BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

DARAPRIM® (pyrimethamine) oral
Pyrimethamine oral

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

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. Individual has a confirmed diagnosis of Toxoplasmosis

  3. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic pyrimethamine** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

4. When approved, will be used simultaneously with a sulfonamide or another appropriate alternative to sulfonamide

5. When approved, the medication will be used in combination with leucovorin

6. Individual has failure, contraindication per FDA label, intolerance, is not a candidate for use, or the organism is proven to be resistant to **ALL** the following agents:
    a. Atovaquone
    b. Sulfamethoxazole-trimethoprim
    c. A compound prescription with pyrimethamine

7. The individual does **NOT** have the FDA-label contraindication of 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 **(samples are not considered for continuation of therapy)**:

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 with worsening defined as the following:
    a. Continues to have fever, chills, sweats or
    b. Confusion, headache, other neurologic deficits or
    c. Ocular inflammation has not improved or
    d. Dyspnea, cough

3. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic pyrimethamine** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

4. The indication for use is one that requires a longer duration than the usual 2 months such as use for treatment of **any** of the following:
    a. Ocular toxoplasmosis
    b. Infection in HIV-infected individual with CD4 < 200 cells/mm^3 and on ART
    c. Encephalitis
    d. Pneumonitis
    e. Disseminated disease
    f. Requires maintenance therapy to prevent relapse
    g. Requires primary prevention

5. Individual has been adherent with the medication **and** sulfonamide or another appropriate alternative to sulfonamide

6. When approved, the medication will be used in combination with leucovorin

7. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    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 toxicity such as leukopenia, thrombocytopenia, pancytopenia, neutropenia
        iii. Cardiac arrhythmia

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; 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.

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The decision to treat ocular disease is dependent on numerous factors including acuteness of the lesion, degree if 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 or pyrimethamine plus clindamycin plus leucovorin calcium. If pyrimethamine is not available, sulfamethoxazole/trimethoprim (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 or atovaquone alone.

Dose and duration of each antimicrobial regimen depends on immune status of the individual. Duration for immunocompetent is 2-4 weeks; for ocular disease a minimum of 6 weeks; for HIV patients 6 weeks using usual doses for an acute infection, who then are transitioned to secondary maintenance therapy using lower doses.

Secondary prophylaxis in HIV patients can be discontinued in: asymptomatic patients who have completed initial therapy; those receiving Anti-Retroviral Therapy (ART); those who have a suppressed HIV viral load; and those that have maintained a CD4 count > 200 cells/microL (or > 200 mm^3) for at least 6 months.

Primary prophylaxis is indicated for patients with HIV and CD4 counts < 100 cells/microL (or < 100 mm^3) who are *T. gondii* IgG-positive using 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 mm^3) for at least 3 months

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Daraprim (pyrimethamine) product information, revised by Tilde Sciences, LLC. 12-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 25, 2024.

Pyrimethamine product information, revised by Teva Pharmaceuticals, Inc. 08-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 25, 2024.

Petersen E. Toxoplasmosis: Acute systemic disease. In: UpToDate, Weller PF, White N. (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through November 2024. Topic last updated September 20, 2024. Accessed December 27, 2024.

Gandhi RT. Toxoplasmosis in patients with HIV. In: UpToDate, Sax PE, Mitty J (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Literature current through November 2024. Topic last updated May 31, 2023. Accessed December 27, 2024.