approximately equivalent to the anticipated exposure in humans at the recommended dose level of 500/200 mg tipranavir/ritonavir BID.

Pregnancy

Teratogenic Effects, Pregnancy Category C.

Investigation of fertility and early embryonic development with tipranavir disodium was performed in rats, teratogenicity studies were performed in rats and rabbits, and pre- and post-natal development were explored in rats.

No teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits up to dose levels of 1000 mg/Kg/day and 150 mg/Kg/day tipranavir, respectively, at exposure levels approximately 1.1-fold and 0.1-fold human exposure. At 400 mg/Kg/day and above in rats, fetal toxicity (decreased sternebrae ossification and body weights) was observed, corresponding to an AUC of 1310 μM·h or approximately 0.8-fold human exposure at the recommended dose. In rats and rabbits, fetal toxicity was not noted at 40 mg/Kg/day and 150 mg/Kg/day, respectively, corresponding accordingly to $C_{max}/AUC_{0\text{-}24h}$ levels of 30.4 μM/340 μM·h and 8.4 μM/120 μM·h. These exposure levels (AUC) are approximately 0.2-fold and 0.1-fold the exposure in humans at the recommended dose.

In pre- and post-development studies in rats, tipranavir showed no adverse effects at 40 mg/Kg/day (~0.2-fold human exposure), but caused growth inhibition in pups and maternal toxicity at dose levels of 400 mg/Kg/day (~0.8-fold human exposure). No post-weaning functions were affected at any dose level.

There are no adequate and well-controlled studies in pregnant women for the treatment of HIV-1 infection. APTIVUS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to APTIVUS, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Because of both the potential for HIV transmission and any possible adverse effects of tipranavir, mothers should be instructed not to breastfeed if they are receiving APTIVUS.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of APTIVUS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration and monitoring of APTIVUS in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

APTIVUS (tipranavir), co-administered with 200 mg of ritonavir, has been studied in a total of 1854 HIV-positive adults as combination therapy in clinical studies. Of these, 1397 patients received the dose of 500/200 mg BID. Seven hundred sixty one (761) adults, including 385 in the 1182.12 and 1182.48 Phase 3 pivotal studies, have been treated for at least 24 weeks.

In 1182.12 and 1182.48 in the APTIVUS/ritonavir arm, the most frequent AEs were diarrhea, nausea, fatigue, headache and vomiting. Adverse events leading to discontinuation were reported by 7.8% of the tipranavir-treated patients and 4.9% of the comparator arm patients.

Due to the need for co-administration of APTIVUS with 200 mg of ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

The most frequent clinical treatment-emergent adverse events reported in Phase 3 clinical studies (1182.12 and 1182.48) in adults are summarized in Table 10 below. Events of moderate to severe intensity (Grades 2-4) reported in at least 2% of highly treatment-experienced subjects in either treatment group are included.

Table 10 Percentage of Patients with Treatment Emergent Adverse Events of at Least Moderate Intensity (Grades 2-4) in ≥ 2% of Patients in Either Treatment Group[a]

	Phase 3 Studies 1182.12 and 1182.48 (24-weeks)	
	Tipranavir/ritonavir (500/200 mg BID) + OBR (n=746)	Comparator PI/ritonavir[b] + OBR (n=737)
Gastrointestinal Disorders		
Diarrhea	10.9%	9.4%
Nausea	6.7%	4.6%
Vomiting	3.4%	3.0%
Abdominal pain[c]	2.8%	3.7%
General Disorders		
Pyrexia	4.6%	4.3%
Fatigue	4.0%	3.9%
Asthenia	1.5%	2.3%
Infections and Infestations		
Bronchitis	2.9%	1.1%
Nervous System Disorders		
Headache	3.1%	3.1%
Psychiatric Disorders		
Depression	2.0%	3.0%
Insomnia	1.2%	2.6%
Respiratory, Thoracic and Mediastinal Disorders		
Cough	0.8%	2.2%
Skin and Subcutaneous Tissue Disorders		
Rash	2.0%	2.0%

[a]Excludes laboratory abnormalities that were Adverse Events
[b]Comparator PI/RTV: lopinavir/ritonavir 400/100 mg BID, indinavir/ritonavir 800/100 mg BID, saquinavir/ritonavir 1000/100 mg BID, amprenavir/ritonavir 600/100 mg BID
[c]Abdominal pain includes Preferred Terms "Abdominal pain" and "Abdominal pain upper"

