in a multiple dose study with Lopinavir/Ritonavir 400/100 mg twice daily. A limited increase in total lopinavir concentrations of approximately 30% has been observed which is not expected to be of clinical relevance (see section 4.2).

Shelf Life

18 months from the date of manufacturing.

Special Precautions for Storage

Store at 2°-8°C. Avoid exposure to excessive heat.

For patient use, refrigerated oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 25°C oral solution should be used within 2 months.

Keep out of reach of children

Nature and Contents of container

60 ml, 100 ml, 240 ml &300 ml oral solution filled in PET bottles; labeled bottle are put in a carton along with a leaflet.

Instructions for user handling

Carefully read the instructions before use. Consult your doctor for further information.

"Use upon doctor's prescription only".

MCABAVIR Oral Solution

Abacavir Oral Solution

COMPOSITION:

Each ml contains: Abacavir Sulphate
Equivalent to Abacavir 20 mg

WARNING:

Hypersensitivity: In clinical studies, approximately 4% of subjects receiving Abacavir developed a hypersensitivity reaction which in rare cases proved fatal.
Description: This is characterised by the appearance of symptoms indicating multiorgan/body-system involvement. The majority of patients have fever and/or rash as part of the syndrome. The symptoms of this hypersensitivity reaction can occur at any time during treatment with Abacavir, but usually appear within the first 6 weeks of initiation of treatment with Abacavir (median time to onset 11 days), and most often include fever, gastrointestinal symptoms (nausea, vomiting, diarrhoea and abdominal pain), rash and fatigue or malaise. Other symptoms may include myalgia, arthralgia, oedema, paraesthesia and respiratory symptoms such as dyspnoea, sore throat or cough.
The symptoms worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of Abacavir.
When patients who have discontinued Abacavir present with an indeterminate diagnosis of hypersensitivity (single symptom), the doctor should:

- Assess the probability that hypersensitivity preceded the interruption
- Assess the risk: benefit of reinitiating Abacavir
- Select the appropriate medical setting in which to re-introduce Abacavir, if such a decision is made.

Prescribers must ensure that patients are fully informed regarding the following hypersensitivity reaction:

- Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death.
- Patients developing signs or symptoms possibly linked with a hypersensitivity reaction MUST CONTACT their doctor IMMEDIATELY.
- Patients who have stopped Abacavir for any reason, and particularly due to adverse reactions or illness, must be advised to contact their doctor before restarting.

PHARMACOLOGICAL CLASSIFICATION:

Antiviral agents

PHARMACOLOGICAL ACTION:

Abacavir is a nucleoside analogue reverse transcriptase inhibitor. It is an antiviral agent against HIV-1 and HIV-2, including HIV-1 isolates that are resistant to zidovudine, lamivudine, zalcitabine, didanosine or nevirapine. In vitro studies have demonstrated that its mechanism of action in relation to HIV is inhibition of the HIV reverse transcriptase enzyme, an event that results in chain termination and interruption of the viral replication cycle. Abacavir shows synergy in vitro in combination with nevirapine and zidovudine. It has been shown to be additive in combination with didanosine, zalcitabine, lamivudine and stavudine.
Abacavir-resistant isolates of HIV-1 have been selected in vitro and are associated with specific genotypic changes in the reverse transcriptase (RT) codon region (codons M184V, K65R, L74V and Y115F). Viral resistance to abacavir develops relatively slowly in vitro and in vivo, requiring multiple mutations to reach an eight-fold increase in IC50 over wild-type virus, which may be a clinically relevant level. Isolates resistant to abacavir may also show reduced sensitivity to lamivudine, zalcitabine and/or didanosine, but remain sensitive to zidovudine and stavudine. Cross-resistance between abacavir and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is unlikely.
Pharmacokinetics:

Absorption:
Abacavir is well absorbed following oral administration. The absolute bioavailability of oral abacavir in adults is about 83%. Following oral administration, the mean time (tmax) to maximal serum concentrations of abacavir is about 1,0 hour. Food delayed absorption and decreased Cmax but did not affect overall plasma concentrations (AUC). Therefore abacavir can be taken with or without food.

Distribution:
Studies in HIV infected patients have shown good penetration of abacavir into the cerebrospinal fluid (CSF), with a CSF to plasma AUC ratio of between 30 to 44%.
In a phase I pharmacokinetic study, the penetration of abacavir into the CSF was investigated following administration of abacavir 300 mg twice a day. The mean concentration of abacavir achieved in the CSF 1,5 hours post dose was 0,14 micrograms/mL.
In a further pharmacokinetic study of 600 mg twice a day, the CSF concentration of abacavir increased over time, from approximately 0,13 micrograms/mL at 0,5 to 1 hour after dosing, to approximately 0,74 micrograms/mL after 3 to 4 hours. While peak concentrations may not have been attained by 4 hours, the observed values are 9-fold greater than the IC50 of abacavir 0,08 micrograms/mL or 0,26 microM.
Plasma protein binding studies in vitro indicate that abacavir binds only moderately (~49%) to human plasma proteins at therapeutic concentrations. This indicates a low likelihood for drug interactions through plasma protein binding displacement.

Metabolism:
Abacavir is primarily metabolised by the liver with less than 2% of the administered dose being renally excreted, as unchanged compound. The primary pathways of metabolism in man are by alcohol dehydrogenase and by glucuronidation to produce the 5'-carboxylic acid and 5'-glucuronide which account for about 66% of the dose in the urine.

Elimination:
The mean half-life of abacavir is about 1,5 hours. Following multiple oral doses of abacavir 300 mg twice a day there is no significant drug accumulation. Elimination of abacavir is via hepatic metabolism with subsequent excretion of metabolites primarily in the urine. The metabolites and unchanged abacavir account for about 83% of the administered abacavir dose in the urine, the remainder is eliminated in the faeces.

Special populations:

Hepatic impairment:
Abacavir is metabolised primarily by the liver. The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5-6).
The results showed that there was a mean increase of 1,89-fold in the abacavir AUC, and 1,58-fold in the half-life of abacavir. The AUCs of the metabolites were not modified by the liver disease. However, the rates of formation and elimination of these were decreased. The pharmacokinetics have not been studied in patients with moderate or severe hepatic impairment, therefore abacavir is contra-indicated in these patient groups.

Renal impairment:
Abacavir is primarily metabolised by the liver with approximately 2% of abacavir excreted unchanged in the urine. The pharmacokinetics of abacavir in patients with end-stage renal disease is similar to patients with normal renal function. Therefore no dosage reduction is required in patients with renal impairment.

Children:
The overall pharmacokinetic parameters in children are comparable to adults, with slightly greater variability in plasma concentrations. The recommended dose for children from 3 months to 12 years is 8 mg/kg twice daily. This will provide slightly higher mean plasma concentrations in children, ensuring that the majority will achieve therapeutic concentrations equivalent to 300 mg twice a day in adults.
There are insufficient safety data to recommend the use of abacavir in infants less than 3 months old.

Elderly:
The pharmacokinetics of abacavir has not been studied in patients over 65 years of age.
When treating elderly patients consideration needs to be given to the greater frequency of decreased hepatic, renal and cardiac function, and concomitant disease or other drug therapy.

INDICATIONS:
Abacavir is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children.

CONTRA-INDICATIONS:

Abacavir is contra-indicated:

- in patients with known hypersensitivity to abacavir or any ingredient of the formulations (see WARNINGS)
- in patients with a hereditary fructose intolerance
- in patients with liver function impairment
- in pregnancy and lactation (see PREGNANCY AND LACTATION)
- in infants under 3 months of age

WARNINGS

Hypersensitivity: Approximately 4% of subjects receiving Abacavir develop a hypersensitivity reaction which in rare cases has proved fatal. This is characterised by the appearance of symptoms indicating multi-organ/body-system involvement.

Patients who develop a hypersensitivity reaction must discontinue Abacavir and MUST not be re-challenged with Abacavir (see SIDE-EFFECTS AND SPECIAL PRECAUTIONS).

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 alone or in combination, including abacavir, in the treatment of HIV infection (see SIDE-EFFECTS AND SPECIAL PRECAUTIONS).

Abacavir contains sorbitol which may cause abdominal pains and diarrhoea.

INTERACTIONS

Based on the results of in vitro experiments and the known major metabolic pathways of abacavir, the potential for drug interactions involving abacavir is low. Abacavir shows no potential to inhibit metabolism mediated by the cytochrome P450 3A4 enzyme.

It has also been shown in vitro not to interact with medicines that are metabolised by CYP3A4, CYP2C9 or CYP2D6 enzymes. Induction of hepatic metabolism has not been observed in clinical studies. Therefore, there is little potential for medicine interactions with antiretroviral protease inhibitors and other medicines metabolised by major P450 enzymes. Clinical studies have shown that there are no clinically significant interactions between abacavir, zidovudine, and lamivudine.

Ethanol:

The metabolism of abacavir is altered by concomitant ethanol resulting in an increase in AUC of abacavir of about 41%. No dose reduction of abacavir is necessary. Abacavir has no effect on the metabolism of ethanol.

Methadone:

In a pharmacokinetic study, co-administration of 600 mg abacavir twice daily with methadone showed a 35% reduction in abacavir Cmax and a one hour delay in tmax, but the AUC was unchanged. The changes in abacavir pharmacokinetics are not considered clinically relevant. In this study abacavir increased the mean methadone systemic clearance by 22%. This change is not considered clinically relevant for the majority of patients, however occasionally methadone re-titration may be required.

Retinoids:

Retinoid compounds such as isotretinoin, are eliminated via alcohol dehydrogenase. Interaction with abacavir is possible but has not been studied.

PREGNANCY AND LACTATION

Abacavir is contra-indicated in pregnancy and lactation

DOSAGE AND DIRECTIONS FOR USE:

Abacavir should be prescribed by physicians experienced in the management of HIV infection.

Abacavir can be taken with or without food.

Adults and adolescents (over 12 years of age):

for these patients groups other formulations with higher amounts of the active substance are available.

Abacavir sulphate oral solution 20mg/ml can be taken with or without food.

Children (under 12 years of age):
Amount of oral solution(ML) by weight band to be taken twice daily(approximately 12 hours apart) .
Children less than three months: the experience in children aged less than three months is limited
Amount of solution by weight band(twice daily):3-5.9kg 6-9.9kg 10-13.9kg 3ml 4ml 6ml.
Renal impairment: no dosage adjustment of Abacavir is necessary in patients with renal dysfunction. However, Abacavir is not recommended for patients with end-stage renal disease.
Hepatic impairment: abacavir is primarily metabolised by the liver. No dose recommendation can be made in patients with mild hepatic impairment. In patients with moderate hepatic impairment, no data are available, therefore the use of abacavir is not recommended unless judged necessary. If abacavir is used in patients with mild or moderate hepatic impairment, then close monitoring is required, and if feasible, monitoring of abacavir plasma levels is recommended (see section 5.2). Abacavir is contraindicated in patients with severe hepatic impairment.
Elderly: no pharmacokinetic data is currently available in patients over 65 years of age

SIDE EFFECTS AND SPECIAL PRECAUTIONS
Side-effects:

Hypersensitivity: In clinical studies, approximately 4% of subjects receiving Abacavir developed a hypersensitivity reaction which in rare cases proved fatal. This is characterised by the appearance of symptoms indicating multi-organ/ body-system involvement.
Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever.
Symptoms can occur at any time while being treated with Abacavir, but usually appear within the first 6 weeks of initiation of treatment with Abacavir (median time to onset 11 days).(see WARNINGS)

The signs and symptoms of this hypersensitivity reaction are listed below.
Blood and the lymphatic system disorders
Less frequent (incidence approximately 5%): lymphadenopathy, lymphopenia
Nervous system disorders
Less frequent (incidence approximately 5%): paraesthesia

Eye disorders
Less frequent (incidence approximately 5%): conjunctivitis
Cardiac disorders
Less frequent (incidence approximately 5%): hypotension
Vascular disorders
Less frequent (incidence approximately 5%): headache
Respiratory, thoracic and mediastinal disorders
Less frequent (incidence approximately 5%): dyspnoea, sore throat, cough
Gastrointestinal disorders
Less frequent (incidence approximately 5%): nausea, vomiting, diarrhoea, abdominal pain, mouth ulceration
Hepato-biliary disorders
Less frequent (incidence approximately 5%): elevated liver function tests, hepatic failure
Skin and subcutaneous tissue disorders
Less frequent (incidence approximately 5%): rash (usually maculopapular or urticarial)
Musculoskeletal, connective tissue and bone disorders
Less frequent (incidence approximately 5%): myalgia, myolysis, arthralgia, elevated creatine phosphokinase
Renal and urinary disorders
Less frequent (incidence approximately 5%): elevated creatinine, renal failure
General disorders and administrative site conditions
Less frequent (incidence approximately 5%): fever, fatigue, malaise, oedema, anaphylaxis
Some patients with hypersensitivity reactions were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in Abacavir being continued or re-introduced, leading to more severe hypersensitivity reactions or death. Therefore, the diagnosis of hypersensitivity reactions should be carefully considered for patients presenting with symptoms of these diseases.
Symptoms worsen with continued therapy, and usually resolve upon discontinuation of Abacavir.

Restarting Endocrine disorders
Rare: pancreatitis
Metabolism and nutrition disorders
Frequency unknown: elevated blood glucose and triglyceride concentrations, anorexia
Vascular disorders
Frequency unknown: headache
Gastrointestinal disorders
Frequent: nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders
Frequency unknown: skin rash (without systemic symptoms), erythema multiforma, Stevens-Johnson syndrome, toxic epidermal necrolysis
General disorders and administrative site conditions
Frequent: fatigue and lethargy
Frequency unknown: fever
Hepato-biliary disorders
Rare: lactic acidosis, severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including abacavir, in the treatment of HIV infection. A majority of these cases have been in women. Caution should be exercised when administering Abacavir to any patient, and particularly to those with known risk factors for liver disease. Treatment with Abacavir should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.
Special Precautions:
Abacavir contains sorbitol which is metabolised to fructose and is therefore unsuitable for patients who have hereditary fructose intolerance (see CONTRAINDICATIONS).
No currently available data suggests that Abacavir affects the ability to drive or operate machinery.
Abacavir was not mutagenic in bacterial tests, but showed activity in vitro in the human lymphocyte chromosome aberration assay, the mouse lymphoma assay, and the in vivo micronucleus test. This is consistent with the known activity of other nucleoside analogues. These results indicate that abacavir is a weak clastogen both in vitro and in vivo at high test concentrations.
Carcinogenicity studies with orally administered abacavir in mice and rats showed an increase in the incidence of malignant and non-malignant tumours. Malignant tumours occurred in the preputial gland of males and the clitoral gland of females of both species, and in rats in the thyroid gland of males and the liver, urinary bladder, lymph nodes and the sub cutis of female rats. The majority of these tumours occurred at the highest dose levels equivalent to 24 to 32 times the expected systemic exposure in humans.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Single doses up to 1200 mg and daily doses up to 1800 mg of abacavir have been administered to patients in clinical studies. No unexpected adverse reactions were reported. The effects of higher doses are not known. If overdosage occurs the patient should be monitored for evidence of toxicity (see **SIDE-EFFECTS AND SPECIAL PRECAUTIONS),** and standard supportive treatment applied as necessary. It is not known whether abacavir can be removed by peritoneal dialysis or haemodialysis

IDENTIFICATION:
Clear colorless syrupy liquid contained in an Amber pet bottle.

