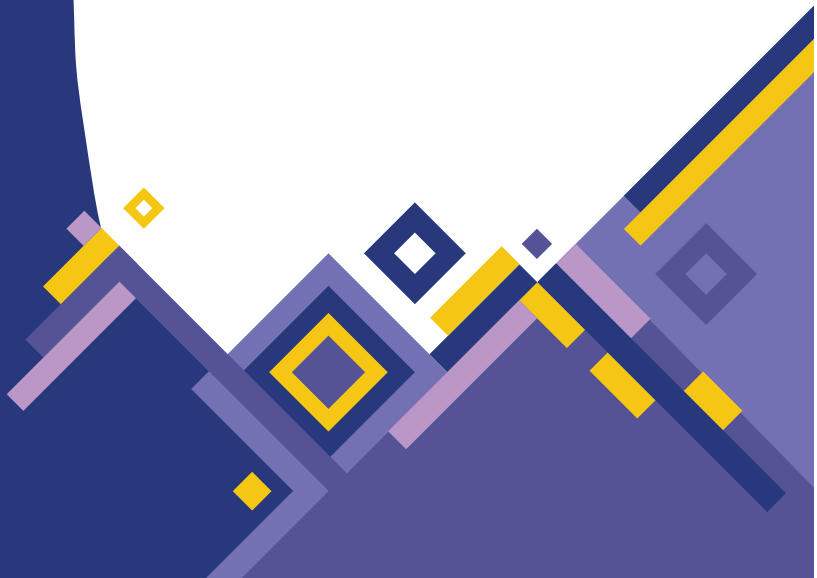
DARAPRIM®
(pyrimethamine) 25mg tablets

DARAPRIM
What you need to know



STARTING TREATMENT

In this Patient Information Brochure, you will learn:

- About the serious health concerns of toxoplasmosis
- The importance of working with your doctor during your toxoplasmosis treatment
- About getting started and the support available to you

Your doctor has prescribed DARAPRIM. Read more about what you can expect during treatment. **Let's get started!**

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ABOUT TOXOPLASMOSIS

What is it and how is it contracted?

- A serious infection caused by a parasite found in cat stool, raw meats, unwashed vegetables, water, and soil.
- A parasite is an organism that lives on or in another (the "host"). Parasites survive by living off of their host.
- Most people who have the parasite will not get seriously ill. However, in some people who have weakened immune systems, the parasite can cause serious illness.
- The parasite most often affects the brain and eyes, but other organs such as the heart and the lungs can also be affected.
- Toxoplasmosis can make you very sick and may even cause death.

INDICATION

DARAPRIM is a prescription medication that contains pyrimethamine, indicated for the treatment of toxoplasmosis when used with a sulfonamide.

NOTE: Do not use DARAPRIM if you:
- are allergic to pyrimethamine or any component of DARAPRIM
- have megaloblastic anemia due to folate deficiency

Not an actual patient

What you need to know:

Toxoplasmosis is an **infection** caused by a parasite that most commonly causes a **serious brain disease** called **encephalitis**.

STARTING TOXOPLASMOSIS TREATMENT

What is DARAPRIM (pyrimethamine)?

DARAPRIM is a pill for the treatment of toxoplasmosis that is used in combination with a sulfonamide (antibiotic). DARAPRIM can cause a side effect (folate deficiency) so your doctor may prescribe another medication (folinic acid) for this purpose.

Your doctor will prescribe the medication that is right for you. It is very important to follow your doctor's treatment plan.

INDICATION

DARAPRIM is a prescription medication that contains pyrimethamine, indicated for the treatment of toxoplasmosis when used with a sulfonamide.

NOTE: DARAPRIM is not for everyone. Do not take DARAPRIM if you are allergic to pyrimethamine or have anemia due to folate deficiency. At the first appearance of a skin rash you should stop use of DARAPRIM and seek medical attention immediately. Other symptoms that may be early indications of serious disorders include sore throat, paleness, and purple spots on skin or swollen tongue.

See pages 8-9 for Important Safety Information

How can I get DARAPRIM?

- ☑ Your doctor will fax your prescription to DARAPRIM Direct's Specialty Mail Order Pharmacy.
- ☑ A Case Manager will call you about available financial assistance programs and to schedule your DARAPRIM delivery.
- ☑ DARAPRIM will be delivered to a convenient location for you.