Clinically meaningful adverse reactions in < 2% of adult patients (n=1397) treated with APTIVUS/ritonavir 500/200mg in Phase 2 and 3 trials listed below by body system:

Blood and Lymphatic System Disorders: anemia, neutropenia, thrombocytopenia

Gastrointestinal Disorders: abdominal distension, dyspepsia, flatulence, gastroesophageal reflux disease, pancreatitis

General Disorders: influenza like illness, malaise, pyrexia

Hepatobiliary Disorders: hepatitis, hepatic failure

Immune System Disorders: hypersensitivity

Infections and infestations: reactivation of herpes simplex and varicella zoster

Investigations: hepatic enzymes increased, liver function test abnormal, lipase increased, weight decreased

Metabolism and Nutrition Disorders: anorexia, decreased appetite, dehydration, diabetes mellitus, facial wasting, hyperamylasemia, hypercholesterolemia, hyperglycemia

Musculoskeletal and Connective Tissue Disorders: muscle cramp, myalgia

Nervous System Disorders: dizziness, neuropathy peripheral, somnolence

Psychiatric Disorders: insomnia, sleep disorder

Renal and Urinary Disorders: renal insufficiency

Respiratory, Thoracic and Mediastinal Disorders: dyspnea

Skin and Subcutaneous System Disorders: exanthem, lipoatrophy, lipodystrophy acquired, lipohypertrophy, pruritus

Laboratory Abnormalities

Treatment-emergent clinical laboratory abnormalities reported at 24 weeks in Phase 3 clinical studies (1182.12 and 1182.48) in adults are summarized in Table 11 below.

Table 11 Treatment Emergent Laboratory Abnormalities Reported in ≥ 2% of Adult Patients

		Studies 1182.12 and 1182.48 (24-weeks)	
	Limit	APTIVUS/ritonavir (500/200 mg BID) + OBR (n = 732)	Comparator PI/ritonavir + OBR* (n = 726)
Hematology			
WBC count decrease			
Grade 3-4	< 2.0 x $10^3/\mu L$	3.6%	5.4%
Chemistry			
Amylase			
Grade 3-4	> 2 x ULN	2.9%	4.8%
ALT			
Grade 2	> 2.5-5 x ULN	10.7%	5.4%
Grade 3	> 5-10 x ULN	3.1%	1.4%
Grade 4	> 10 x ULN	2.7%	0.4%
AST			
Grade 2	> 2.5-5 x ULN	6.0%	5.8%
Grade 3	> 5-10 x ULN	3.3%	1.0%
Grade 4	> 10 x ULN	0.7%	0.4%
ALT and/or AST			
Grade 2-4	> 2.5 x ULN	17.5%	9.9%
Cholesterol			
Grade 2	> 300 – 400 mg/dL	11.3%	4.3%
Grade 3	> 400 – 500 mg/dL	2.5%	0.3%
Grade 4	> 500 mg/dL	0.8%	0%
Triglycerides			
Grade 2	400 – 750 mg/dL	26.2%	14.7%
Grade 3	> 750 – 1200 mg/dL	12.8%	5.6%
Grade 4	> 1200 mg/dL	6.1%	3.4%

*Comparator PI/RTV: lopinavir/ritonavir 400/100 mg BID, indinavir/ritonavir 800/100 mg BID, saquinavir/ritonavir 1000/100 mg BID, amprenavir/ritonavir 600/100 mg BID

In clinical trials extending up to 48 weeks, the proportion of patients who developed Grade 2-4 ALT and/or AST elevations increased to 24.4% with APTIVUS/ritonavir and to 12.8% with CPI/ritonavir.

OVERDOSAGE

There is no known antidote for tipranavir overdose. Treatment of overdose should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. If indicated, elimination of unabsorbed tipranavir should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since tipranavir is highly protein bound, dialysis is unlikely to be beneficial in significant removal of this medicine.

DOSAGE AND ADMINISTRATION

General

The recommended dose of APTIVUS (tipranavir) Capsules is 500 mg (two 250 mg capsules), co-administered with 200 mg of ritonavir, twice daily.

APTIVUS Capsules, co-administered with 200 mg of ritonavir should be taken with food. Bioavailability is increased with a high fat meal.