STORAGE INSTRUCTIONS:
Store below 30ºC. Protect from light.
KEEP OUT OF REACH OF CHILDREN.

PACKING: Plastic bottle of 100ml or 240ml in a carton.

NEVIRAPINE Suspension

Nevirapine 50 mg/5ml

COMPOSITION:
Each 5mL contains:
Nevirapine 50mg

PRESENTATION:
Oral Suspension

PHARMACOLOGY:
MECHANISM OF ACTION:
Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. Nevirapine binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The HIV-2 reverse transcriptase and human DNA polymerases (such as DNA polymerases, or) are not inhibited by nevirapine.In cell culture, nevirapine demonstrated additive to synergistic activity against HIV in drug combination regimens with zidovudine, didanosine, stavudine, lamivudine, saquinavir and indinavir.

INDICATIONS:
Nevirapine is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.
Resistant virus emerges rapidly and uniformly when nevirapine is administered as monotherapy. Therefore, nevirapine should always be administered in combination with at least one additional antiretroviral agent.

CONTRINDICATIONS:
Nevirapine is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the tablet or the oral suspension.

DOSAGE AND ADMINISTRATION:
Paediatric patients
The recommended oral dose of Nevirapine for paediatric patients 2 months up to 8 years of age is 4 mg/kg once daily for the first 14 days followed by 7 mg/kg twice daily thereafter. For patients 8 years and older the recommended dose is 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

Monitoring of patients
Clinical chemistry tests, which include liver function tests, should be performed prior to initiating nevirapine therapy and at appropriate intervals during therapy.

Dosage Adjustment
Nevirapine should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (See Warnings and Precautions). Patients experiencing rash during the 14-day lead-in period of 200 mg/day (or 4 mg/kg/day in paediatric patients) should not have their nevirapine dose increased until the rash has resolved.
Nevirapine administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities (excluding GGT), until the liver function test elevations have returned to baseline. Nevirapine may then be restarted at 200 mg per day (or 4 mg/kg/day in paediatric patients). Increasing the daily dose to 200 mg twice daily (4 or 7 mg/kg twice daily, according to age, in paediatric patients) should be done with caution, after extended observation. Nevirapine should be permanently discontinued if moderate or severe liver function test abnormalities recur.
Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing, using one 200 mg tablet daily (or 4 mg/kg/day in paediatrics) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (4 or 7 mg/kg twice daily, according to age, in paediatric patients).
No data are available to recommend a dosage of nevirapine in patients with hepatic dysfunction, renal insufficiency, or undergoing dialysis.

WARNINGS AND PRECAUTIONS:

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise and/or significant hepatic abnormalities) must discontinue nevirapine as soon as possible.

Nevirapine therapy must be initiated with a 14-day lead-in period of 200 mg/day (4 mg/kg/day in paediatric patients), 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.

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis (transaminase elevations, with or without hyperbilirubinemia, prolonged partial thromboplastin time, or eosinophilia), has occurred in patients treated with nevirapine. Some of these cases began in the first few weeks of therapy, and some were accompanied by rash. Nevirapine administration should be interrupted in patients experiencing moderate or severe ALT or AST abnormalities until these return to baseline values. Nevirapine should be permanently discontinued if liver function abnormalities recur upon readministration. Monitoring of ALT and AST is strongly recommended, especially during the first six months of nevirapine treatment.

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

IMPAIRED RENAL AND HEPATIC FUNCTION:

Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. However, the pharmacokinetics of nevirapine have not been evaluated in patients with either hepatic or renal dysfunction. Therefore, nevirapine should be used with caution in these patient populations.

DRUG INTERACTION:

The induction of CYP3A by nevirapine may result in lower plasma concentrations of other concomitantly administered drugs that are extensively metabolized by CYP3A. Thus, if a patient has been stabilized on a dosage regimen for a drug metabolized by CYP3A, and begins treatment with nevirapine, dose adjustments may be necessary.

Rifampin/Rifabutin: There are insufficient data to assess whether dose adjustments are necessary when nevirapine and rifampin or rifabutin are coadministered. Therefore, these drugs should only be used in combination if clearly indicated and with careful monitoring.

Ketoconazole: Nevirapine and ketoconazole should not be administered concomitantly. Coadministration of nevirapine and ketoconazole results in a significant reduction in ketoconazole plasma concentrations.

Oral Contraceptives: There are no clinical data on the effects of nevirapine on the pharmacokinetics of oral contraceptives. Nevirapine may decrease plasma concentrations of oral contraceptives (also other hormonal contraceptives); therefore, these drugs should not be administered concomitantly with nevirapine.

Methadone: Based on the known metabolism of methadone, nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Pregnancy

Category C. There are no adequate and well-controlled studies in pregnant women. Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

Data indicate that nevirapine is found in breast milk. It is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Mothers should discontinue nursing if they are receiving nevirapine.

SIDE EFFECTS:
The most clinically important adverse events associated with nevirapine therapy are rash and increases in liver function tests. Cases of hypersensitivity reactions have been observed.
The major clinical toxicity of nevirapine is rash, with nevirapine-attributable rash occurring in 16% of patients on combination regimens in Phase II/III controlled studies. Thirty-five percent of patients treated with nevirapine experienced rash compared with 19% of patients treated in control groups of either zidovudine + didanosine or zidovudine alone. Severe or life-threatening rash occurred in 6.6% of nevirapine-treated patients compared with 1.3% of patients treated in the control groups.
Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions; with or without pruritus, located on the trunk, face and extremities. The majority of severe rashes occurred within the first 28 days of treatment. 25% of the patients with severe rashes required hospitalization, and one patient required surgical intervention. Overall, 7% of patients discontinued nevirapine due to rash.
With respect to laboratory abnormalities, asymptomatic elevations in GGT levels are more frequent in nevirapine recipients than in controls. Because clinical hepatitis has been reported in nevirapine-treated patients, monitoring of ALT (SGPT) and AST (SGOT) is strongly recommended, especially during the first six months of nevirapine treatment (See Warnings and Precautions). Decreased neutrophils (< 750/mm3), platelets (< 50,000/mm3) and Hb (< 8.0 g/dL), and increased total bilirubin (> 2.5 mg/dL) have also been reported.
Grenulocytopenia has been more commonly observed in children. The safety profile of nevirapine in neonates has not been established.

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

STORAGE CONDITION:
Store in a cool place, protected from light, keep out of reach of children.

STORAGE LIFE IS 2 YEARS:
The preparation should not be used after the expiry date.

DISTRIBUTION CONDITION:
With prescription

PACKING:
Plastic bottle of 100ml or 240ml in a carton.

MCNEIL & ARGUS PHARMACEUTICALS LTD.

STV COMP -30

(Stavudine. Lamivudine & Nevirapine Tablets)

Composition:
Each tablet contains:

Stavudine	30 mg
Lamivudine	150 mg
Nevirapine	200 mg

Pharmacology:
STV Comp - 30 is a combination of three drugs commonly used in the management of Human Immunodeficiency Virus (HIV) infection. Stavudine, Nevirapine and lamivudine belong to the nucleoside analogue class of antiretroviral drugs. These drugs act by inhibiting the reverse transcriptase of HIV, and by terminating the growth of the DNA chain. Stavudine in combination with lamivudine & Nevirapine has been shown to have synergistic antiretroviral activity.
Each tablet of STV Comp – 30 contains half of the commonly prescribed daily doses of stavudine, Nevirapine and lamivudine. With the availability of this combination tablet patients may be better able to adhere to complex drug treatment regimens, thereby enhancing compliance.

Pharmacokinetics:
Lamivudine:
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 administration of 2 mg/kg twice a day to nine adults with HIV, the peak serum lamivudine concentration (Cmax) was 1.5 ± 0.5 µg/ml (mean ± SD). The area under the plasma concentration versus time curve (AUC) and Cmax increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.
An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on two occasions, once in the fasted state and once with food (1099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (Tmax: 3.2 ± 1.3 hours) compared with the fasted state (Tmax: 0.9 ± 0.3 hours); Cmax in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC¥) in the fed and fasted states; therefore, Lamivudine may be administered with or without food.
The accumulation ratio of lamivudine in HIV-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2mg/kg b.i.d.
The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.
Binding of lamivudine to human plasma proteins is low (<36%). In vitro studies showed that, over the concentration range of 0.1 to 100 mg/mL, the amount of lamivudine associated with erythrocytes ranged from 53% to 57% and was independent of concentration.
Metabolism of lamivudine is a minor route of elimination. In man, the only known metabolite of lamivudine is the trans-sulfoxide metabolite. Within 12 hours after a single oral dose of lamivudine in six HIV-infected adults, 5.2% ± 1.4% (mean ± SD) of the dose was excreted as the trans-sulfoxide metabolite in the urine. Serum concentrations of this metabolite have not been determined.
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 ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.
In most single-dose studies in HIV-infected patients with serum sampling for 24 hours after dosing, the observed mean elimination half-life (T ½) ranged from 5 to 7 hours. Total clearance was 0.37 ± 0.05 L/hr•kg (mean ± SD). Oral clearance and elimination half-life were independent of dose and body weight over an oral dosing range from 0.25 to 10 mg/kg.

Stavudine:
The pharmacokinetics of stavudine have been evaluated in HIV-infected adult and pediatric patients. Peak plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03 to 4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

Absorption: Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution.
Distribution: Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 µg/mL. Stavudine distributes equally between red blood cells and plasma.
Metabolism: The metabolic fate of stavudine has not been elucidated in humans. Excretion- Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.
Nevirapine

Absorption: Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Peak plasma nevirapine concentrations of 2 ± 0.4 mc g/mL (7.5 mc M) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 mc g/mL (17 ± 7 mc M), (n = 242) were attained at 400 mg/day. When Nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 30 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 (AUCt) was not significantly altered by ddI, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid or ddI.
Distribution: Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 mc g/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% (± 5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.
Metabolism/Elimination: In vivo studies in humans and in vitro studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. In vitro studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 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 given twice daily followed by a single 50 mg dose of 14C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%).

Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.
Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of autoinduction are characterized by an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200 - 400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200 - 400 mg/day.

Indications:
Lamivudine + Stavudine + Nevirapine is indicated for the treatment of HIV infection.

Contra-indications:
Lamivudine + Stavudine + Nevirapine Tablets is contraindicated in patients with clinically significant hypersensitivity to the active substance or to any of the excipients.

Dosage and directions for use:
1 tablet twice daily for patients weighing > 60 kg
Dose Adjustment: Because it is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment, such as those with reduced renal function (creatinine clearance < 50 ml/min), those with low body weight (< 50 kg or 110 lbs), or those experiencing dose-limiting adverse events.

Warning:

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Lactic acidosis/severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including stavudine, Nevirapine and lamivudine. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Caution should be exercised when administering stavudine to any patient, and particularly to those with known risk factors for liver disease. Cases have also been reported in patients with no known risk factors. Treatment should be discontinued 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 aminotransferase elevations).

PERIPHERAL NEUROPATHY

Stavudine therapy can be associated with severe peripheral neuropathy, which is dose-related. It has occurred more frequently in patients with advanced HIV infection, a history of neuropathy, or concurrent neurotoxic drug therapy, including didanosine.

Patients should be monitored for the development of neuropathy that is usually characterized by numbness, tingling or pain in the feet or hands. Stavudine-related peripheral neuropathy may resolve if therapy is withdrawn promptly. In some cases, symptoms may worsen temporarily following discontinuation of therapy.

If symptoms resolve completely, resumption of treatment with stavudine may be considered using the following dosage schedule for adults:

20 mg twice daily for patients > 60 kg

15 mg twice daily for patients < 60 kg

IMPAIRED RENAL FUNCTION

Reduction of the dosage of stavudine, Nevirapine and lamivudine is required in patients with a creatinine clearance of 50 ml/min or less. Hence, it cannot be used in this patient population.

PATIENTS WITH HIV AND HEPATITIS B VIRUS COINFECTION

In clinical trials, some patients with HIV infection who have chronic liver disease due to hepatitis B virus infection experienced clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine. Consequences may be more severe in patients with decompensated liver disease.

Side-effects & special precautions:

Lamivudine

Pancreatitis has been reported with the use of lamivudine.

Lactic acidosis and hepatic steatosis, hepatitis and liver failure have been reported with the use of antiretroviral nucleoside analogs, alone or in combination.

Other side effects associated with the use of lamivudine are diarrhea, malaise and fatigue, headache, nausea and vomiting, abdominal pain and discomfort, peripheral neuropathy, arthralgias, myalgias, skin rash, pruritus, transient neutropenia and thrombocytopenia and rarely, pancreatitis. Transiently elevated levels of hepatic enzymes and bilirubin (> 5 times the normal level) have also been observed occasionally during treatment with the drug. Resolution of transient neutropenia and raised hepatic and bilirubin levels occurred without dosage modification or discontinuation of therapy.

Stavudine

Therapy with stavudine can be associated with severe peripheral neuropathy, which is dose related and occurs more frequently in patients with advanced HIV infection or who have previously experienced peripheral neuropathy.

Lactic acidosis and hepatic steatosis, hepatitis and liver failure have been reported with the use of antiretroviral nucleoside analogues, alone or in combination.

Rash, diarrhoea, nausea/vomiting, pancreatitis, dementia and other peripheral neurologic symptoms have also been associated with the use of stavudine.

Nevirapine

Rash, usually within first six weeks of therapy. D/C drug for severe rash or rash accompanied by other symptoms; Stevens-Johnson syndrome has occurred. Fever, headache, nausea, diarrhea, abdominal pain, thrombocytopenia, anemia, leukopenia, ulcerative stomatitis, hepatitis, peripheral neuropathy, paresthesia, or myalgia may also occur.

