DARAPRIM® (pyrimethamine) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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Description:

Daraprim (pyrimethamine) is an antiparasitic agent indicated for the treatment of toxoplasmosis when used simultaneously with a sulfonamide; for the treatment of acute malaria in combination with a sulfonamide; and for the chemoprophylaxis of malaria due to susceptible strains of plasmodia.

Pyrimethamine is a folic acid antagonist and the rationale for its use is based on the different requirements between host and parasite for nucleic acid precursors involved in growth. This activity is highly selective against plasmodia and Toxoplasma gondii (T. gondii). The action of pyrimethamine against T. gondii is greatly enhanced when used simultaneously with a sulfonamide. Pyrimethamine possesses blood schizonticidal and some tissue schizonticidal activity against malaria parasites of humans.

Malaria is a serious and sometimes fatal disease caused by a parasite that commonly infects a certain type of mosquito. Malaria parasites are micro-organisms that belong to the genus Plasmodium. There are more than 100 species of Plasmodium, which can infect many animal species such as reptiles, birds, and various mammals.
Several species of *Plasmodium* have long been recognized to infect humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*.

Although Daraprim (pyrimethamine) is FDA-approved for acute malaria and malaria prophylaxis, the United States Centers for Disease Control and Prevention (CDC) does not recommend the use of pyrimethamine for these indications. With acute malaria, fast-acting agents such as Chloroquine or Quinine or other agents are preferred. With prophylaxis of malaria, resistance to pyrimethamine is prevalent worldwide and the package label states it is not suitable as a prophylactic agent for travelers to most areas.

Toxoplasmosis is a disease caused by the parasite *T. gondii*. It can infect humans, birds and most warm-blooded animals. The CDC estimates that more than 60 million Americans may be infected with the parasite. But the infection only progresses to illness in individuals with compromised immune systems, such as HIV, cancer, and pregnant women because their immune system is unable to control the parasite. Treatment of immunocompetent adults with lymphadenopathic toxoplasmosis is rarely indicated; this form of the disease is usually self-limited.

Diagnosis of toxoplasmosis is usually made by detection of *Toxoplasma*-specific IgG, IgM, or IgA antibodies. Treatment for ocular diseases should be based on a complete ophthalmologic evaluation. The decision to treat ocular disease is dependent on numerous parameters including acuteness of the lesion, degree of inflammation, visual acuity, and lesion size, and location.

Daraprim (pyrimethamine) is FDA-approved for the treatment of toxoplasmosis. Generic Sulfamethoxazole-Trimethoprim has been used off-label for this condition for several years.

**Definitions:**

**Drug related events:**

**Ineffective / failure**

Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

**Adverse Drug Event:** Allergic reaction / Hypersensitivity / Intolerance

Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.
Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.
DARAPRIM® (pyrimethamine) oral tablet (cont.)

- Precertification for Daraprim (pyrimethamine) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- Initial therapy: FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Daraprim (pyrimethamine) is considered medically necessary when ALL of the following criteria are met:

  1. Medical record documentation of a confirmed diagnosis of ONE of the following:
     - Acute malaria, when used simultaneously with a sulfonamide
     - Chemoprophylaxis of malaria due to susceptible strains of plasmodia
     - Toxoplasmosis, when used simultaneously with a sulfonamide

  2. Individual is unable to use the following:
     - **For acute malaria**: unable to use ALL of the following: Artemether/Lumefantrine, Atovaquone-proguanil, Chloroquine, Hydroxychloroquine, Mefloquine, Primaquine, Quinine, or a compound prescription with pyrimethamine due to ONE of the following:
       - Not effective
       - Experienced intolerant reaction
       - Has a contraindication
       - Organism is resistant

     - **For prophylaxis of malaria**: unable to use ALL of the following: Artemether/Lumefantrine, Atovaquone-proguanil, Chloroquine, Doxycycline, Hydroxychloroquine, Mefloquine, Primaquine, Quinine, or a compound prescription with pyrimethamine due to ONE of the following:
       - Not effective
       - Experienced intolerant reaction
       - Has a contraindication
       - Organism is resistant

     - **For treatment of Toxoplasmosis**: unable to use Atovaquone, Sulfamethoxazole-Trimethoprim, or a compound prescription with pyrimethamine due to ONE of the following:
       - Not effective
       - Experienced intolerant reaction
       - Has a contraindication
       - Organism is resistant

  3. Absence of ALL of the following contraindications:
     - Known hypersensitivity to pyrimethamine or to any component of the formulation
     - Documented megaloblastic anemia due to folate deficiency

- Continuation of coverage (renewal request): Daraprim (pyrimethamine) is considered medically necessary with documentation of ALL of the following:

  1. The individual has benefited from therapy but remains at high risk
2. The condition has not progressed or worsened while on therapy

3. Individual has not developed any contraindications or other exclusions to its continued use

Daraprim (pyrimethamine) for all other indications not previously listed is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

Resources:


2013 CDC: Treatment Guidelines Treatment of Malaria (Guidelines for Clinician)

2013 CDC: Guidelines for the Treatment of Malaria in the United States

2015 CDC, NIH, HIV Med Assoc, IDSA: Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents


FDA-approved indication and dosage:

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<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<td>Treatment of Toxoplasmosis: DARAPRIM is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination.</td>
<td>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 of 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</td>
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sulfapyrimidines 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.

### 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.

### For the 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 the 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 dose 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 period of early recrudescence and late relapse, i.e., for at least 10 weeks in each case.

### 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.

### 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