HOW SUPPLIED

APTIVUS (tipranavir) Capsules 250 mg are pink, oblong soft gelatin capsules imprinted in black with "TPV 250". They are packaged in HDPE unit-of-use bottles with a child resistant closure and 120 capsules. (NDC 0597-0003-02)

APTIVUS capsules should be **stored in a refrigerator 2°-8°C (36°-46°F)** prior to opening the bottle. After opening the bottle, the capsules may be **stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)** and must be used within 60 days.

Store in a safe place out of the reach of children.

Address medical inquiries to: http://us.boehringer-ingelheim.com, (800) 542-6257 or (800) 459-9906 TTY.

RX ONLY

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

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APTIVUS Capsules are covered by U.S. Patents 5,852,195; 6,147,095; 6,169,181 and 6,231,887

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Revision Date: June 21, 2005

Patient Information

Aptivus® (ap' · ti · vəs) (tipranavir) **Capsules, 250 mg**	Boehringer Ingelheim

ALERT: Find out about medicines that should not be taken with Aptivus. Please also read the section "WHO SHOULD NOT TAKE APTIVUS".

Read the Patient Information that comes with APTIVUS before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. You should stay under a doctor's care while taking APTIVUS.

What is the most important information I should know about APTIVUS?

Patients taking APTIVUS, together with 200 mg NORVIR® (ritonavir), may develop severe liver disease that can cause death. If you develop any of the following symptoms of liver problems, you should stop taking APTIVUS/ritonavir treatment and call your doctor right away: tiredness, general ill feeling or "flu-like" symptoms, loss of appetite, nausea (feeling sick to your stomach), yellowing of your skin or whites of your eyes, dark (tea-colored) urine, pale stools (bowel movements), or pain, ache, or sensitivity on your right side below your ribs. If you have chronic Hepatitis B or C infection, your doctor should check your blood tests more often because you have an increased chance of developing liver problems.

What is APTIVUS?

APTIVUS is a medicine called a "protease inhibitor" that is used to treat adults with Human Immunodeficiency Virus (HIV). APTIVUS blocks HIV protease, an enzyme which is needed for HIV to make more virus. When used with other anti-HIV medicines, APTIVUS may reduce the amount of HIV in your blood and increase the number of CD4+ cells. Reducing the amount of HIV in the blood may keep your immune system healthy, so it can help fight infection.

APTIVUS is always taken with NORVIR® (ritonavir) and at the same time as NORVIR When you take APTIVUS with NORVIR, you must always use at least 2 other anti-HIV medicines.

Does APTIVUS cure HIV or AIDS?

APTIVUS does not cure HIV infection or AIDS. The long-term effects of APTIVUS are not known at this time. People taking APTIVUS may still get infections or other conditions common in people with HIV (opportunistic infections). It is very important that you stay under the care of your doctor during treatment with APTIVUS.

Does APTIVUS lower the chance of passing HIV to other people?

APTIVUS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. Continue to practice safer sex. Use a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Never use or share dirty needles.

Ask your doctor if you have any questions about safer sex or how to prevent passing HIV to other people.

Who should not take APTIVUS?

Do not take APTIVUS if you:

- are allergic to tipranavir or any of the other ingredients in APTIVUS. See the end of this leaflet for a list of major ingredients.
- are allergic to ritonavir (NORVIR®)
- have moderate to severe liver problems
- take any of the following types of medicines because **you could have serious side effects:**
    - Migraine headache medicines called "ergot alkaloids". If you take migraine headache medicines, ask you doctor or pharmacist if any of them are "ergot alkaloids".
    - Halcion® (triazolam)
    - Hismanal® (astemizole)
    - Orap® (pimozide)
    - Propulsid® (cisapride)
    - Seldane® (terfenadine)
    - Versed® (midazolam)
    - Pacenone® (amiodarone)
    - Vascor® (bepridil)
    - Tambocor® (flecainide)
    - Rythmol® (propafenone)
    - Quinaglute dura® (quinidine)

What should I tell my doctor before I take APTIVUS?

Tell your doctor about all of your medical conditions, including if you:

- **have liver problems** or are infected with Hepatitis B or Hepatitis C. These patients may have worsening of their liver disease.
- **are allergic to sulfa medicines.**
- **have hemophilia.** APTIVUS may cause increased bleeding.
- **have diabetes.** APTIVUS may worsen your diabetes or high blood sugar levels.