Grenulocytopenia has been more commonly observed in children. The safety profile of nevirapine in neonates has not been established.

Special precautions:

PREGNANCY

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

LACTATION
It is recommended that HIV-infected mothers do not breast-feed their infants to avoid risking postnatal transmission of HIV infection. It is not known whether stavudine, nevirapine or lamivudine are excreted in human milk.
PAEDIATRICS
Lamivudine, nevirapine and Stavudine are not intended for use in paediatric patients.

Drug Interaction:
Trimethoprim 160 mg/sulphamethoxazole 800 mg once daily has been shown to increase lamivudine exposure (AUC).
Nevirapine
The induction of CYP3A by nevirapine may result in lower plasma concentrations of other concomitantly administered drugs that are extensively metabolized by CYP3A. Thus, if a patient has been stabilized on a dosage regimen for a drug metabolized, by CYP3A, and begins treatment with nevirapine, dose adjustments may be necessary.

RifampinlRifabutin: There are insufficient data to assess whether dose adjustments are necessary when nevirapine and rifampin or rifabutin are coadministered. Therefore, these drugs should only be used in combination if clearly indicated and with careful monitoring.
Ketoconazole: Nevirapine and ketoconazole should not be administered concomitantly. Coadministration of nevirapine and ketoconazole results in a significant reduction in ketoconazole plasma concentrations.
Oral Contraceptives: There are no clinical data on the effects of nevirapine on the pharmacokinetics of oral contraceptives. Nevirapine may decrease plasma concentrations of oral contraceptives (also other hormonal contraceptives); therefore, these drugs should not be administered concomitantly with nevirapine.
Methadone: Based on the known metabolism of methadone, nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Known symptoms of overdosage and particulars of its treatment:
Lamivudine
There is no known antidote for lamivudine. It is not known whether lamivudine can be removed by peritoneal dialysis or hemodialysis.
Stavudine
Stavudine can be removed by hemodialysis. Experience with adults treated with 12 to 24 times the recommended daily dosage revealed no acute toxicity. Complications of chronic overdosage include peripheral neuropathy and hepatic toxicity.

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

Storage conditions:
Store in cool, dry & dark place, preferably below 25°C.

Shelf life:
2 years.

Presentation:
HDPE Bottle pack of 1x60's

TENMAC-EF

(Tenofovir Disoproxil Fumarate, Emtricitabine & Efavirenz Tablets)

COMPOSITION

Each tablet contains:

Tenofovir Disoproxil Fumarate	300 mg
Emtricitabine	200mg
Efavirenz	600mg

PHARMACOLOGY

TENMAC-EF is a fixed-dose combination of antiviral drugs tenofovir disoproxil fumarate, emtricitabine and efavirenz.
Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5`-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase gamma.
Emtricitabine works by inhibiting reverse transcriptase, the enzyme that copies HIV RNA into new viral DNA. Emtricitabine is a synthetic nucleoside analogue of cytidine. It is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, which is responsible for the inhibition of HIV-1 reverse transcriptase. It competes with the natural substrate deoxycytidine 5'-triphosphate and incorporates into nascent viral DNA, resulting in early chain termination. Therefore emtricitabine inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate deoxycytidine 5'-triphosphate and by its incorporation into viral DNA. By inhibiting HIV-1 reverse transcriptase, emtricitabine can help to lower the amount of HIV, or "viral load", in a patient's body and can indirectly increase the number of immune system cells (called T cells or CD4+ T-cells). Both of these changes are associated with healthier immune systems and decreased likelihood of serious illness.
Efavirenz is a non-nucleoside reverse transcriptase (RT) inhibitor of HIV-1. Efavirenz activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ, and σ are not inhibited by efavirenz.

PHARMACOKINETICS

Emtricitabine: Following oral administration of emtricitabine tablets, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Less than 4% of emtricitabine binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.02–200 µg/mL. Following administration of radiolabelled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine, the plasma emtricitabine half-life is approximately 10 hours.
Tenofovir Disoproxil Fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 6. Following oral administration of Tenofovir Disoproxil Fumarate:, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.01–25 µg/mL. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of Tenofovir Disoproxil Fumarate:, the terminal elimination half-life of tenofovir is approximately 17 hours.

Efavirenz: In HIV-1 infected subjects time-to-peak plasma concentrations were approximately 3–5 hours and steady-state plasma concentrations were reached in 6–10 days. In 35 HIV-1 infected subjects receiving efavirenz 600 mg once daily, steady-state Cmax was 12.9 ± 3.7 µM (mean ± SD), Cmin was 5.6 ± 3.2 µM, and AUC was 184 ± 73 µM•hr. Efavirenz is highly bound (approximately 99.5–99.75%) to human plasma proteins, predominantly albumin. Following administration of 14C-labeled efavirenz, 14–34% of the dose was recovered in the urine (mostly as metabolites) and 16–61% was recovered in feces (mostly as parent drug). In vitro studies suggest CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52–76 hours after single doses and 40–55 hours after multiple doses.

INDICATIONS

TENMAC-EF, a combination of 2 nucleoside analog HIV-1 reverse transcriptase inhibitors and 1 non-nucleoside HIV-1 reverse transcriptase inhibitor, is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

DOSAGE AND ADMINISTRATION:

Adults and pediatric patients 12 years of age and older with body weight at least 40 kg: One tablet once daily taken orally on an empty stomach. Dosing at bedtime may improve the tolerability of nervous system symptoms.
Renal Impairment: Because TENMAC-EF is a fixed-dose combination, it should not be prescribed for patients requiring dosage adjustment such as those with moderate or severe renal impairment (creatinine clearance below 50 mL/min).
Rifampin Coadministration: When TENMAC-EF is administered with rifampin to patients weighing 50 kg or more, an additional 200 mg/day of efavirenz is recommended.

CONTRAINDICATIONS:

Previously demonstrated hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz, a component of TENMAC-EF.
For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression).

PRECAUTIONS AND WARNING:

Serious psychiatric symptoms: Immediate medical evaluation is recommended.
Nervous system symptoms (NSS): NSS are frequent, usually begin 1–2 days after initiating therapy and resolve in 2–4 weeks. Dosing at bedtime may improve tolerability. NSS are not predictive of onset of psychiatric symptoms.
New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with TENMAC-EF. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering TENMAC-EF with concurrent or recent use of nephrotoxic drugs.
Rash: Discontinue if severe rash develops.
Hepatotoxicity: Monitor liver function tests before and during treatment in patients with underlying hepatic disease, including hepatitis B or C coinfection, marked transaminase elevations, or who are taking medications associated with liver toxicity. Among reported cases of hepatic failure, a few occurred in patients with no pre-existing hepatic disease.
Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathological fracture or other risk factors for osteoporosis or bone loss.
Convulsions: Use caution in patients with a history of seizures.
Immune reconstitution syndrome: May necessitate further evaluation and treatment.
Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy.

Coadministration with other products: Do not use with drugs containing emtricitabine or tenofovir disoproxil fumarate or with drugs containing lamivudine. efavirenz should not be coadministered with TENMAC-EF unless required for dose-adjustment when coadministered with rifampin. Do not administer in combination with adefovir dipivoxil.
Pregnancy: Fetal harm can occur when administered to a pregnant woman during the first trimester. Women should be apprised of the potential harm to the fetus. Women should avoid pregnancy while receiving TENMAC-EF and for 12 weeks after discontinuation.
Nursing mothers: Women infected with HIV should be instructed not to breastfeed.
Hepatic impairment: TENMAC-EF is not recommended for patients with moderate or severe hepatic impairment. Use caution in patients with mild hepatic impairment.
Pediatrics: The incidence of rash was higher than in adults.

SIDE EFFECTS:

Most common adverse reactions (incidence greater than or equal to 10%) observed in an active-controlled clinical trial of efavirenz, emtricitabine, and tenofovir DF are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash.

DRUG INTERACTIONS

Efavirenz: Coadministration of efavirenz can alter the concentrations of other drugs and other drugs may alter the concentrations of efavirenz. The potential for drug-drug interactions must be considered before and during therapy.
Didanosine: Tenofovir disoproxil fumarate increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted.
Atazanavir: Coadministration of TENMAC-EF and atazanavir or atazanavir/ritonavir is not recommended.
Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity.

OVERDOSAGE

Tenofovir Disoproxil Fumarate

Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. In one trial, 600 mg tenofovir DF was administered to 8 subjects orally for 28 days, and no severe adverse reactions were reported. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir DF, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.
Emtricitabine
Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology trial single doses of emtricitabine 1200 mg were administered to 11 subjects..Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min).

Efavirenz

Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

PACKING:

HDPE Bottle pack of 30 tablets and packed in a unit carton along with package insert.

SHELF LIFE:

24 months from the date of manufacturing

STORAGE:.

Keep in a dry place at a temperature below 30°C.

MCNEIL & ARGUS PHARMACEUTICALS LTD.

TENMAC-EM

(Tenofovir Disoproxil Fumarate & Emtricitabine Tablets)

COMPOSITION

Each tablet contains:

Tenofovir Disoproxil Fumarate	300 mg
Emtricitabine	200mg

PHARMACOLOGY

TENMAC-EM is a fixed-dose combination of antiviral drugs emtricitabine and tenofovir disoproxil fumarate.

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5`-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases alpha and beta, and mitochondrial DNA polymerase gamma.

Emtricitabine works by inhibiting reverse transcriptase, the enzyme that copies HIV RNA into new viral DNA. Emtricitabine is a synthetic nucleoside analogue of cytidine. It is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, which is responsible for the inhibition of HIV-1 reverse transcriptase. It competes with the natural substrate deoxycytidine 5'-triphosphate and incorporates into nascent viral DNA, resulting in early chain termination. Therefore emtricitabine inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate deoxycytidine 5'-triphosphate and by its incorporation into viral DNA. By inhibiting HIV-1 reverse transcriptase, emtricitabine can help to lower the amount of HIV, or "viral load", in a patient's body and can indirectly increase the number of immune system cells (called T cells or CD4+ T-cells). Both of these changes are associated with healthier immune systems and decreased likelihood of serious illness.

PHARMACOKINETICS

Emtricitabine: Following oral administration of emtricitabine tablets, emtricitabine is rapidly absorbed with peak plasma concentrations occurring at 1–2 hours post-dose. Less than 4% of emtricitabine binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.02–200 µg/mL. Following administration of radiolabelled emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and their glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of emtricitabine, the plasma emtricitabine half-life is approximately 10 hours.

Tenofovir Disoproxil Fumarate: The pharmacokinetic properties of tenofovir disoproxil fumarate are summarized in Table 6. Following oral administration of Tenofovir Disoproxil Fumarate:, maximum tenofovir serum concentrations are achieved in 1.0 ± 0.4 hour. Less than 0.7% of tenofovir binds to human plasma proteins in vitro and the binding is independent of concentration over the range of 0.01–25 µg/mL. Approximately 70–80% of the intravenous dose of tenofovir is recovered as unchanged drug in the urine.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of Tenofovir Disoproxil Fumarate:, the terminal elimination half-life of tenofovir is approximately 17 hours.

INDICATIONS

TENMAC-EM is a combination of Tenofovir Disoproxil Fumarate & Emtricitabine, both nucleoside analog HIV-1 reverse transcriptase inhibitors.

TENMAC-EM is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older.

TENMAC-EM is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

DOSAGE AND ADMINISTRATION:

Treatment of HIV-1 Infection

- Recommended dose in adults and pediatric patients (12 years of age and older and weighing greater than or equal to 35 kg): One tablet once daily taken orally with or without food.
- Recommended dose in renally impaired HIV-1 infected adult patients: Creatinine clearance 30-49 mL/min: 1 tablet every 48 hours. CrCl below 30 mL/min or hemodialysis: Do not use TENMAC-EM.

Pre-exposure Prophylaxis

- Recommended dose in HIV-1 uninfected adults: One tablet once daily taken orally with or without food.
- Recommended dose in renally impaired HIV-uninfected individuals: Do not use TRUVADA in HIV-uninfected individuals if CrCl is below 60 mL/min. If a decrease in CrCl is observed in uninfected individuals while using TENMAC-EM for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use.

CONTRAINDICATIONS:

Do not use TENMAC-EM for pre-exposure prophylaxis in individuals with unknown or positive HIV-1 status. TENMAC-EM should be used in HIV-infected patients only in combination with other antiretroviral agents.

PRECAUTIONS AND WARNING:

- Recommended dose in renally impaired HIV-uninfected individuals: Do not use TENMAC-EM in HIV-uninfected individuals if CrCl is below 60 mL/min. If a decrease in CrCl is observed in uninfected individuals while using TENMAC-EM for PrEP, evaluate potential causes and re-assess potential risks and benefits of continued use.
- New onset or worsening renal impairment: Can include acute renal failure and Fanconi syndrome. Assess creatinine clearance (CrCl) before initiating treatment with TENMAC-EM. Monitor CrCl and serum phosphorus in patients at risk. Avoid administering TENMAC-EM with concurrent or recent use of nephrotoxic drugs.
- Coadministration with Other Products: Do not use with drugs containing emtricitabine or tenofovir disoproxil fumarate including efavirenz + emtricitabine + tenofovir disoproxil fumarate, emtricitabine+rilpivirine+tenofovir, emtricitabine, tenofovir Disoproxil Fumarate; or with drugs containing lamivudine. Do not administer in combination with adefovir dipivoxil,.
- Decreases in bone mineral density (BMD): Consider assessment of BMD in patients with a history of pathologic fracture or other risk factors for osteoporosis or bone loss.
- Redistribution/accumulation of body fat: Observed in patients receiving antiretroviral therapy.
- Immune reconstitution syndrome: May necessitate further evaluation and treatment.
- Triple nucleoside-only regimens: Early virologic failure has been reported in HIV-infected patients. Monitor carefully and consider treatment modification.
- Comprehensive management to reduce the risk of acquiring HIV-1: Use as part of a comprehensive prevention strategy including other prevention measures; strictly adhere to dosing schedule.
- Management to reduce the risk of acquiring HIV-1 drug resistance: Prior to initiating TENMAC-EM for PrEP - if clinical symptoms consistent with acute viral infection are present and recent (<1 month) exposures are suspected, delay starting PrEP for at least one month and reconfirm negative HIV-1 status or use a test approved by the FDA as an aid in the diagnosis of HIV-1 infection, including acute or primary HIV-1 infection.

