



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 1/21/2016
LAST REVIEW DATE: 2/17/2022
LAST CRITERIA REVISION DATE: 2/17/2022
ARCHIVE DATE:

DARAPRIM® (pyrimethamine) oral tablet 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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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.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the [request form](#) in its entirety with the chart notes as documentation. **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 or forms without the chart notes will be returned.**



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Criteria:

- **Criteria for initial therapy:** Daraprim (pyrimethamine) and Pyrimethamine is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
 1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Infectious Disease Specialist
 2. A confirmed diagnosis of Toxoplasmosis
 3. When approved, will be used simultaneously with a sulfonamide
 4. Individual has failure, contraindication, intolerance or the organism is proven to be resistant to **ALL** the following preferred step therapy agents:
 - a. Atovaquone
 - b. Sulfamethoxazole-trimethoprim
 - c. A compound prescription with pyrimethamine
 5. There are **NO** FDA-label contraindications:
 - a. Contraindications include:
 - i. Documented megaloblastic anemia due to folate deficiency

Initial approval duration: 2 months

- **Criteria for continuation of coverage (renewal request):** Daraprim (pyrimethamine) and Pyrimethamine is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
 1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Infectious Disease Specialist
 2. Individual's condition has not worsened while on therapy
 - a. Worsening is defined as:
 - i. Continues to have fever, chills, sweats or
 - ii. Confusion, headache, other neurologic deficits or
 - iii. Ocular inflammation has not improved or
 - iv. Dyspnea, cough
 3. The indication for use is one that requires a longer duration than the usual 2 months such as use for treatment of:
 - a. Ocular toxoplasmosis
 - b. Infection in HIV-infected individual with CD4 < 200 cells/mm³ and on ART
 - c. Encephalitis
 - d. Pneumonitis



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- e. Disseminated disease
 - f. Requires maintenance therapy to prevent relapse
 - g. Require primary prevention
4. Individual has been adherent with the medication **and** sulfonamide
5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
- a. Contraindications as listed in the criteria for initial therapy section
 - b. Significant adverse effect such as:
 - i. Hypersensitivity (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, anaphylaxis)
 - ii. Bone marrow suppression
 - iii. Cardiac arrhythmia
6. There are no significant interacting drugs

Renewal duration: 8 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:
1. **Off-Label Use of Non-cancer Medications**
 2. **Off-Label Use of Cancer Medications**

Description:

Daraprim (pyrimethamine) is an antiparasitic agent indicated for the treatment of toxoplasmosis when used simultaneously with a sulfonamide.

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 *Toxoplasma gondii* (*T. gondii*). The action of pyrimethamine against *T. gondii* is greatly enhanced when used simultaneously with a sulfonamide.

Toxoplasmosis is a disease caused by the intracellular protozoan parasite *Toxoplasma gondii* (*T. gondii*). It can infect humans, birds and most warm-blooded animals. Felines are the only animal where *T. gondii* can complete its reproductive cycle where the infectious oocytes are found in the feces.

There are four means of acquiring toxoplasmosis in humans: ingestion of infectious oocysts from the environment; ingestion of tissue cysts in meat from an infected animals or contaminated fruits or vegetables;

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vertical transmission from an infected mother to her fetus; and transmission through an organ transplantation from an infected donor.

The Center for Disease Control (CDC) estimates that more than 60 million Americans may be infected with the parasite. The diagnosis of toxoplasmosis is usually made by detection of *Toxoplasma*-specific IgG, IgM, or IgA antibodies. The infection 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 needed; this form of the disease is usually self-limited and benign. However, some immunocompetent individuals can present as an acute infection or as ocular disease, such as iritis, vitritis or chorioretinitis.

The decision to treat ocular disease is dependent on numerous factors including acuteness of the lesion, degree of inflammation, visual acuity, and lesion size, and location. Treatment for ocular diseases should be based on a complete ophthalmologic evaluation. Ocular toxoplasmosis is treated with the same agents as those used for systemic illness with or without a corticosteroid. Duration of treatment is at least 6 weeks or longer based on resolution of inflammation and retinitis.

Antimicrobial regimens used to treat immunocompetent individuals are the same as those used in immunocompromised patients; however, the duration is shorter for the immunocompetent individual. Daraprim (pyrimethamine) is FDA-approved for the treatment of toxoplasmosis. Generic sulfamethoxazole-trimethoprim (SMX-TMP) has been used off-label for this condition for several years.

- Some suggested regimens for acute infection include:
 - Pyrimethamine plus sulfadiazine plus leucovorin calcium
 - Pyrimethamine plus clindamycin plus leucovorin calcium
 - If pyrimethamine is not available, SMX-TMP (given intravenously or orally twice daily; dosing is based upon the trimethoprim component) can be administered
 - In patients with a sulfonamide allergy, atovaquone alone should be initiated, and sulfa desensitization should be attempted in those **without** a history of a severe reaction (such as Stevens Johnson Syndrome)
 - Patients can then be transitioned to SMX-TMP
 - Alternative regimens include:
 - Pyrimethamine plus atovaquone plus leucovorin calcium
 - Pyrimethamine plus azithromycin plus leucovorin calcium
 - Atovaquone plus sulfadiazine
 - Atovaquone alone
- Dose and duration of each antimicrobial regimen depends on immune status of the individual
 - Duration for immunocompetent is 2-4 weeks
 - Duration for ocular disease is a minimum of 6 weeks
 - Duration for HIV patients is 6 weeks using usual doses for an acute infection, who then are transitioned to secondary maintenance therapy using lower doses
 - Secondary prophylaxis can be discontinued in:
 - Asymptomatic patients who have completed initial therapy



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- If they are receiving Anti-Retroviral Therapy (ART)
- Have a suppressed HIV viral load
- Have maintained a CD4 count > 200 cells/microL (or > 200 mm³) for at least 6 months
- Primary prophylaxis is indicated for patients with HIV and CD4 counts < 100 cells/microL (or < 100 mm³) who are *T. gondii* IgG-positive
 - Pyrimethamine in combination with other agents (it should not be used as monotherapy) an alternative to TMP-SMX
 - Primary prophylaxis can be discontinued if the HIV viral load is suppressed and the CD4 count is > 200 cells/microL (or > 200 mm³) for at least 3 months

Resources:

Daraprim (pyrimethamine) product information, revised by Vvera Pharmaceuticals, LLC. 08-2017. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed December 13, 2021.

Pyrimethamine product information, revised by Dr. Reddys Laboratories, Inc. 02-2020. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed December 13, 2021.

Petersen E. Toxoplasmosis: Acute systemic disease. In: UpToDate, Weller PF, Mitty J (Eds), UpToDate, Waltham MA.: UpToDate Inc. <http://uptodate.com>. Topic last updated November 23, 2021. Accessed December 13, 2021.

Gandhi RT. Toxoplasmosis in patients with HIV. In: UpToDate, Sax PE, Mitty J (Eds), UpToDate, Waltham MA.: UpToDate Inc. <http://uptodate.com>. Topic last updated March 24, 2021. Accessed December 12, 2021.