- **are pregnant or planning to become pregnant.** It is not known if APTIVUS can harm your unborn baby. You and your doctor will need to decide if APTIVUS is right for you. If you take APTIVUS while you are pregnant, talk to your doctor about how you can be in the Antiretroviral Pregnancy Registry.

- **are breast-feeding.** Do not breast-feed if you are taking APTIVUS. You should not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. Talk with your doctor about the best way to feed your baby.

- **are using estrogens for birth control or hormone replacement.** Women who use estrogens for birth control or hormone replacement have an increased chance of developing a skin rash while taking APTIVUS. If a rash occurs, it is usually mild to moderate, but you should talk to your doctor as you may need to temporarily stop taking either APTIVUS or the other medicine that contains estrogen or female hormones.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. **APTIVUS and many other medicines can interact. Sometimes serious side effects will happen if APTIVUS is taken with certain other medicines (see "Who should not take APTIVUS?").**

- Some medicines cannot be taken at all with APTIVUS
- Some medicines will require a change in dosage if taken with APTIVUS
- Some medicines will require close monitoring if taken with APTIVUS.

Women taking birth control pills need to use another birth control method. APTIVUS makes birth control pills work less well.

Know all the medicines you take and keep a list of them with you. Show this list to all your doctors and pharmacists anytime you get a new medicine you take. They will tell you if you can take these other medicines with APTIVUS. **Do not start any new medicines while you are taking APTIVUS without first talking with your doctor or pharmacist.** You can ask your doctor or pharmacist for a list of medicines that can interact with APTIVUS.

How should I take APTIVUS?

- Take APTIVUS exactly as your doctor has prescribed. You should check with your doctor or pharmacist if you are not sure. **You must take APTIVUS at the same time as NORVIR® (ritonavir).** The usual dose is 500 mg (two 250 mg capsules) of APTIVUS, together with 200 mg (two 100 mg capsules or 2.5 mL of solution) of NORVIR, twice per day. APTIVUS with NORVIR must be used together with other anti-HIV medicines.

APTIVUS comes in a capsule form and you should **swallow APTIVUS capsules whole. Do not chew the capsules.**

- Always take APTIVUS with food.
- Do not change your dose or stop taking APTIVUS without first talking with your doctor.
- If you take too much APTIVUS, call your doctor or poison control center right away.
- If you forget to take APTIVUS, take the next dose of APTIVUS, together with NORVIR® (ritonavir), as soon as possible. Do not take a double dose to make up for a missed dose.

- It is very important to take all your anti-HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop working to fight HIV (drug resistance).
- When your APTIVUS supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short period of time. The HIV virus may develop resistance to APTIVUS and become harder to treat. You should NEVER stop taking APTIVUS or your other HIV medicines without talking with your doctor.

What are the possible side effects of APTIVUS?

APTIVUS may cause serious side effects, including:

- **liver problems, including liver failure and death.** Your doctor should do blood tests to monitor your liver function during treatment with APTIVUS. Patients with liver diseases such as Hepatitis B and Hepatitis C may have worsening of their liver disease with APTIVUS and should have more frequent monitoring blood tests.

- **rash.** Mild to moderate rash, including flat or raised rashes or sensitivity to the sun, have been reported in approximately 10% of subjects receiving APTIVUS. Some patients who developed rash also had joint pain or stiffness, throat tightness, or generalized itching.

- **increased bleeding in patients with hemophilia.** This can happen in patients taking APTIVUS or other protease inhibitor medicines.

- **diabetes and high blood sugar (hyperglycemia).** This can happen in patients taking APTIVUS or other protease inhibitor medicines. Some patients have diabetes before starting treatment with APTIVUS which gets worse. Some patients get diabetes during treatment with APTIVUS. Some patients will need changes in their diabetes medicine. Some patients will need new diabetes medicine.

- **increased blood fat (lipid) levels.** Your doctor should do blood tests to monitor your blood fat (triglycerides and cholesterol) during treatment with APTIVUS. Some patients taking APTIVUS have large increases in triglycerides and cholesterol. The long-term chance of having a heart attack or stroke due to increases in blood fats caused by APTIVUS is not known at this time.