  While using TENMAC-EM for PrEP - HIV-1 screening tests should be repeated at least every 3 months.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs such as TENMAC-EM alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs such as TENMAC-EM to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with TENMAC-EM should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients with HIV and Hepatitis B Virus Coinfection

It is recommended that all patients with HIV be tested for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy. TENMAC-EM is not indicated for the treatment of chronic HBV infection and the safety and efficacy of TENMAC-EM have not been established in patients coinfected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of emtricitabine (200 mg) and tenofovir disoproxil fumarate. Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue TENMAC-EM and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney. Dosing interval adjustment of **TENMAC-EM** is recommended in all patients with creatinine clearance 30 –49 mL/min,. TENMAC-EM should not be administered to patients with creatine clearance < 30 mL/min or patients requiring hemodialysis.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir. The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents, however, some cases occurred in patients without identified risk factors. **TENMAC-EM** should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance”have been observed in patients receiving antiretroviral therapy.

The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

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

Nursing mothers:

Women infected with HIV-1 should be instructed not to breast feed.

Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

Geriatric Use

Clinical studies of emtricitabine (200 mg) or tenofovir did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

SIDE EFFECTS:

In HIV1 infected patients, the most common adverse reactions (incidence greater than or equal to 10%) are diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash.

In HIV-1 uninfected individuals in PrEP trials, adverse reactions that were reported by more than 2% of TENMAC-EM subjects and more frequently than by placebo subjects were headache, abdominal pain and weight decreased.

DRUG INTERACTIONS

Didanosine: Tenofovir disoproxil fumarate increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy) when coadministered. Consider dose reductions or discontinuations of didanosine if warranted.

- **Atazanavir:** Coadministration decreases atazanavir concentrations and increases tenofovir concentrations. Use atazanavir with TENMAC-EM only with ritonavir; monitor for evidence of tenofovir toxicity.

Lopinavir/ritonavir: Coadministration increases tenofovir concentrations. Monitor for evidence of tenofovir toxicity.

OVERDOSAGE

If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of Emtricitabine. In one clinical pharmacology trial, single doses of emtricitabine 1200 mg were administered to 11 subjects. No severe adverse reactions were reported.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir Disoproxil Fumarate: Limited clinical experience at doses higher than the therapeutic dose of Tenofovir Disoproxil Fumarate 300 mg is available. In one trial, 600 mg tenofovir disoproxil fumarate was administered to 8 subjects orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of Tenofovir Disoproxil Fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

PACKING:

HDPE Bottle pack of 30 tablets and packed in a unit carton along with package insert.

SHELF LIFE:

24 months from the date of manufacturing

STORAGE:.

Keep in a dry place at a temperature below 30°C.

TENMAC-LEF TABLETS

(Tenofovir Disoproxil Fumarate, Lamivudine & Emtricitabine Tablets)

PROPRIETARY NAME
(and dosage form):
TENMAC-LEF (tablets)

COMPOSITION:
Each tablet contains:
Tenofovir Disoproxil Fumarate 300 mg
Lamivudine 300 mg
Efavirenz 600mg

PHARMACOLOGICALACTION:
Tenofovir disoproxil fumarate
Tenofovir disoproxil fumarate is an antiviral drug.

Pharmacokinetics
The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption
Tenofovir is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from Tenofovir in fasted subjects is approximately 25%. Following oral administration of a single dose of Tenofovir 300 mg to HIV-1 infected subjects in the fasted state, maximum serum concentrations (Cmax) are achieved in 1.0 ± 0.4 hrs. Cmax and AUC values are 0.30 ± 0.09 µg/mL and 2.29 ± 0.69 µg·hr/mL, respectively.
The pharmacokinetics of tenofovir are dose proportional over a Tenofovir dose range of 75 to 600 mg and are not affected by repeated dosing.

Distribution
In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.
Metabolism and Elimination
In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.
Following IV administration of tenofovir, approximately 70–80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of Tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of Tenofovir 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.
Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Lamivudine
Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication in vitro, including zidovudine-resistant clinical isolates of the human immunodeficiency virus (HIV). Lamivudine is metabolised intracellularly to the active 5'-triphosphate which inhibits the RNA-and DNA-dependant activities of HIV reverse transcriptase by termination of the viral DNA chain. Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content. In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells. In vitro, lamivudine therefore has a high therapeutic index. Reduced in-vitro sensitivity to lamivudine has been reported for HIV isolated from patients who have received lamivudine therapy before.
Lamivudine has been shown to act additively or synergistically with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture.
In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine.

Efavirenz

Efavirenz is a non-nucleoside reverse transcriptase (RT) inhibitor of HIV-1. Efavirenz activity is mediated predominantly by non-competitive inhibition of HIV-1 reverse transcriptase(RT).
HIV-2 RT and human cellular DNA polymerases α, β, γ, and σ are not inhibited by efavirenz.

Pharmacokinetics:

Pharmacokinetics in adults:
Following oral administration, lamivudine is well absorbed with bioavailability of approximately 80%. The mean time (Tmax) to maximum serum concentration (Cmax) is about an hour. At therapeutic dose levels of 4 mg/kg/day (as two 12-hourly doses), Cmaxis in the order of 1-1.5 micrograms/mL.
The mean volume of distribution from intravenous studies has been reported as 1.3 L/kg and the mean terminal half-life of elimination as 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 L/kg/h, with predominantly renal clearance of more than 70% via active tubular secretion, but little hepatic metabolism, at less than 10 L. The intracellular half-life of the lamivudine triphosphate active metabolite is prolonged, averaging over 10 hours in peripheral blood lymphocytes. A delay in Tmax, and reduction in Cmax have been observed when co-administered with food, but no dose adjustment is needed, as lamivudine bioavailability is not altered. Lamivudine displays limited binding to albumin and exhibits linear pharmacokinetics over the therapeutic dose range. Co-administration of zidovudine results in a 13% increase in zidovudine exposure and a 28% increase in peak plasma levels. No dosage adjustments are necessary, as this is not considered to be of significance to patient safety. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The true extent of penetration or relationship with any clinical efficacy is unknown.
Pharmacokinetics in children:
In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability is reduced to approximately 65%, in paediatric patients, with an increased clearance of 0.52 L/kg/hr.
There are limited pharmacokinetic data for patients <3 months of age.

Efavirenz: In HIV-1 infected subjects time-to-peak plasma concentrations were approximately 3–5 hours and steady-state plasma concentrations were reached in 6–10 days. In 35 HIV-1 infected subjects receiving efavirenz 600 mg once daily, steady-state Cmax was 12.9 ± 3.7 μM (mean ± SD), Cmin was 5.6 ± 3.2 μM, and AUC was 184 ± 73 μM•hr. Efavirenz is highly bound (approximately 99.5–99.75%) to human plasma proteins, predominantly albumin. Following administration of 14C-labeled efavirenz, 14–34% of the dose was recovered in the urine (mostly as metabolites) and 16–61% was recovered in feces (mostly as parent drug). In vitro studies suggest CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce CYP enzymes, resulting in induction of its own metabolism. Efavirenz has a terminal half-life of 52–76 hours after single doses and 40–55 hours after multiple doses

INDICATIONS

TENMAC-LEF is indicated as part of antiretroviral combination therapy for treatment of HIV infected adults and children.

CONTRA-INDICATIONS

Hypersensitivity to any of the ingredients.

WARNINGS

Patients receiving Lamivudine, Tenofovir disoproxil fumarate and other antiretroviral agents may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases.
Current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, in the treatment of HIV infection.

INTERACTIONS

Zidovudine plasma levels are not significantly altered when co-administered with lamivudine (see Pharmacokinetics). An interaction with trimethoprim, a constituent of co-trimoxazole. causes a 40% increase in lamivudine plasma concentrations at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment. Administration of co-trimoxazole with the Lamivudine/zidovudine combinations in patients with renal impairment should be carefully assessed. lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Adults and adolescents more than 12 years of age:
The recommended dose of TENMAC-LEF is one tablet daily.

Children >3 months to 12 years of age:
The recommended dose is 4 mg/kg twice daily up to a maximum of 300 mg daily.

Children <3 months of age:
There are limited data to propose specific dosage recommendations
TENMAC-LEF can be taken with or without food.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Tenofovir disoproxil fumarate
The following adverse reactions have been identified during use of Tenofovir disoproxil fumarate. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Immune System Disorders
allergic reaction, including angioedema
Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia
Respiratory, Thoracic, and Mediastinal Disorders
dyspnea
Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain
Hepatobiliary Disorders
hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)
Skin and Subcutaneous Tissue Disorders
rash
Musculoskeletal and Connective Tissue Disorders
rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy
Renal and Urinary Disorders
acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria
General Disorders and Administration Site Conditions
asthenia
The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

Lamivudine

The following side-effects have been reported during therapy of HIV disease with Lamivudine alone, and in combination with other anti-retrovirals.

Gastro-intestinal disorders:

Pancreatitis, upper abdominal pain, nausea; vomiting and diarrhoea have been reported.

Blood and lymphatic system disorders:

Neutropenia, thrombocytopenia and anaemia have occurred.

Skin and appendages disorders:

Alopecia has been reported.

Central and Peripheral Nervous system disorders:

Peripheral neuropathy, paraesthesia, and headache have been reported.

Musculo-skeletal system disorders:

Arthralgia, muscle disorders including less frequently, rhabdomyolysis have been reported.

Body as a whole:

Malaise, fatigue and fever have occurred.

Hypersensitivity reactions:

Skin rash.

Changes in laboratory test parameters:

Transient rises in serum liver enzymes (AST; ALT) and rises in serum amylase have been reported.

Special precautions:

Lamivudine should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection, as there is a small risk of rebound hepatitis post treatment.

Pancreatitis:

Pancreatitis has been observed in some patients receiving Lamivudine. However it is unclear whether this is due to Lamivudine or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of Lamivudine until diagnosis of pancreatitis is excluded.

Lactic acidosis/severe hepatomegaly with steatosis:

Long-term use of Lamivudine can result in potentially fatal lactic acidosis. Symptomatic hyperlactacaemia and lactic acidosis are uncommon. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

In patients with suspicious symptoms or biochemistry. measure the venous lactate level (normal <2 mmol/L), and respond as follows:

Lactate 2 - 5 mmol/L: monitor regularly, and be alert for clinical signs.

Lactate 5 - 10 mmol/L without symptoms: monitor closely.

Lactate 5 - 10 mmol/L with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia. diabetic ketoacidosis, thyrotoxicosis, lymphoma).

Lactate 5 - 10 mmol/L: STOP all therapy (80% mortality in case studies).

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with raised lactate level.

Blood for lactate assays should be heparinised and stored on ice.

After recovery, NRTI's should be avoided. Seek expert advice on medicine selection. The above lactate values may not be applicable to paediatric patients.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of Lamivudine alone or in combination, in the treatment of HIV infection. Most cases were women.

Caution should be exercised when administering Lamivudine to patients with known risk factors for liver disease.

Treatment with Lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Opportunistic infections:
Patients receiving Lamivudine may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by medical practitioners experienced in the treatment of patients with associated HIV disease.

The risk of HIV transmission to others:
Patients should be advised that current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Patients with moderate to severe renal impairment:
In patients with moderate to severe renal impairment, the terminal half-life of lamivudine is increased due to decreased clearance. The dose should therefore be adjusted

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

IDENTIFICATION:
TENMAC-LEF tablets are Light blue color, elongated, biconvex, uncoated tablet, having a break line on one side of each tablet

STORAGE INSTRUCTIONS:
Store below 30ºC. Protect from light.
KEEP OUT OF REACH OF CHILDREN.

SHELF LIFE:
24 months from the date of manufacturing

PACKING:
HDPE Bottle pack of 30 tablets and packed in a unit carton along with package insert.

TENMAC-LM TABLETS

Tenofovir Disoproxil Fumarate & Lamivudine

COMPOSITION:

Each tablet contains:
Tenofovir Disoproxil Fumarate 300 mg
Lamivudine 300 mg.

PHARMACOLOGICALACTION:

antiviral drug.

Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.
Absorption
Tenofovir is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from Tenofovir in fasted subjects is approximately 25%. Following oral administration of a single dose of Tenofovir 300 mg to HIV-1 infected subjects in the fasted state, maximum serum concentrations (Cmax) are achieved in 1.0 ± 0.4 hrs. Cmax and AUC values are 0.30 ± 0.09 μg/mL and 2.29 ± 0.69 μg·hr/mL, respectively.
The pharmacokinetics of tenofovir are dose proportional over a Tenofovir dose range of 75 to 600 mg and are not affected by repeated dosing.

Distribution

In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 μg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ± 0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.
Metabolism and Elimination
In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP enzymes.
Following IV administration of tenofovir, approximately 70–80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of Tenofovir, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of Tenofovir 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.
Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Lamivudine

Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication in vitro, including zidovudine-resistant clinical isolates of the human immunodeficiency virus (HIV). Lamivudine is metabolised intracellularly to the active 5'-triphosphate which inhibits the RNA-and DNA-dependant activities of HIV reverse transcriptase by termination of the viral DNA chain. Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content. In vitro, lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells. In vitro, lamivudine therefore has a high therapeutic index. Reduced in-vitro sensitivity to lamivudine has been reported for HIV isolated from patients who have received lamivudine therapy before.
Lamivudine has been shown to act additively or synergistically with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture.
In vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine.

Pharmacokinetics:

Pharmacokinetics in adults:
Following oral administration, lamivudine is well absorbed with bioavailability of approximately 80%. The mean time (Tmax) to maximum serum concentration (Cmax) is about an hour. At therapeutic dose levels of 4 mg/kg/day (as two 12-hourly doses), Cmaxis in the order of 1-1.5 micrograms/mL.
The mean volume of distribution from intravenous studies has been reported as 1.3 L/kg and the mean terminal half-life

of elimination as 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32 L/kg/h, with predominantly renal clearance of more than 70% via active tubular secretion, but little hepatic metabolism, at less than 10 L. The intracellular half-life of the lamivudine triphosphate active metabolite is prolonged, averaging over 10 hours in peripheral blood lymphocytes. A delay in Tmax, and reduction in Cmax have been observed when co-administered with food, but no dose adjustment is needed, as lamivudine bioavailability is not altered. Lamivudine displays limited binding to albumin and exhibits linear pharmacokinetics over the therapeutic dose range. Co-administration of zidovudine results in a 13% increase in zidovudine exposure and a 28% increase in peak plasma levels. No dosage adjustments are necessary, as this is not considered to be of significance to patient safety. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The true extent of penetration or relationship with any clinical efficacy is unknown.
Pharmacokinetics in children:
In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability is reduced to approximately 65%, in paediatric patients, with an increased clearance of 0.52 L/kg/hr.
There are limited pharmacokinetic data for patients <3 months of age.