DON'T FORGET to:

- Provide a reliable phone number to reach you.
- Answer the phone when a Case Manager calls.
- Be available at the appropriate location to sign for the delivery of your DARAPRIM medication.

Please make sure to answer the phone when DARAPRIM Direct's Specialty Mail Order Pharmacy calls.

Not an actual patient

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STAYING ON YOUR TREATMENT PLAN

What happens if you don't take your medicine as prescribed?

It is important to make sure you take your medication as prescribed. If you do not take your medication as directed, your health may worsen.

Life gets busy and routines change, so let your doctor know if you're having trouble taking your medication regularly.

Here are a few tips that can help you stay on top of your treatment:

- **Let your medication become part of your daily routines** so you'll be less likely to forget it.
- **Set an alarm** on your phone, or put a sticky note on your door, to remind you to take your medication with you when you'll be away from home.
- **Answer calls from the Specialty Mail Order Pharmacy** and respond to their refill reminders so you don't run out of pills.
- **Financial help may be available** so that cost does not prevent you from taking your medication.
- **Stay engaged.** If you're taking multiple medications, don't let it become overwhelming. Speak with your doctor about your concerns.

IMPORTANT SAFETY INFORMATION

INDICATION

DARAPRIM is a prescription medication that contains pyrimethamine for the treatment of:

- Toxoplasmosis or acute malaria when used with a sulfonamide (e.g., sulfadoxine)
  - DARAPRIM is not for use by itself to treat acute malaria and only for patients infected in areas where susceptible plasmodia (the parasite that causes malaria) exist. Other medicines such as chloroquine or quinine are preferred for the treatment of acute malaria
- For prevention of malaria when the plasmodia is susceptible. It is not suitable as a prophylactic agent for travelers to most areas since resistance to pyrimethamine is prevalent worldwide

IMPORTANT SAFETY INFORMATION

Do not use DARAPRIM if you:

- are allergic to pyrimethamine or any component of DARAPRIM
- have megaloblastic anemia due to folate deficiency

Taking DARAPRIM may result in allergic reactions that can be severe (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and anaphylaxis). Symptoms of an allergic reaction or the severe reactions may include: fever, body aches, facial or tongue swelling, skin pain, peeling of skin, blisters on your skin and mucous membranes, itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. At the first appearance of a skin rash or any of the above symptoms, stop the medication and immediately seek medical attention. Other signs and symptoms of serious disorders may include sore throat, paleness, tongue changes, and purple skin color.

Make sure to tell your healthcare provider if you have any heart conditions, especially if you experience irregular heartbeat.

The most common side effects that may occur with DARAPRIM include allergic reactions (see above), blood disorders, tongue changes, blood in the urine, heart rhythm disorders, anorexia, and vomiting.

Tell your healthcare provider if you have any side effects while taking DARAPRIM.

Notify your healthcare provider if you become pregnant or intend to become pregnant during therapy or if you intend to breast-feed or are breast-feeding an infant.

Tell your healthcare provider if you have problems with your kidney or liver, decreased intestinal absorption problems, alcoholism, or any other medical conditions.

Make sure you tell your healthcare provider about all of the prescription and non-prescription medications you take, including supplements, and especially sulfonamides or trimethoprim-sulfamethoxazole combination, proguanil (another antimalarial medicine), zidovudine (a medicine to treat Human Immunodeficiency Virus, HIV), or cytostatic agents (medicines that block cell division e.g., methotrexate, a medicine used for cancer or rheumatoid arthritis), phenytoin (a medicine to treat seizures), or lorazepam (a medicine to treat anxiety).

Be sure to take your medicine as instructed. Do not exceed the recommended dosage. You may take DARAPRIM with or without food. However, taking DARAPRIM with food may minimize associated anorexia and vomiting.

Keep out of the reach of infants and children:
Deaths in pediatric patients have been reported after accidental ingestion.

Note: The above information for patients being treated with DARAPRIM is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. Please read the accompanying Full Prescribing Information and talk to your healthcare provider for more information concerning your treatment if you have questions.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. To report SUSPECTED ADVERSE REACTIONS contact Turing Pharmaceuticals at 1-877-258-2033.

Please See Accompanying Full Prescribing Information

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DARAPRIM®
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DARAPRIM DIRECT—A TRUSTED RESOURCE

The DARAPRIM Direct Program was created to help you obtain quick and affordable access to DARAPRIM. Through enrollment in the DARAPRIM Direct program, you may be able to benefit from a range of financial assistance programs.[1]

- Uninsured patients have access to DARAPRIM for **no out-of-pocket** cost through the patient assistance program.
- Through co-pay assistance, patients with commercial insurance are not obligated to pay more than **$10 out-of-pocket** for their DARAPRIM prescription.
- Patients with Medicare Part D insurance coverage have access to an independent charitable foundation that may **assist with affordability** of their disease treatment.