- **changes in body fat.** These changes have happened in patients taking APTIVUS. and other anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects include diarrhea, nausea, vomiting, stomach pain, tiredness and headache. Women taking birth control pills may get a skin rash.

It may be hard to tell the difference between side effects caused by APTIVUS, by the other medicines you are also taking, or by the complications of HIV infection. For this reason it is very important that

you tell your doctor about any changes in your health. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

The list of side effects is **not** complete. Ask your doctor or pharmacist for more information.

How should I store APTIVUS?

- Store APTIVUS capsules in a refrigerator at approximately **36°F to 46°F (2°C to 8°C).** Once the bottle is opened, the contents must be used within 60 days. Patients may take the bottle with them for use away from home so long as the bottle remains at a temperature of approximately **59°F to 86°F (15°C to 30°C).** You can write the date of opening the bottle on the label. Do not use after the expiration date written on the bottle.

- **Keep APTIVUS and all medicines out of the reach of children.**

General advice about APTIVUS

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use APTIVUS for a condition for which it was not prescribed. Do not give APTIVUS to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about APTIVUS. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about APTIVUS that is written for health professionals.

For additional information, you may also call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906. You may also request information through the company website at http://us.boehringer-ingelheim.com.

What are the ingredients in APTIVUS?

Active Ingredient: tipranavir

Major Inactive Ingredients: dehydrated alcohol, polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.

Rx only

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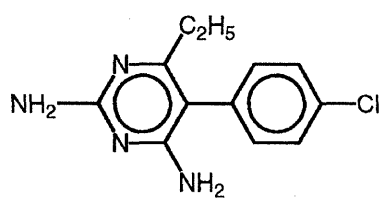
DARAPRIM®
(pyrimethamine)
25-mg Scored Tablets

DESCRIPTION

DARAPRIM (pyrimethamine) is an antiparasitic compound available in tablet form for oral administration. Each scored tablet contains 25 mg pyrimethamine and the inactive ingredients corn and potato starch, lactose, and magnesium stearate.

Pyrimethamine, known chemically as 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine, has the following structural formula:



$C_{12}H_{13}ClN_4$
Mol. Wt 248.71

CLINICAL PHARMACOLOGY

Pyrimethamine is well absorbed with peak levels occurring between 2 to 6 hours following administration. It is eliminated slowly and has a plasma half-life of approximately 96 hours. Pyrimethamine is 87% bound to human plasma proteins.

Microbiology: Pyrimethamine is a folic acid antagonist and the rationale for its therapeutic action is based on the differential requirement between host and parasite for nucleic acid precursors involved in growth. This activity is highly selective against plasmodia and *Toxoplasma gondii.*

Pyrimethamine possesses blood schizonticidal and some tissue schizonticidal activity against malaria parasites of humans. However, the 4-amino-quinoline compounds are more effective against the erythrocytic schizonts. It does not destroy gametocytes, but arrests sporogony in the mosquito.

The action of pyrimethamine against *Toxoplasma gondii* is greatly enhanced when used in conjunction with sulfonamides. This was demonstrated by Eyles and Coleman[1] in the treatment of experimental toxoplasmosis in the mouse. Jacobs et al[2] demonstrated that combination of the 2 drugs effectively prevented the development of severe uveitis in most rabbits following the inoculation of the anterior chamber of the eye with toxoplasma.

INDICATIONS AND USAGE

Treatment of Toxoplasmosis: DARAPRIM is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination.

Treatment of Acute Malaria: DARAPRIM is also indicated for the treatment of acute malaria. It should not be used alone to treat acute malaria. Fast-acting schizonticides such as chloroquine or quinine are indicated and preferable for the treatment of acute malaria. However, conjoint use of DARAPRIM with a sulfonamide (e.g., sulfadoxine) will initiate transmission control and suppression of susceptible strains of plasmodia.

Chemoprophylaxis of Malaria: DARAPRIM is indicated for the chemoprophylaxis of malaria due to susceptible strains of plasmodia. However, resistance to pyrimethamine is prevalent worldwide. It is not suitable as a prophylactic agent for travelers to most areas.

CONTRAINDICATIONS

Use of DARAPRIM is contraindicated in patients with known hypersensitivity to pyrimethamine or to any component of the formulation. Use of the drug is also contraindicated in patients with documented megaloblastic anemia due to folate deficiency.