INDICATIONS
TENMAC-LM is indicated as part of antiretroviral combination therapy for treatment of HIV infected adults and children.

CONTRA-INDICATIONS
Hypersensitivity to any of the ingredients.

WARNINGS
Patients receiving Lamivudine, Tenofovir disoproxil fumarate and other antiretroviral agents may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases.
Current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, in the treatment of HIV infection.

INTERACTIONS
Zidovudine plasma levels are not significantly altered when co-administered with lamivudine (see Pharmacokinetics).
An interaction with trimethoprim, a constituent of co-trimoxazole. causes a 40% increase in lamivudine plasma concentrations at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment.
Administration of co-trimoxazole with the Lamivudine/zidovudine combinations in patients with renal impairment should be carefully assessed. lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Lamivudine is therefore not recommended to be used in combination with zalcitabine.

PREGNANCY AND LACTATION
Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Adults and adolescents more than 12 years of age:
The recommended dose of TENMAC-LM is one tablet daily.

Children >3 months to 12 years of age:
The recommended dose is 4 mg/kg twice daily up to a maximum of 300 mg daily.

Children <3 months of age:
There are limited data to propose specific dosage recommendations
TENMAC-LM can be taken with or without food.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Tenofovir disoproxil fumarate

The following adverse reactions have been identified during use of Tenofovir disoproxil fumarate. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders
allergic reaction, including angioedema
Metabolism and Nutrition Disorders
lactic acidosis, hypokalemia, hypophosphatemia
Respiratory, Thoracic, and Mediastinal Disorders
dyspnea
Gastrointestinal Disorders
pancreatitis, increased amylase, abdominal pain
Hepatobiliary Disorders
hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)
Skin and Subcutaneous Tissue Disorders
rash
Musculoskeletal and Connective Tissue Disorders
rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy
Renal and Urinary Disorders
acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria
General Disorders and Administration Site Conditions
asthenia
The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

Lamivudine

The following side-effects have been reported during therapy of HIV disease with Lamivudine alone, and in combination with other anti-retrovirals.

Gastro-intestinal disorders:
Pancreatitis, upper abdominal pain, nausea; vomiting and diarrhoea have been reported.
Blood and lymphatic system disorders:
Neutropenia, thrombocytopenia and anaemia have occurred.
Skin and appendages disorders:
Alopecia has been reported.
Central and Peripheral Nervous system disorders:
Peripheral neuropathy, paraesthesia, and headache have been reported.

Musculo-skeletal system disorders:
Arthralgia, muscle disorders including less frequently, rhabdomyolysis have been reported.

Body as a whole:
Malaise, fatigue and fever have occurred.

Hypersensitivity reactions:
Skin rash.

Changes in laboratory test parameters:
Transient rises in serum liver enzymes (AST; ALT) and rises in serum amylase have been reported.

Special precautions:
Lamivudine should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection, as there is a small risk of rebound hepatitis post treatment.

Pancreatitis:
Pancreatitis has been observed in some patients receiving Lamivudine. However it is unclear whether this is due to Lamivudine or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of Lamivudine until diagnosis of pancreatitis is excluded.

Lactic acidosis/severe hepatomegaly with steatosis:
Long-term use of Lamivudine can result in potentially fatal lactic acidosis. Symptomatic hyperlactacaemia and lactic acidosis are uncommon. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.
In patients with suspicious symptoms or biochemistry. measure the venous lactate level (normal <2 mmol/L), and respond as follows:

Lactate 2 - 5 mmol/L: monitor regularly, and be alert for clinical signs.
Lactate 5 - 10 mmol/L without symptoms: monitor closely.
Lactate 5 - 10 mmol/L with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia. diabetic ketoacidosis, thyrotoxicosis, lymphoma).
Lactate 5 - 10 mmol/L: STOP all therapy (80% mortality in case studies).
Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with raised lactate level.
Blood for lactate assays should be heparinised and stored on ice.
After recovery, NRTI's should be avoided. Seek expert advice on medicine selection. The above lactate values may not be applicable to paediatric patients.
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of Lamivudine alone or in combination, in the treatment of HIV infection. Most cases were women.
Caution should be exercised when administering Lamivudine to patients with known risk factors for liver disease.
Treatment with Lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Opportunistic infections:
Patients receiving Lamivudine may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by medical practitioners experienced in the treatment of patients with associated HIV disease.

The risk of HIV transmission to others:
Patients should be advised that current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Patients with moderate to severe renal impairment:
In patients with moderate to severe renal impairment, the terminal half-life of lamivudine is increased due to decreased clearance. The dose should therefore be adjusted

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

IDENTIFICATION:
TENMAC-LM tablets are Light blue color, elongated, biconvex, uncoated tablet, having a break line on one side of each tablet

STORAGE INSTRUCTIONS:
Store below 30ºC. Protect from light.
KEEP OUT OF REACH OF CHILDREN.

SHELF LIFE:
24 months from the date of manufacturing

PACKING:
HDPE Bottle pack of 30 tablets and packed in a unit carton along with package insert.

MCNEIL & ARGUS PHARMACEUTICALS LTD.

ZVD-PLUS

(Zidovudine & Lamivudine Tablets)

COMPOSITION:
Each tablet contains:
Zidovudine 300mg
Lamivudine 150mg

PHARMACOLOGICAL CLASSIFICATION:
Antiretroviral

PHARMACOLOGY:
Zidovudine, a thymidine analogue, is anti-retroviral drug acting against human immunodeficiency virus (HIV). Lamivudine and zidovudine are potent, selective inhibitors of HIV-1 and HIV-2. Lamivudine has been shown to be highly synergistic with zidovudine, inhibiting the replication of HIV in cell culture. Both active substances are metabolised sequentially by intracellular kinases to the 5'-triphosphate (TP). Lamivudine-TP and zidovudine-TP are substrates for and competitive inhibitors of HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases.

PHARMACOKINETICS:

Absorption: Lamivudine and zidovudine are well absorbed from the gut. The bioavailability of oral lamivudine in adults is normally between 80-85% and for zidovudine 60-70%. A bioequivalence study compared ZVD-PLUS with 3TC 150mg and Retrovir 300mg tablets taken together. The effect of food on the rate and extent of absorption was also studied. ZVD-PLUS was shown to be bioequivalent to 3TC 150mg and Retrovir 300mg given as separate tablets, when administered to fasting subjects.

ZVD-PLUS administration, lamivudine and zidovudine Cmax (95% confidence interval) values were 1.5 (1.3-1.8)mg/mL and 1.8 (1.5-2.2)mg/mL respectively. The median (range) lamivudine and zidovudine tmax values were 0.75 (0.50-2.00) hours and 0.50 (0.25-2.00) hours respectively. The extent (AUC) of lamivudine and zidovudine absorption and estimates of half-life following administration of ZVD-PLUS with food were similar when compared to fasting subjects, although the rate of absorption (Cmax, tmax) was slowed. Based on these data it may be administered with or without food.

Distribution: Intravenous studies with lamivudine and zidovudine showed that the mean apparent volume of distribution is 1.3 and 1.6L/kg respectively. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited binding to the major plasma protein albumin (less than 36% serum albumin in vitro). Zidovudine plasma protein binding is 34% to 38%. Interactions with medicinal products involving binding site displacement are not anticipated with ZVD-PLUS.
Data show that lamivudine and zidovudine penetrate the central nervous system and reach the cerebrospinal fluid (CSF). The mean ratios of CSF/serum lamivudine and zidovudine concentrations 2-4 hours after oral administration were approximately 0.12 and 0.5 respectively. The true extent of penetration of lamivudine or relationship with any clinical efficacy is unknown.

Metabolism: Metabolism of lamivudine is a minor route of elimination. Lamivudine is predominately cleared by renal excretion of the unchanged active substance. The likelihood of metabolic interactions with lamivudine is low due to the small extent of hepatic metabolism (5-10%) and low plasma binding.

The 5'-glucuronide of zidovudine is the major metabolite in both plasma and urine, accounting for approximately 50-80% of the administered dose eliminated by renal excretion. 3'-amino-3'-deoxythymidine (AMT) has been identified as a metabolite of zidovudine following intravenous dosing.

Elimination: The observed lamivudine half-life of elimination is 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0.32L/h/kg, with predominantly renal clearance (greater than 70%) via the organic cationic transport system.
From studies with intravenous zidovudine, the mean terminal plasma half-life was 1.1 hours and the mean systemic clearance was 1.6L/h/kg. Renal clearance of zidovudine is estimated to be 0.34L/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys.

Renally impaired: Studies in patients with renal impairment show lamivudine elimination is affected by renal dysfunction, due to decreased renal clearance. Dose reduction is required for patients with creatinine clearance of less than 50mL/min. Zidovudine concentrations have also been shown to be increased in patients with advanced renal failure.

Hepatically impaired: Limited data in patients with cirrhosis suggest that accumulation of zidovudine may occur in patients with hepatic impairment because of decreased glucuronidation. Dosage adjustment of zidovudine may be necessary in patients with severe hepatic impairment.

Elderly: The pharmacokinetics of lamivudine and zidovudine have not been studied in patients over 65 years of age.

Pregnancy: The pharmacokinetics of lamivudine and zidovudine were similar to that of non-pregnant adults. In humans, consistent with passive transmission of lamivudine across the placenta, lamivudine concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery. Zidovudine was measured in plasma and gave similar results to those observed for lamivudine.

INDICATIONS:
Zidovudine & Lamivudine is indicated for the treatment of HIV infection when antiretroviral therapy is warranted.
The duration of clinical benefit from antiretroviral therapy may be limited. Alteration in antiretroviral therapy should be considered if disease progression occurs during treatment.
Maternal Foetal HIV Transmission: Zidovudine is also indicated for the prevention of maternal foetal HIV transmission.
The safety of zidovudine for the mother or foetus during the first trimester of pregnancy has not been assessed.

DOSAGE AND DIRECTION OF USE:
The recommended oral dose of Lamivudine & Zidovudine for adults and adolescents (at least 12 years of age) is one capsule (containing 150mg of Lamivudine and 300mg of Zidovudine) twice daily with or without food.

Dose adjustment: Because it is a fixed dose combination, Lamivudine & Zidovudine should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance< 50ml/min), those with low body weight (<50kg or II 0 lb), or those experiencing dose-limiting adverse events.

CONTRAINDICATIONS:
Patients who exhibit potentially life-threatening allergic reactions to any of the components of the formulation.

WARNINGS AND PRECAUTIONS:
Before combination therapy with Zidovudine is initiated, consult the complete prescribing information for each drug.
The safety profile of Zidovudine plus other antiretroviral agents reflects the individual safety profiles of each component.
The incidence of adverse reactions appears to increase with disease progression, and patients should be monitored carefully, especially as disease progression occurs.
Current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination.
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, in the treatment of HIV infection.

BONE MARROW SUPPRESSION
Zidovudine & Lamivudine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 cells/mm3 or hemoglobin <9.5 g/dL. There have been reports of pancytopenia associated with the use of Zidovudine & Lamivudine, which was reversible in most instances after discontinuance of the drug.
Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with zidovudine. For patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anaemia or neutropenia develops, dosage adjustments may be necessary.

MYOPATHY

Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of Zidovudine & Lamivudine.

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Rare occurrences of potentially fatal lactic acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis have been reported with the use of certain antiretroviral nucleoside analogues. Therapy with Zidovudine & Lamivudine should be Pended until the diagnosis of lactic acidosis has been excluded. Caution should be exercised when administering Zidovudine & Lamivudine to any patient, particularly obese women, with hepatomegaly, hepatitis, or other known risk factors for liver disease. Treatment with Zidovudine & Lamivudine should be spender in the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly, or metabolic/lactic acidosis of unknown aetiology.

OTHER SERIOUS ADVERSE REACTIONS

Reports of pancreatitis, sensitization reactions, 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 & Lamivudine.

PREGNANCY

Category C. Congenital abnormalities were found to occur with similar frequency between infants born to mothers who received Zidovudine & Lamivudine and infants born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognised on ultrasound before or immediately after initiation of study drugs.

NURSING MOTHERS

HIV infected women are advised not to breast feed to avoid postnatal transmission of HIV to a child who may not yet be infected. Zidovudine & Lamivudine is excreted in human milk.

IMPAIRED RENAL AND HEPATIC FUNCTION

Zidovudine & Lamivudine is eliminated from the body primarily by renal excretion following metabolism in the liver. In patients with severely impaired renal function, dosage reduction is recommended. Although very little data are available, patients with severely impaired hepatic function may be at greater risk of toxicity.

Special precautions:

Lamivudine should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection, as there is a small risk of rebound hepatitis post treatment.

Pancreatitis:

Pancreatitis has been observed in some patients receiving Lamivudine. However it is unclear whether this is due to Lamivudine or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of Lamivudine until diagnosis of pancreatitis is excluded.

Lactic acidosis/severe hepatomegaly with steatosis:

Long-term use of Lamivudine can result in potentially fatal lactic acidosis. Symptomatic hyperlactacaemia and lactic acidosis are uncommon. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.

In patients with suspicious symptoms or biochemistry. measure the venous lactate level (normal <2 mmol/L), and **respond as follows:**

Lactate 2 - 5 mmol/L: monitor regularly, and be alert for clinical signs.
Lactate 5 - 10 mmol/L without symptoms: monitor closely.
Lactate 5 - 10 mmol/L with symptoms: STOP all therapy. Exclude other causes (e.g. sepsis, uraemia. diabetic ketoacidosis, thyrotoxicosis, lymphoma).
Lactate 5 - 10 mmol/L: STOP all therapy (80% mortality in case studies).

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with raised lactate level.

Blood for lactate assays should be heparinised and stored on ice.

After recovery, NRTI's should be avoided. Seek expert advice on medicine selection. The above lactate values may not be applicable to paediatric patients.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of Lamivudine alone or in combination, in the treatment of HIV infection. Most cases were women.

Caution should be exercised when administering Lamivudine to patients with known risk factors for liver disease.
Treatment with Lamivudine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Opportunistic infections:
Patients receiving Lamivudine may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by medical practitioners experienced in the treatment of patients with associated HIV disease.