Be sure to sign the patient authorization on the DARAPRIM Enrollment Form (HIPAA form) to allow a Case Manager to assess your eligibility.

[1]Financial assistance programs are subject to terms and conditions and patient eligibility requirements. Restrictions, including where prohibited by law, may apply. Offers are subject to change or discontinuance without notice. Financial assistance programs are not insurance nor are they intended to be a substitute for insurance.

Not actual patients

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ADDITIONAL TOXOPLASMOSIS INFORMATION

CDC

http://www.cdc.gov/parasites/toxoplasmosis/
http://www.cdc.gov/parasites/toxoplasmosis/gen_info/faqs.html
1-800-CDC-INFO (1-800-232-4636)
TTY: 1-888-232-6348

Medicine.net

http://www.medicinenet.com/script/main/mobileart.asp?articlekey=7812

Mayo Clinic

http://www.mayoclinic.org/diseases-conditions/toxoplasmosis/basics/definition/con-20025859

Harvard

http://www.patienteducationcenter.org/articles/toxoplasmosis/

To learn more about DARAPRIM, **visit daraprimdirect.com**

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WHAT YOU NEED TO REMEMBER

You have received a DARAPRIM prescription. Your DARAPRIM Direct's Specialty Mail Order Pharmacy will arrange delivery of your medication and provide information on any financial assistance programs that may be available to you.

How do I get my medication?

Answer your phone when a Case Manager calls to tell you that your medication is ready for delivery.
It is very important that you answer this call so that you can receive your medication.

A Case Manager will schedule when you will receive your medication and at the most convenient location.

Make sure you are available to sign for the delivery of your medication.

How do I take my medication?

- You will likely be prescribed more than one medication as part of your treatment.
- Always take all of the medications as your doctor has directed.
- Finish your full course of therapy even if you are feeling better.

DARAPRIM may cause negative side effects. Speak to your doctor for more information.

How long do I have to take my medication?

Your doctor will determine how long you will need to take DARAPRIM. It is extremely important that you take your medication exactly as your doctor tells you.

What are the 3 most important things I must remember to do to get my medication?

- ☑ Provide a reliable phone number to reach you.
- ☑ Answer the phone when a Case Manager calls.
- ☑ Be available at the appropriate location to sign for the delivery of your DARAPRIM medication.

DON'T FORGET YOUR NEXT APPOINTMENT

Dr _____

Location: _____

Date: _____

Time: _____

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NOTES

DARAPRIM® (pyrimethamine) 25mg tablets | TURING PHARMACEUTICALS

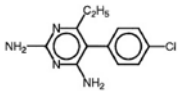
DARAPRIM® (pyrimethamine) 25 mg tablets
Rx Only

PRESCRIBING INFORMATION

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 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 (½ tablet) once weekly

Infants and children under 4 years – 6.25 mg (¼ tablet) once weekly.

HOW SUPPLIED:

White, scored tablets containing 25 mg pyrimethamine, imprinted with "DARAPRIM" and "A3A" in bottles of 100 (NDC 69413-330-10) and bottles of 30 (69413-330-30).

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

REFERENCES

1. Eyles DE, Coleman N. Synergistic effect of sulfadiazine and Daraprim against experimental toxoplasmosis in the mouse. *Antibiot Chemother* 1953;3:483-490.
2. Jacobs L, Melton ML, Kaufman HE. Treatment of experimental ocular toxoplasmosis. *Arch Ophthalmol.* 1964;71:111-118.
3. Jim RTS, Elizaga FV. Development of chronic granulocytic leukemia in a patient treated with pyrimethamine. *Hawaii Med J.* 1977;36:173-176.
4. Sadoff L. Antimalarial drugs and Burkitt's lymphoma. *Lancet.* 1973;2:1262-1263.
5. Bahna L. Pyrimethamine. *LARC Monogr Eval Carcinog Risk Chem.* 1977;13:233-242.
6. Clive D, Johnson KO, Spector JKS, et al. Validation and characterization of the L5178Y/TK +/- mouse lymphoma mutagen assay system. *Mut Res.* 1979;59:61-108.

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