WARNINGS

The dosage of pyrimethamine required for the treatment of toxoplasmosis is 10 to 20 times the recommended antimalaria dosage and approaches the toxic level. If signs of folate deficiency develop (see ADVERSE REACTIONS), reduce the dosage or discontinue the drug according to the response of the patient. Folinic acid (leucovorin) should be administered in a dosage of 5 to 15 mg daily (orally, IV, or IM) until normal hematopoiesis is restored.

Data in 2 humans indicate that pyrimethamine may be carcinogenic: a 51-year-old female who developed chronic granulocytic leukemia after taking pyrimethamine for 2 years for toxoplasmosis,[3] and a 56-year-old patient who developed reticulum cell sarcoma after 14 months of pyrimethamine for toxoplasmosis.[4]

Pyrimethamine has been reported to produce a significant increase in the number of lung tumors in mice when given intraperitoneally at doses of 25 mg/kg.[5]

DARAPRIM should be kept out of the reach of infants and children as they are extremely susceptible to adverse effects from an overdose. Deaths in pediatric patients have been reported after accidental ingestion.

PRECAUTIONS

General: The recommended dosage for chemoprophylaxis of malaria should not be exceeded. A small "starting" dose for toxoplasmosis is recommended in patients with convulsive disorders to avoid the potential nervous system toxicity of pyrimethamine. DARAPRIM should be used with caution in patients with impaired renal or hepatic function or in patients with possible folate deficiency, such as individuals with malabsorption syndrome, alcoholism, or pregnancy, and those receiving therapy, such as phenytoin, affecting folate levels (see Pregnancy subsection).

Information for Patients: Patients should be warned that at the first appearance of a skin rash they should stop use of DARAPRIM and seek medical attention immediately. Patients should also be warned that the appearance of sore throat, pallor, purpura, or glossitis may be early indications of serious disorders which require treatment with DARAPRIM to be stopped and medical treatment to be sought.

Women of childbearing potential who are taking DARAPRIM should be warned against becoming pregnant. Patients should be warned to keep DARAPRIM out of the reach of children. Patients should be advised not to exceed recommended doses. Patients should be warned that if anorexia and vomiting occur, they may be minimized by taking the drug with meals.

Concurrent administration of folinic acid is strongly recommended when used for the treatment of toxoplasmosis in all patients.

Laboratory Tests: In patients receiving high dosage, as for the treatment of toxoplasmosis, semiweekly blood counts, including platelet counts, should be performed.

Drug Interactions: Pyrimethamine may be used with sulfonamides, quinine and other antimalarials, and with other antibiotics. However, the concomitant use of other antifolic drugs or agents associated with myelosuppression including sulfonamides or trimethoprim-sulfamethoxazole combinations, proguanil, zidovudine, or cytostatic agents (e.g., methotrexate), while the patient is receiving pyrimethamine, may increase the risk of bone marrow suppression. If signs of folate deficiency develop, pyrimethamine should be discontinued. Folinic acid (leucovorin) should be administered until normal hematopoiesis is restored (see WARNINGS). Mild hepatotoxicity has been reported in some patients when lorazepam and pyrimethamine were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS section for information on carcinogenesis.

Mutagenesis: Pyrimethamine has been shown to be nonmutagenic in the following in vitro assays: the Ames point mutation assay, the Rec assay, and the *E. coli* WP2 assay. It was positive in the L5178Y/TK +/- mouse lymphoma assay in the absence of exogenous metabolic activation.[6] Human blood lymphocytes cultured in vitro had structural chromosome aberrations induced by pyrimethamine.

In vivo, chromosomes analyzed from the bone marrow of rats dosed with pyrimethamine showed an increased number of structural and numerical aberrations.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Pyrimethamine has been shown to be teratogenic in rats when given in oral doses 7 times the human dose for chemoprophylaxis of malaria or 2.5 times the human dose for treatment of toxoplasmosis. At these doses in rats, there was a significant increase in abnormalities such as cleft palate, brachygnathia, oligodactyly, and microphthalmia. Pyrimethamine has also been shown to produce terata such as meningocele in hamsters and cleft palate in miniature pigs when given in oral doses 170 and 5 times the human dose, respectively, for chemoprophylaxis of malaria or for treatment of toxoplasmosis.