The risk of HIV transmission to others:
Patients should be advised that current antiretroviral therapy, including Lamivudine, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Patients with moderate to severe renal impairment:
In patients with moderate to severe renal impairment, the terminal half-life of lamivudine is increased due to decreased clearance. The dose should therefore be adjusted.

SIDE EFFECTS:
MONOTHERAPY
Adults: The frequency and severity of adverse events associated with the use of Zidovudine & Lamivudine in adults are greater in patients with more advanced infection at the time of initiation of therapy.
The anaemia reported in patients with advanced HIV disease receiving Zidovudine & Lamivudine appeared to be the result of impaired erythrocyte maturation. Thrombocytopenia has also been reported in patients with advanced disease. Mild drug-associated elevations in total bilirubin levels have been reported as an uncommon occurrence in patients treated for asymptomatic HIV infection.
Clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with 1,500 mg/day of Zidovudine & Lamivudine were: fever, headache, nausea, vomiting, anorexia, myalgia, insomnia, dizziness, paraesthesia, dyspnoea and rash. Malaise, gastrointestinal pain, dyspepsia, and taste perversion were also reported.
Paediatrics: Anaemia and granulocytopenia among paediatric patients with advanced HIV disease receiving zidovudine occurred with similar incidence to that reported for adults with AIDS or advanced AIDS-Related complex. Macrocytosis was frequently observed.

Lamivudine
The following side-effects have been reported during therapy of HIV disease with Lamivudine alone, and in combination with other anti-retrovirals.
Gastro-intestinal disorders:
Pancreatitis, upper abdominal pain, nausea; vomiting and diarrhoea have been reported.
Blood and lymphatic system disorders:
Neutropenia, thrombocytopenia and anaemia have occurred.
Skin and appendages disorders:
Alopecia has been reported.
Central and Peripheral Nervous system disorders:
Peripheral neuropathy, paraesthesia, and headache have been reported.
Musculo-skeletal system disorders:
Arthralgia, muscle disorders including less frequently, rhabdomyolysis have been reported.
Body as a whole:
Malaise, fatigue and fever have occurred.
Hypersensitivity reactions:
Skin rash.

Other adverse events were similar to that observed in adults.
Maternal-Foetal Transmission
The most commonly reported adverse experiences were anaemia and neutropenia. The long-term consequences of in vitro and infant exposure to Zidovudine & Lamivudine are unknown.

DRUG INTERACTIONS:

Ganciclovir, interferon alpha: Use of Zidovudine & Lamivudine in combination with either ganciclovir or interferon alpha increases the risk of hematologic toxicities in some patients with advanced HIV disease. Hematologic parameters should be monitored frequently in all patients receiving either of these combinations.

Bone Marrow Suppressive Agents/Cytotoxic Agents: Co administration of Zidovudine & Lamivudine 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.

Probenecid: Limited data suggests that probenecid may increase Zidovudine & Lamivudine levels by inhibiting glucuronidation and/or by reducing renal excretion of Zidovudine & Lamivudine.

Phenytoin: Phenytoin plasma levels have been reported to be low in some patients receiving Zidovudine & Lamivudine. In one study, a 30% decrease in oral Zidovudine & Lamivudine clearance was observed with phenytoin.

Methadone: No adjustments in methadone maintenance requirements were reported in a study of nine HIV positive patients receiving methadone maintenance.

Fluconazole: The co administration of fluconazole with Zidovudine & Lamivudine has been reported to interfere with the oral clearance and metabolism of Zidovudine & Lamivudine.

Atovaquone: A decrease in Zidovudine & Lamivudine oral clearance was observed.

Valproic Acid: Data suggests that valproic acid increases the oral bioavailability of Zidovudine & Lamivudine through inhibition of first pass hepatic metabolism. Patients should be monitored for a possible increase in Zidovudine & Lamivudine related adverse events.

Lamivudine: Co-administration of zidovudine with lamivudine resulted in an increase in the maximum concentration (Cmax) of zidovudine.

Other nucleoside analogues: Experimental nucleoside analogues affecting DNA replication such as ribavirin antagonize the in vitro antiviral activity of zidovudine against HIV.

OVERDOSAGE:

No reported cases of acute overdosage (up to 50 gms) in both children and adults have been fatal. The consistent finding in these cases was spontaneous or induced nausea and vomiting. Hematologic changes were transient and not severe. Hemodialysis and peritoneal dialysis appear to have a negligible effect on the removal of Zidovudine & Lamivudine while elimination of its primary metabolite is enhanced.

STORAGE CONDITIONS:

Store in a cool & dry place, protected from light.
Keep out of reach of children.

PRESENTATION:

1X60's HDPE Bottles.

MCNEIL & ARGUS PHARMACEUTICALS LTD.

E. F. 200/600

(Efavirenz Tablets)

COMPOSITION:
Each tablet contains:
Efavirenz 200/600mg

PHARMACOLOGICAL CLASSIFICATION:
Antiretroviral

PHARMACOLOGY:
Efavirenz is a non- nucleoside reverse transcriptase (RT) inhibitor of human immunodeficiency virus type 1 (HIV-1). Efavirenz activity is mediated predominantly by non- competitive inhibition of HIV-1 RT. HIV-2 RT and human cellular DNA polymerases alpha, beta, gamma, and delta are not inhibited by efavirenz.

PHARMACOKINETICS:
Absorption: Peak efavirenz plasma concentrations of 1.6-9.1 m M were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose- related increases in C max and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses.

In HIV- infected patients at steady- state, mean C max , mean C min , and mean AUC were dose proportional following 200 mg, 400 mg, and 600 mg daily doses. Time- to- peak plasma concentrations were approximately 3-5 hours and steady-state plasma concentrations were reached in 6-10 days. In 35 patients receiving efavirenz 600 mg QD, steady-state C max was 12.9 ± 3.7 m M (mean ± S. D.), steady-state C min was 5.6 ± 3.2 m M, and AUC was 184 ± 73 m M"" h.

Effect of Food on Oral Absorption: In uninfected volunteers, meals of normal composition had no appreciable effect on the bioavailability of 100 mg of an investigational efavirenz formulation administered twice a day for 10 days with meals (Breakfast: 662 kcal, 13.8 g protein, 27.9 g fat, 94.6 g carbohydrate; Dinner: 567 kcal, 44.5 g protein, 12.5 g fat, 73.8 g carbohydrate). The relative bioavailability of a single 1200 mg dose of an investigational efavirenz formulation in uninfected volunteers (N= 5) was increased 50% (range 11%- 126%) following a high fat meal (1070 kcal, 82 g fat, 69% of calories from fat)

Distribution: Efavirenz is highly bound (approximately 99.5- 99.75%) to human plasma proteins, predominantly albumin. In HIV- 1 infected patients (N= 9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3- fold higher than the non-protein- bound (free) fraction of efavirenz in plasma.

Metabolism: Studies in humans and in vitro studies using human liver microsomes have demonstrated that efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1.

The in vitro studies suggest that C.P.A. and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. Multiple doses of 200- 400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22-42% lower) and a shorter terminal half- life of 40-55 hours (single dose half-life 52-76 hours).

Elimination: Efavirenz has a terminal half- life of 52- 76 hours after single doses and 40- 55 hours after multiple doses. A one-month mass balance/ excretion study was conducted using 400 mg per day with a 14 C-labeled dose administered on Day 8. Approximately 14- 34% of the radiolabel was recovered in the urine and 16-61% was recovered in the feces. Nearly all of the urinary excretion of the radiolabeled drug was in the form of metabolites. Efavirenz accounted for the majority of the total radioactivity measured in feaces.

INDICATIONS:
Efavirenz is indicated for the treatment of HIV infection in children and adults. Efavirenz is most effective when used as part of a triple combination therapy regimen with two other anti-HIV drugs.

DOSAGE AND DIRECTION OF USE:
Adults: Orally 600mg once daily. It is recommended that efavirenz be taken on an empty stomach, preferably at bedtime. Increased absorption occurs when efavirenz is taken with food and may lead to adverse events. Taking efavirenz before bedtime may improve the tolerability of neurological side effects.
Paediatric: For children older than 3 years, administered efavirenz once daily as follows: 200mg (10 to <15kg); 250mg (15 to <20kg); 300mg (20 to <25kg); 350mg (25 to < 32.5kg); 400mg (32.5 to 40kg) ; 600mg (>40kg).

CONTRAINDICATIONS:
Previously demonstrated hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to efavirenz.
For some drugs, competition for CYP3A by efavirenz could result in inhibition of their metabolism and create the potential for serious and/or life-threatening adverse reactions (e.g., cardiac arrhythmias, prolonged sedation, or respiratory depression).

SPECIAL POPULATION:
Hepatic Impairment: The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment.

Renal Impairment: The pharmacokinetics of efavirenz have not been studied in patients with renalinsufficiency; however, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal.

Gender and Race: The pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied.

WARNINGS:
Efavirenz must not be used as a single agent to treat HIV or added on a a sole agent to a failing regimen. As with all other non – nucleoside reverse transcriptase inhibitors, resistance virus emerges rapidly when efavirenz is administered as monotheraphy. The choice of new antiretroviral agent to be used in combination with efavirenz should take into consideration the potential for viral cross-resistance.

DRUG INTERACTION:
Grapefruit juice may effect plasma efavirenz concentration.

Antibacterials: increased risk of rash with clarithromycin. Rifampicin reduces plasma concentration of efavirenz.
Antidepressants: avoid concomitant use of st. john's wort
Antihistaminics: increased risk of ventricular arrhythmias when used with terfenadine. Other antivirals: Efavirenz reduces plasma concentration of amprenavir, indinavir and lipinavir. Efavirenz reduces plasma concentration of saquinavir.
Anxiolytics: Risk of prolonged sedation with midazolam.

Oestrogen and progestogens: possibly reduced efficacy of oral contraceptives.

SIDE EFFECTS AND PRECAUTIONS:
side effects included dizziness; sleep disturbance, vivid dreams, nightmares, hallucinations, and confusion. These lasted for a median 21 days and occurred in more than 50% of patients. In the expanded access program involving 4,000 individuals, serious depression (requiring hospitalization) was reported in six patients; treatment-related psychosis was reported in four patients. The serious psychiatric episodes occurred in patients with past depression or psychotic illness. Patients with a history of psychiatric symptoms or suicidal thoughts should be warned about the probable CNS effects of efavirenz and the potential for their symptoms to worsen.

Rash was reported in more than 30% of patients. It was mainly grade 1 or 2 maculopapular skin eruptions; most cases resolved when treatment was interrupted and did not recur when drug was resumed. Greater incidence and severity of rash have been reported in children (including grade 4 in 3.5%). According to one study, Hispanics or people with a history of sulfa rash had a greater risk of rash upon beginning NNRTI therapy (Derisi).

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150,

or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. In studies in which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600-mg/day dose. The exposure in rats was lower than that in humans. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, efavirenz showed no evidence of mutagenic or clastogenic activity in a battery of in vitro and in vivo studies. These included bacterial mutation assays in S. typhimurium and E. coli, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an in vivo mouse bone marrow micronucleus assay. Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms in efavirenz-treated mice is not known.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

Use in Pregnancy and the Neonatal Period

Reproductive Risk Potential: Pregnancy Category D. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving Efavirenz. Barrier contraception should always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of Efavirenz. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies in pregnant women. Efavirenz should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options. As of July 2004, the Antiretroviral Pregnancy Registry has received prospective reports of 237 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (232 pregnancies). Birth defects occurred in 5 of 188 live births (first-trimester exposure) and 0 of 13 live births (second/third-trimester exposure). None of these prospectively reported defects were neural tube defects. However, there have been four retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of Efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital days 20-150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of Efavirenz. Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of Efavirenz. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of Efavirenz.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Although it is not known if efavirenz is secreted in human milk, efavirenz is secreted into the milk of lactating rats. Because of the potential for HIV transmission and the potential for serious adverse effects in nursing infants, mothers should be instructed not to breast-feed if they are receiving Efavirenz.

Pediatric Use

ACTG 382 is an ongoing, open-label study in 57 NRTI-experienced pediatric patients to characterize the safety, pharmacokinetics, and antiviral activity of Efavirenz in combination with nelfinavir (20-30 mg/kg TID) and NRTIs. Mean age was 8 years (range 3-16). Efavirenz has not been studied in pediatric patients below 3 years of age or who

weigh less than 13 kg. At 48 weeks, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of rash, which was reported in 46% (26/57) of pediatric patients compared to 26% of adults, and a higher frequency of Grade 3 or 4 rash reported in 5% (3/57) of pediatric patients compared to 0.9% of adults.
The starting dose of Efavirenz was 600 mg once daily adjusted to body size, based on weight, targeting AUC levels in the range of 190-380 μM•h. The pharmacokinetics of efavirenz in pediatric patients were similar to the pharmacokinetics in adults who received 600-mg daily doses of Efavirenz. In 48 pediatric patients receiving the equivalent of a 600-mg dose of Efavirenz, steady-state Cmax was 14.2 ± 5.8 μM (mean ± SD), steady-state Cmin was 5.6 ± 4.1 μM, and AUC was 218 ± 104 μM•h.

Geriatric Use
Clinical studies of Efavirenz did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.
Animal carcinogenicity studies
Long-term animal carcinogenicity studies with efavirenz in rats and mice are not completed; in vitro screening tests have been negative.
Reproduction/fertility animal studies
No effect of efavirenz on reproduction or fertility in rodents has been seen. An increase in fetal resorptions has been observed in rats at doses comparable to or lower than those used to achieve human therapeutic exposure.

Teratogenicity/developmental toxicity animal studies
Malformations were observed in three of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational days 20 to 150 at a dose of 30 mg/kg twice daily (resulting in plasma concentrations comparable to systemic human therapeutic exposure). The malformations included anencephaly and unilateral anophthalmia in one; microphthalmia in another; and cleft palate in the third. Primate teratogenicity studies have not been conducted for delavirdine or nevirapine.
Placental and breast milk passage in animal studies
Efavirenz crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. It is unknown whether efavirenz is excreted in human breast milk.
Human studies in pregnancy
No studies with efavirenz in pregnant humans are planned at this time. Because teratogenic effects were seen in primates at drug exposures similar to those representing human therapeutic exposure, pregnancy should be avoided in women receiving efavirenz.

SPECIAL PRECAUTIONS:
Pregnancy:
Efavirenz has not been formally studied in pregnant women, but preliminary studies indicate that women should avoid becoming pregnant while on this drug. A study conducted in pregnant monkeys showed that there were malformations in fetuses the monkeys were given a dose similar to the recommended human dose.
Lactation:
Women should also be cautions of breast feeding while taking efavirenz because it may be passed through breast milk resulting in potential toxicity to the child. A study is planned to look at whether efavirenz can prevent or reduce the risk of transmission of HIV from moter to child.