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

Concurrent administration of folinic acid is strongly recommended when used for the treatment of toxoplasmosis during pregnancy.

Nursing Mothers: Pyrimethamine is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pyrimethamine and from concurrent use of a sulfonamide with DARAPRIM for treatment of some patients with toxoplasmosis, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS and PRECAUTIONS: Pregnancy).

Pediatric Use: See DOSAGE AND ADMINISTRATION section.

Geriatric Use: Clinical studies of DARAPRIM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Hypersensitivity reactions, occasionally severe (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and anaphylaxis), and hyperphenylalaninemia, can occur particularly when pyrimethamine is administered concomitantly with a sulfonamide. Consult the complete prescribing information for the relevant sulfonamide for sulfonamide-associated adverse events. With doses of pyrimethamine used for the treatment of toxoplasmosis, anorexia and vomiting may occur. Vomiting may be minimized by giving the medication with meals; it usually disappears promptly upon reduction of dosage. Doses used in toxoplasmosis may produce megaloblastic anemia, leukopenia, thrombocytopenia, pancytopenia, atrophic glossitis, hematuria, and disorders of cardiac rhythm. Hematologic effects, however, may also occur at low doses in certain individuals (see PRECAUTIONS: General).

Pulmonary eosinophilia has been reported rarely.

OVERDOSAGE

Following the ingestion of 300 mg or more of pyrimethamine, gastrointestinal and/or central nervous system signs may be present, including convulsions. The initial symptoms are usually gastrointestinal and may include abdominal pain, nausea, severe and repeated vomiting, possibly including hematemesis. Central nervous system toxicity may be manifest by initial excitability, generalized and prolonged convulsions which may be followed by respiratory depression, circulatory collapse, and death within a few hours. Neurological symptoms appear rapidly (30 minutes to 2 hours after drug ingestion), suggesting that in gross overdosage pyrimethamine has a direct toxic effect on the central nervous system.

The fatal dose is variable, with the smallest reported fatal single dose being 375 mg. There are, however, reports of pediatric patients who have recovered after taking 375 to 625 mg.

There is no specific antidote to acute pyrimethamine poisoning. In the event of overdosage, symptomatic and supportive measures should be employed. Gastric lavage is recommended and

is effective if carried out very soon after drug ingestion. Parenteral diazepam may be used to control convulsions. Folinic acid should also be administered within 2 hours of drug ingestion to be most effective in counteracting the effects on the hematopoietic system (see WARNINGS). Due to the long half-life of pyrimethamine, daily monitoring of peripheral blood counts is recommended for up to several weeks after the overdose until normal hematologic values are restored.

DOSAGE AND ADMINISTRATION

For Treatment of Toxoplasmosis: The dosage of DARAPRIM for the treatment of toxoplasmosis must be carefully adjusted so as to provide maximum therapeutic effect and a minimum of side effects. At the dosage required, there is a marked variation in the tolerance to the drug. Young patients may tolerate higher doses than older individuals. Concurrent administration of folinic acid is strongly recommended in all patients.

The adult *starting* dose is 50 to 75 mg of the drug daily, together with 1 to 4 g daily of a sulfonamide of the sulfapyrimidine type, e.g., sulfadoxine. This dosage is ordinarily continued for 1 to 3 weeks, depending on the response of the patient and tolerance to therapy. The dosage may then be reduced to about one half that previously given for each drug and continued for an additional 4 to 5 weeks.

The pediatric dosage of DARAPRIM is 1 mg/kg/day divided into 2 equal daily doses; after 2 to 4 days this dose may be reduced to one half and continued for approximately 1 month. The usual pediatric sulfonamide dosage is used in conjunction with DARAPRIM.

For Treatment of Acute Malaria: DARAPRIM is NOT recommended alone in the treatment of acute malaria. Fast-acting schizonticides, such as chloroquine or quinine, are indicated for treatment of acute malaria. However, DARAPRIM at a dosage of 25 mg daily for 2 days with a sulfonamide will initiate transmission control and suppression of non-falciparum malaria. DARAPRIM is only recommended for patients infected in areas where susceptible plasmodia exist. Should circumstances arise wherein DARAPRIM must be used alone in semi-immune persons, the adult dosage for acute malaria is 50 mg for 2 days; children 4 through 10 years old may be given 25 mg daily for 2 days. In any event, clinical cure should be followed by the once-weekly regimen described below for chemoprophylaxis. Regimens which include suppression should be extended through any characteristic periods of early recrudescence and late relapse, i.e., for at least 10 weeks in each case.