OVERDOSAGE:
Efavirenz:
Some patients accidently taking 600mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

DRUG INTERACTIONS:
Efavirenz: Coadministration of efavirenz can alter the concentrations of other drugs and other drugs may alter the concentrations of efavirenz. The potential for drug-drug interactions must be considered before and during therapy.

STORAGE CONDITIONS:
Store in a cool & dry place, protected from light.
Keep out of reach of children.

SHELF LIFE:
2 years

PRESENTATION:
30/60 tablets packed in HDPE Bottles.

MCLAMI PLUS

(Zidovudine,Lamivudine & Nevirapine Tablets)

COMPOSITION:
Each tablet contains:
Zidovudine 300mg
Lamivudine 150mg
Nevirapine 200mg

PHARMACOLOGICAL CLASSIFICATION:
Antiretroviral

PHARMACOLOGY:
Zidovudine, a thymidine analogue, is anti-retroviral drug acting against human immunodeficiency virus (HIV). Lamivudine-TP and zidovudine-TP are substrates for and competitive inhibitors of HIV reverse transcriptase. However, their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine and zidovudine triphosphates show significantly less affinity for host cell DNA polymerases. Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases a , ß, g , or d) are not inhibited by nevirapine.

PHARMACOKINETICS:
LAMIVUDINE:
The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HlV-infected adult patients after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (b.i.d. regimen) oral doses ranging from 0.25 to 10 mg/kg.

Absorption and Bio-availability
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 administration of 2 mg/kg twice a day to nine adults with HIV, the peak serum lamivudine concentration (Cmax) was 1.5 ± 0.5 µg/ml (mean ± SD). The area under the plasma concentration versus time curve (AUC) and Cmax increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.
An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on two occasions, once in the fasted state and once with food (1099 kcal; 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (Tmax: 3.2 ± 1.3 hours) compared with the fasted state (Tmax: 0.9 ± 0.3 hours); Cmax in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC¥) in the fed and fasted states; therefore, EPIVIR Tablets and Oral Solution may be administered with or without food.
The accumulation ratio of lamivudine in HIV-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2mg/kg b.i.d.

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

Metabolism

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

Elimination

The majority of lamivudine is eliminated unchanged in urine. In 20 patients given a single IV dose, renal clearance was 0.22 ± 0.06 L/hr•kg (mean ± SD), representing 71% ± 16% (mean ± SD) of total clearance of lamivudine.
In most single-dose studies in HIV-infected patients with serum sampling for 24 hours after dosing, the observed mean elimination half-life (T ½) ranged from 5 to 7 hours. Total clearance was 0.37 ± 0.05 L/hr•kg (mean ± 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.

ZIDOVUDINE:

Adults

The pharmacokinetics of zidovudine has been evaluated in 22 adult HIV-infected patients in a Phase 1 dose-escalation study. After oral dosing (tablets), zidovudine was rapidly absorbed from the gastrointestinal tract with peak serum concentrations occurring within 0.5 to 1.5 hours. Dose-independent kinetics was observed over the range of 2 mg/kg every 8 hours to 10 mg/kg every 4 hours. The mean zidovudine half-life was approximately 1 hour and ranged from 0.78 to 1.93 hours following oral dosing.
Zidovudine is rapidly metabolized to 3'-azido-3'-deoxy-5'-O-a-D-glucopyra-nuronosylthymidine (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. However, as a result of first-pass metabolism, the average oral tablet bioavailability of zidovudine is 65% (range 52% to 75%). A second metabolite, 3-amino- 3-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous (IV) 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.
Additional 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 1900 mL/min per 70 kg and the apparent volume of distribution was 1.6 L/kg. Renal clearance is estimated to be 400 mL/min per 70 kg, indicating glomerular filtration and active tubular secretion by the kidneys. Zidovudine plasma protein binding is 34% to 38%, indicating that drug interactions involving binding site displacement are not anticipated.
The zidovudine cerebrospinal fluid (CSF)/ plasma concentration ratio was determined in 39 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.
Adults with Impaired Renal Function
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 ± 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 five times daily for 8 weeks. Daily doses of 500 mg or less were well tolerated despite significantly elevated plasma levels of GZDV. Apparent oral clearance 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.

Pediatrics

The pharmacokinetics and bioavailability of zidovudine have been evaluated in 21 HIV-infected pediatric patients, 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 IV solution administered over the range of 90 to 240 mg/m2 every 6 hours. After

discontinuation of the IV 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 per kg, respectively. These values compare to mean half-life and total body clearance in adults of 1.1 hours and 27.1 mL/min per kg.

The mean oral bioavailability of 65% was independent of dose. This value is the same as the bioavailability in adults. Doses of 1 80 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 have been studied in pediatric patients 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 eight neonates who were exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In another study, the pharmacokinetics of zidovudine were evaluated in pediatric patients (ranging in age of 1 day to 3 months) of normal birth weight for gestational age and with normal renal and hepatic function. In neonates less than or equal to 14 days old, mean ± SD total body clearance was 10.9 ± 4.8 mL/min per kg (n = 18) and half-life was 3.1 ± 1.2 hours (n = 21). In neonates and infants greater than 14 days old, total body clearance was 19.0 ± 4.0 mL/min per 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 patients older than 14 days.

Pregnancy

The pharmacokinetics of zidovudine have 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 were 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.

Nursing Mothers

The U.S. Public Health Service Centers for Disease Control and Prevention advises HIV- infected women not to breastfeed to avoid postnatal transmission of HIV to a child who may not yet be infected. 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.

Effect of Food on Absorption

Administration of zidovudine tablets with food decreased peak plasma concentrations by greater than 50%; however, bioavailability as determined by AUC may not be affected. The effect of food on the absorption of zidovudine from the tablet formulation is not known.

NEVIRAPINE

Absorption and Bioavailability:

Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean ±SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 mc g/mL (7.5 mc M) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 mc g/mL (17 ± 7 mc M), (n = 242) were attained at 400 mg/day. Nevirapine tablets and sBPension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When Nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 30 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 (AUCt) was not significantly altered by ddI, which is formulated with an alkaline buffering agent. NEVIRAPINEmay be administered with or without food, antacid or ddI.

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

Metabolism/Elimination:
In vivo studies in humans and in vitro studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. In vitro studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 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 given twice daily followed by a single 50 mg dose of 14C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.
Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of autoinduction are characterized by an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200 - 400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200 - 400 mg/day.

INDICATIONS:
Zidovudine, Lamivudine & Nevirapine is indicated for the treatment of HIV infection when antiretroviral therapy is warranted.

DOSAGE AND DIRECTION OF USE:
The recommended oral dose of Zidovudine, Lamivudine & Nevirapine for adults and adolescents (at least 12 years of age) is one tablet (containing 150mg of Lamivudine and 300mg of Zidovudine & 200mg of Nevirapine) twice daily with or without food.

Dose adjustment: Because it is a fixed dose combination, Zidovudine, Lamivudine & Nevirapine should not be prescribed for patients requiring dosage adjustment such as those with reduced renal function (creatinine clearance< 50ml/min), those with low body weight (<50kg or II 0 lb), or those experiencing dose-limiting adverse events.

CONTRAINDICATIONS:
Patients who exhibit potentially life-threatening allergic reactions to any of the components of the formulation.

WARNINGS AND PRECAUTIONS:
Since it is a fixed dose combination of Lamivudine, Nevirapine & Zidovudine , it should ordinaly not be administered concomitantly with either Lamivudine or Zidovudine.
BONE MARROW SUPPRESSION
Zidovudine, Lamivudine & Nevirapine should be used with caution in patients who have bone marrow compromise evidenced by granulocyte count <1000 cells/mm3 or hemoglobin <9.5 g/dL. There have been reports of pancytopenia associated with the use of Zidovudine & Lamivudine, which was reversible in most instances after discontinuance of the drug.
Frequent blood counts are strongly recommended in patients with advanced HIV disease who are treated with zidovudine. For patients with asymptomatic or early HIV disease, periodic blood counts are recommended. If anaemia or neutropenia develops, dosage adjustments may be necessary.

MYOPATHY

Myopathy and myositis with pathological changes, similar to that produced by HIV disease, have been associated with prolonged use of Zidovudine, Lamivudine & Nevirapine.

LACTIC ACIDOSIS/SEVERE HEPATOMEGALY WITH STEATOSIS

Rare occurrences of potentially fatal lactic acidosis in the absence of hypoxemia, and severe hepatomegaly with steatosis have been reported with the use of certain antiretroviral nucleoside analogues. Therapy with Zidovudine, Lamivudine & Nevirapine should be Pended until the diagnosis of lactic acidosis has been excluded. Caution should be exercised when administering Zidovudine & Lamivudine to any patient, particularly obese women, with hepatomegaly, hepatitis, or other known risk factors for liver disease. Treatment with Zidovudine, Lamivudine & Nevirapine should be spender in the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly, or metabolic/lactic acidosis of unknown aetiology.

OTHER SERIOUS ADVERSE REACTIONS

Reports of pancreatitis, sensitization reactions, 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, Lamivudine & Nevirapine.

PREGNANCY

Category C. Congenital abnormalities were found to occur with similar frequency between infants born to mothers who received Zidovudine, Lamivudine & Nevirapine and infants born to mothers who received placebo. Abnormalities were either problems in embryogenesis (prior to 14 weeks) or were recognised on ultrasound before or immediately after initiation of study drugs.

NURSING MOTHERS

HIV infected women are advised not to breast feed to avoid postnatal transmission of HIV to a child who may not yet be infected. Zidovudine, Lamivudine & Nevirapine is excreted in human milk.

IMPAIRED RENAL AND HEPATIC FUNCTION

Zidovudine, Lamivudine & Nevirapine is eliminated from the body primarily by renal excretion following metabolism in the liver. In patients with severely impaired renal function, dosage reduction is recommended. Although very little data are available, patients with severely impaired hepatic function may be at greater risk of toxicity.

Special precautions:

Impaired Renal Function:

Reduction of the dosages of lamivudine, Neviraoine and Zidovudine is recommended for patients with impaired renal function. Patients with creatinine clearance< 50ml/min should not receive Zidovudine, Lamivudine & Nevirapine.

Pregnancy:

Category C. There are no adequate and well-controlled studies of this combination in pregnant women. Zidovudine, Lamivudine & Nevirapine should be used during pregnancy only if the potential benefits outweigh risks.

Lactation:

It is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV infection Zidovudine is excreted in breast milk. No data are available on this combination or lamivudine. Mothers should be instructed not to breast- feed if they are receiving Zidovudine, Lamivudine & Nevirapine.

Paediatric Use:

Zidovudine, Lamivudine & Nevirapine should not be administered to paediatric patients less than 12 years of age because it is a fixed dose combination that cannot be adjusted for this patient population.

Oters:

Reduction of doses of lamivudine is recommended for patients with low body weight (less than 50kg or 110 lb). Therefore patients with low body weight should not receive Zidovudine, Lamivudine & Nevirapine.

SIDE EFFECTS:

MONOTHERAPY

Adults: The frequency and severity of adverse events associated with the use of Zidovudine, Lamivudine & Nevirapine in adults are greater in patients with more advanced infection at the time of initiation of therapy.

The anaemia reported in patients with advanced HIV disease receiving Zidovudine, Lamivudine & Nevirapine appeared to be the result of impaired erythrocyte maturation. Thrombocytopenia has also been reported in patients with advanced disease. Mild drug-associated elevations in total bilirubin levels have been reported as an uncommon occurrence in

patients treated for asymptomatic HIV infection.
Clinical adverse events or symptoms which occurred in at least 5% of all patients with advanced HIV disease treated with 1,500 mg/day of Zidovudine, Lamivudine & Nevirapine were: fever, headache, nausea, vomiting, anorexia, myalgia, insomnia, dizziness, paraesthesia, dyspnoea and rash. Malaise, gastrointestinal pain, dyspepsia, and taste perversion were also reported.
Paediatrics: Anaemia and granulocytopenia among paediatric patients with advanced HIV disease receiving zidovudine occurred with similar incidence to that reported for adults with AIDS or advanced AIDS-Related complex. Macrocytosis was frequently observed.
The most commonly observed side effects during clinical trials were Headache, malaise and fatigue, nausea, vomiting ,diarrhea,anorexia,fever/chills,neuropathy,insomnia,dizziness,nasal signs and symptoms. Cough,muscloskeletal pain and neutropenia.

DRUG INTERACTIONS:

Ganciclovir, interferon alpha: Use of Zidovudine, Lamivudine & Nevirapine in combination with either ganciclovir or interferon alpha increases the risk of hematologic toxicities in some patients with advanced HIV disease. Hematologic parameters should be monitored frequently in all patients receiving either of these combinations.
Bone Marrow Suppressive Agents/Cytotoxic Agents: Co administration of Zidovudine, Lamivudine & Nevirapine 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.
Probenecid: Limited data suggests that probenecid may increase Zidovudine, Lamivudine & Nevirapine levels by inhibiting glucuronidation and/or by reducing renal excretion of Zidovudine, Lamivudine & Nevirapine Phenytoin: Phenytoin plasma levels have been reported to be low in some patients receiving Zidovudine & Lamivudine. In one study, a 30% decrease in oral Zidovudine & Lamivudine clearance was observed with phenytoin.
Methadone: No adjustments in methadone maintenance requirements were reported in a study of nine HIV positive patients receiving methadone maintenance.
Fluconazole: The co administration of fluconazole with Zidovudine, Lamivudine & Nevirapine has been reported to interfere with the oral clearance and metabolism of Zidovudine, Lamivudine & Nevirapine.
Atovaquone: A decrease in Zidovudine, Lamivudine & Nevirapine oral clearance was observed.
Valproic Acid: Data suggests that valproic acid increases the oral bioavailability of Zidovudine, Lamivudine & Nevirapine through inhibition of first pass hepatic metabolism. Patients should be monitored for a possible increase in Zidovudine, Lamivudine & Nevirapine related adverse events.
Lamivudine: Co-administration of zidovudine with lamivudine resulted in an increase in the maximum concentration (Cmax) of zidovudine.

STORAGE CONDITIONS:

Store in a cool & dry place, protected from light.
Keep out of reach of children.

SHELF LIFE:

2 years

PRESENTATION:

1X60's HDPE Bottles.