For Chemoprophylaxis of Malaria:

Adults and pediatric patients over 10 years — 25 mg (1 tablet) once weekly
Children 4 through 10 years — 12.5 mg (1/2 tablet) once weekly
Infants and children under 4 years — 6.25 mg (1/4 tablet) once weekly

HOW SUPPLIED

White, scored tablets containing 25 mg pyrimethamine, imprinted with "DARAPRIM" and "A3A" in bottles of 100 (NDC 0173-0201-55).

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

REFERENCES

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Manufactured by
DSM Pharmaceuticals, Inc.
Greenville, NC 27834 for

GlaxoSmithKline
Research Triangle Park, NC 27709

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EPIVIR® Tablets

(lamivudine tablets)

EPIVIR® Oral Solution

(lamivudine oral solution)

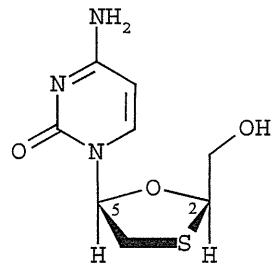
WARNING

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

EPIVIR TABLETS AND ORAL SOLUTION (USED TO TREAT HIV INFECTION) CONTAIN A HIGHER DOSE OF THE ACTIVE INGREDIENT (LAMIVUDINE) THAN EPIVIR-HBV® TABLETS AND ORAL SOLUTION (USED TO TREAT CHRONIC HEPATITIS B). PATIENTS WITH HIV INFECTION SHOULD RECEIVE ONLY DOSING FORMS APPROPRIATE FOR TREATMENT OF HIV (SEE WARNINGS AND PRECAUTIONS).

DESCRIPTION

EPIVIR (also known as 3TC) is a brand name for lamivudine, a synthetic nucleoside analogue with activity against human immunodeficiency virus-1 (HIV-1) and hepatitis B virus (HBV). The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

EPIVIR Tablets are for oral administration. Each 150-mg film-coated tablet contains 150 mg of lamivudine and the inactive ingredients hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Each 300-mg film-coated tablet contains 300 mg of lamivudine and the inactive ingredients black iron oxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

EPIVIR Oral Solution is for oral administration. One milliliter (1 mL) of EPIVIR Oral Solution contains 10 mg of lamivudine (10 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose.

MICROBIOLOGY

Mechanism of Action: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5′-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue into viral DNA. L-TP is a weak inhibitor of mammalian DNA polymerases α and β, and mitochondrial DNA polymerase γ.

Antiviral Activity In Vitro: The in vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. IC_{50} values (50% inhibitory concentrations) were in the range of 2 nM to 15 μM. Lamivudine had anti-HIV-1 activity in all acute virus-cell infections tested. In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. The relationship between in vitro susceptibility of HIV-1 to lamivudine and the

inhibition of HIV-1 replication in humans has not been established. Please see the EPIVIR-HBV package insert for information regarding the inhibitory activity of lamivudine against HBV.

Drug Resistance: Lamivudine-resistant variants of HIV-1 have been selected in vitro. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine residue to either isoleucine or valine.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Mutations in the HBV polymerase YMDD motif have been associated with reduced susceptibility of HBV to lamivudine in vitro. In studies of non-HIV-infected patients with chronic hepatitis B, HBV isolates with YMDD mutations were detected in some patients who received lamivudine daily for 6 months or more, and were associated with evidence of diminished treatment response; similar HBV mutants have been reported in HIV-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus (see PRECAUTIONS and EPIVIR-HBV package insert).

Cross Resistance: Lamivudine-resistant HIV-1 mutants were cross resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From Patients With Virologic Failure (see INDICATIONS AND USAGE: Description of Clinical Studies): The clinical relevance of genotypic and phenotypic changes associated with lamivudine therapy has not been fully established.

Study EPV20001: Fifty-three of 554 (10%) patients enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level ≥400 copies/mL) by Week 48. Twenty-eight patients were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA levels of patients in the lamivudine once-daily group and lamivudine twice-daily groups were 4.9 $\log_{10}$ copies/mL and 4.6 $\log_{10}$ copies/mL,