NEV-200

(Nevirapine Tablets)

COMPOSITION:
Each tablet contains:
Nevirapine 200mg

PHARMACOLOGICAL CLASSIFICATION:
Antiretroviral

PHARMACOLOGY:
Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases a , ß, g , or d) are not inhibited by nevirapine.

PHARMACOKINETICS:
NEVIRAPINE
Absorption and Bioavailability:
Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean ±SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 mc g/mL (7.5 mc M) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 mc g/mL (17 ± 7 mc M), (n = 242) were attained at 400 mg/day. Nevirapine tablets and sBPension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When Nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 30 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 (AUCt) was not significantly altered by ddI, which is formulated with an alkaline buffering agent. NEVIRAPINEmay be administered with or without food, antacid or ddI.

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

Metabolism/Elimination:
In vivo studies in humans and in vitro studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. In vitro studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 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 given twice daily followed by a single 50 mg dose of 14C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.
Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of

autoinduction are characterized by an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200 - 400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200 - 400 mg/day.

INDICATIONS:
Nevirapine is indicated for the treatment of HIV infection when antiretroviral therapy is warranted.

DOSAGE AND DIRECTION OF USE:
Nevirapine should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (See Warnings and Precautions). Patients experiencing rash during the 14-day lead-in period of 200 mg/day (or 4 mg/kg/day in paediatric patients) should not have their nevirapine dose increased until the rash has resolved.
Nevirapine administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities (excluding GGT), until the liver function test elevations have returned to baseline. Nevirapine may then be restarted at 200 mg per day (or 4 mg/kg/day in paediatric patients). Increasing the daily dose to 200 mg twice daily (4 or 7 mg/kg twice daily, according to age, in paediatric patients) should be done with caution, after extended observation.
Nevirapine should be permanently discontinued if moderate or severe liver function test abnormalities recur.
Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing, using one 200 mg tablet daily (or 4 mg/kg/day in paediatrics) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (4 or 7 mg/kg twice daily, according to age, in paediatric patients).
No data are available to recommend a dosage of nevirapine in patients with hepatic dysfunction, renal insufficiency, or undergoing dialysis.

CONTRAINDICATIONS:
Patients who exhibit potentially life-threatening allergic reactions to any of the components of the formulation.

WARNINGS AND PRECAUTIONS:
Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise and/or significant hepatic abnormalities) must discontinue nevirapine as soon as possible.
Nevirapine therapy must be initiated with a 14-day lead-in period of 200 mg/day (4 mg/kg/day in paediatric patients), 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.
Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis (transaminase elevations, with or without hyperbilirubinemia, prolonged partial thromboplastin time, or eosinophilia), has occurred in patients treated with nevirapine. Some of these cases began in the first few weeks of therapy, and some were accompanied by rash. Nevirapine administration should be interrupted in patients experiencing moderate or severe ALT or AST abnormalities until these return to baseline values. Nevirapine should be permanently discontinued if liver function abnormalities recur upon readministration. Monitoring of ALT and AST is strongly recommended, especially during the first six months of nevirapine treatment.
The duration of clinical benefit from antiretroviral therapy may be limited. Patients receiving nevirapine or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

IMPAIRED RENAL AND HEPATIC FUNCTION:
Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. However, the pharmacokinetics of nevirapine have not been evaluated in patients with either hepatic or renal dysfunction. Therefore, nevirapine should be used with caution in these patient populations.

DRUG INTERACTION:
The induction of CYP3A by nevirapine may result in lower plasma concentrations of other concomitantly administered drugs that are extensively metabolized by CYP3A. Thus, if a patient has been stabilized on a dosage regimen for a drug metabolized by CYP3A, and begins treatment with nevirapine, dose adjustments may be necessary.
Rifampin/Rifabutin: There are insufficient data to assess whether dose adjustments are necessary when nevirapine and

rifampin or rifabutin are coadministered. Therefore, these drugs should only be used in combination if clearly indicated and with careful monitoring.
Ketoconazole: Nevirapine and ketoconazole should not be administered concomitantly. Coadministration of nevirapine and ketoconazole results in a significant reduction in ketoconazole plasma concentrations.
Oral Contraceptives: There are no clinical data on the effects of nevirapine on the pharmacokinetics of oral contraceptives. Nevirapine may decrease plasma concentrations of oral contraceptives (also other hormonal contraceptives); therefore, these drugs should not be administered concomitantly with nevirapine.
Methadone: Based on the known metabolism of methadone, nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Pregnancy
Category C. There are no adequate and well-controlled studies in pregnant women. Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Lactation
Data indicate that nevirapine is found in breast milk. It is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Mothers should discontinue nursing if they are receiving nevirapine.

SIDE EFFECTS:

The most clinically important adverse events associated with nevirapine therapy are rash and increases in liver function tests. Cases of hypersensitivity reactions have been observed.
The major clinical toxicity of nevirapine is rash, with nevirapine-attributable rash occurring in 16% of patients on combination regimens in Phase II/III controlled studies. Thirty-five percent of patients treated with nevirapine experienced rash compared with 19% of patients treated in control groups of either zidovudine + didanosine or zidovudine alone. Severe or life-threatening rash occurred in 6.6% of nevirapine-treated patients compared with 1.3% of patients treated in the control groups.
Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions; with or without pruritus, located on the trunk, face and extremities. The majority of severe rashes occurred within the first 28 days of treatment. 25% of the patients with severe rashes required hospitalization, and one patient required surgical intervention. Overall, 7% of patients discontinued nevirapine due to rash.
With respect to laboratory abnormalities, asymptomatic elevations in GGT levels are more frequent in nevirapine recipients than in controls. Because clinical hepatitis has been reported in nevirapine-treated patients, monitoring of ALT (SGPT) and AST (SGOT) is strongly recommended, especially during the first six months of nevirapine treatment (See Warnings and Precautions). Decreased neutrophils (< 750/mm3), platelets (< 50,000/mm3) and Hb (< 8.0 g/dL), and increased total bilirubin (> 2.5 mg/dL) have also been reported.
Grenulocytopenia has been more commonly observed in children. The safety profile of nevirapine in neonates has not been established.

OVERDOSAGE:

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

SIDE EFFECTS:

The most commonly observed side effects during clinical trials were Headache, malaise and fatigue, nausea, vomiting ,diarrhea,anorexia,fever/chills,neuropathy,insomnia,dizziness,nasal signs and symptoms. Cough,muscloskeletal pain and neutropenia.

DRUG INTERACTIONS:

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A4 and 2B6. Nevirapine is known to be an inducer of these enzymes. Thus, if a patient has been stabilized on a dosage regimen for a drug metabolized by CYP3A, and begins treatment with nevirapine, dose adjustments may be necessary.

Clinical comments about possible dosage modifications are given below:
Established Drug Interactions with nevirapine
Ketoconazole: Nevirapine and ketoconazole should not be administered concomitantly, because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.

Clarithromycin: Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against Mycobacterium avium-intracellulare complex, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Efavirenz: Efavirenz concentrations are decreased. Appropriate doses for this combination are not established.
Ethinyl estradiol and Norethindrone: Concentrations of both drugs are decreased. 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.
Rifabutin: Concentrations of rifabutin and its metabolite 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 and rifampin should not be administered concomitantly because potentially reduce the efficacy of the drug and also increase the hepatotoxicity risk. Physicians needing treat patients co-infected with tuberculosis should preferentially use alternative drugs (e.g., efavirenz, abacavir).If using a nevirapine-containing regimen, caution should be used in concomitant administration.
Fluconazole: Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapineassociated adverse events.
Indinavir: Concentrations of indinavir are decreased. Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Lopinavir/Ritonavir: A dose increase of lopinavir/ritonavir from 400/100 mg to 533/133 mg twice daily with food is recommended in combination with nevirapine.
Nelfinavir: The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Saquinavir: Apropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.
Methadone: Methadone levels may be decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Potential drug interactions are listed below:
Examples of drugs in which plasma concentrations may be decreased by Co-administration with nevirapine
Antiarrhythmics: e.g. Amiodarone, disopyramide, and lidocaine
Anticonvulsants: e.g. Carbamazepine, clonazepam, and ethosuximide
Antifungals: e.g. Itraconazole
Calcium channel blockers: Diltiazem, nifedBPine, verapamil
Cancer chemotherapy: Cyclophosphamide
Ergot alkaloids: Ergotamine
Immunosuppressants: Cyclosporin, tacrolimus, sirolimus
Motility agents: Cisapride
Opiate agonists: Fentanyl

Examples of drugs in which plasma concentrations may be increased by co-administration with nevirapine.
Anticoagulants e.g. warfarin. Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

STORAGE CONDITIONS:
Store in a cool & dry place, protected from light.
Keep out of reach of children.

SHELF LIFE:
2 years

PRESENTATION:
1X60's HDPE Bottles.

D-SINE-25/50/100/250/400

(Didanosine Chewable and Buffered Tablets)

COMPOSITION:

Each tablet contains:
Didanosine 25/50/100/250/400 mg
(Chewable and Buffered Tablets)

Pharmacodynamics / Pharmacokinetics

PHARMACODYNAMICS:

Nucleoside reverse transcriptase inhibitor: ATC Code: J05AF02
Didanosine is an inhibitor of the in vitro replication of the Human Immunodeficiency Virus (HIV) [(also known as HTLV III, LAV)] in human primary cell cultures and in established cell lines. After Didanosine enters the cell, it is enzymatically converted to dideoxyadenosine-triphosphate (ddATP), its active metabolite. In viral nucleic acid replication, incorporation of this 2',3'-dideoxynucleoside prevents chain extension and thereby inhibits viral replication. In addition, ddATP inhibits HIV-reverse transcriptase by competing with dATP for binding to the enzyme's active site, preventing proviral DNA synthesis.
The relationship between in vitro susceptibility of HIV to didanosine and clinical response to therapy has not been established. Likewise, in vitro sensitivity results vary greatly and methods to establish virologic responses have not been pro

PHARMACOKINETIC:Adults

Absorption: Didanosine is rapidly degraded at an acidic pH. Therefore, the tablets contain buffering agents designed to increase gastric pH. The administration of didanosine with a meal results in a significant decrease (about 50%) in bioavailability. Didanosine tablets should be administered at least 30 minutes before a meal. A study in 10 asymptomatic HIV seropositive patients demonstrated that administration of Didanosine tablets 30 min to 1 hour before a meal did not result in any significant changes in the bioavailability of didanosine compared to administration under fasting conditions.
Administration of the tablets 1 to 2 hours after a meal was associated with a 55% decrease in Cmax and AUC values, which was comparable to the decrease observed when the formulation was given immediately after a meal.
In 30 patients receiving didanosine 400 mg once daily in the fasted state as Didanosine buffered tablets, single dose AUC was 2516 ± 847 ng·h/ml (34%) (mean ± SD [%CV]) and Cmax was 1475 ± 673 ng/ml (46%).

Contraindications

Didanosine is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the formulation.

Pregnancy and Lactation

Pregnancy: There are no adequate and well-controlled studies in pregnant women and it is not known whether didanosine can cause foetal harm or affect reproductive capacity when administered during pregnancy. Lactic acidosis, sometimes fatal, has been reported in pregnant women who received the combination of didanosine and stavudine with or without other antiretroviral treatment. Therefore, the use of didanosine during pregnancy should be considered only if clearly indicated, and only when the potential benefit outweighs the possible risk. Teratology studies in rats and rabbits did not produce evidence of embryotoxic, foetotoxic, or teratogenic effects. A study in rats showed that didanosine and/or its metabolites are transferred to the foetus through the placenta.

Lactation: It is not known whether didanosine is excreted in human milk. It is recommended that women taking didanosine do not breast-feed because of the potential for serious adverse reactions in nursing infants. At the 1000 mg/kg/day dose levels in rats, didanosine was slightly toxic to females and pups during mid and late lactation (reduced food intake and body weight gains), but the physical and functional development of the subsequent offsprings were not impaired. A further study showed that, following oral administration, didanosine and/or its metabolites were excreted into the milk of lactating rats.

Side Effects

The major toxicity of didanosine is pancreatitis. Other important toxicities include lactic acidosis/ severe hepatomegaly with steatosis and retinal/visual changes.

Adults: Clinical adverse events that occurred in at least 5% of adult patients in clinical trials with didanosine monotherapy are diarrhoea, neuropathy, chills/fever, rash/pruritus, abdominal pain, asthenia, headache, pain, nausea and vomiting and pancreatitis. The incidence of adverse events has been reported to be generally lower in patients with less advanced HIV disease.

The most frequently reported serious laboratory abnormalities with didanosine monotherapy are leukopenia, granulocytopenia and elevations of amylase, SGOT and SGPT values.

Children: Almost all 98 children treated in the clinical trials presented with various signs and symptoms at the time of enrollment. During the studies, the most frequently reported adverse signs and symptoms were generally those also seen in adults.

Other serious paediatric clinical adverse events reported include retinal depigmentation, seizure, neurologic effects, pneumonia, diabetes mellitus and diabetes insipidus.

Dosage and Administration

Adults Dosage: The dosing interval should be 12 hours. Didanosine should be administered on an empty stomach, at least 30 minutes before or 2 hours after eating. Adult patients should take 2 tablets at each dose so that adequate buffering is provided to prevent gastric acid degradation of didanosine. No more than 4 tablets should be taken at each dose to reduce the risk of gastrointestinal side effects. The recommended starting dose in adults is dependent on weight, as outlined in the table below:

Patient Weight	Didanosine Tablets
> 60 kg	200 mg b.d.
< 60 kg	125 mg b.d.

Method of administration

Adults: Patients should take minimally two tablets of 25mg in each dose, to provide sufficient antacid against acid degradation of didanosine. The tablets should be thoroughly chewed or dispersed in at least 30 ml of water prior to consumption. To disperse tablets, stir until a uniform dispersion forms, and drink the entire dispersion immediately. If additional flavoring is desired, the dispersion may be diluted with 30 ml of clear apple juice. Stir the further dispersion just prior to consumption.

Children: Children older than 1 year of age should receive a 2-tablet of 25mg dose, children under year should receive a 1-tablet of 25mg dose. Tablets should be chewed or dispersed in water prior to consumption, as described above. When a one tablet of 25mg dose is required, the volume of water for dispersion should be 15 ml. Fifteen ml of clear apple juice may be added to the dispersion as a flavouring. Stir the further dispersion just prior to con

Shelf life

24 months

Storage Condition

Store in cool, dark and dry place.

PACKING:

HDPE Bottle pack of 30's& 60's tablets and packed in a unit carton along with package insert.

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