BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/21/16**
SECTION: DRUGS	**LAST REVIEW DATE: 1/18/18**
	LAST CRITERIA REVISION DATE: 1/18/18
	ARCHIVE DATE:

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.

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.**

DARAPRIM® (pyrimethamine) oral tablet (cont.)

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

Toxoplasmosis

- 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
  - Transmission through an organ transplantation from an infected donor
- The CDC estimates that more than 60 million Americans may be infected with the parasite
- 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 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) oral tablet (cont.)

- 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
      - If they are receiving Anti-retroviral Therapy (ART)
      - Have a suppressed HIV viral load
      - 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
      - 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

Daraprim (pyrimethamine)

Medication class:
Antimalarial agent

FDA-approved indication(s):
- Treatment of Toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination

Recommended Dose:
- Toxoplasmosis:
  - Starting dose of 50-75 mg daily with 1-4 g daily of a sulfonamide of the sulfapyrimidine type (sulfadoxime) for 1-3 weeks; then reduce dose of both by 50% and continue for an additional 4-5 weeks
  - The pediatric dose is 1 mg/kg/day divided into 2 equal doses for 2-4 days; then reduce dose to one-half and continue for 1 month. Use the recommended pediatric dose of the sulfonamide.

Maximum dosage
- Not stated

Available Dosage Forms:
- 25 mg scored tablets

Warnings, Precautions and other Clinical Information:
- Simultaneous use of folic acid is strongly recommended when Daraprim is used for treatment of toxoplasmosis in all patients
- If folate deficiency develops, reduce Daraprim dose or discontinue
- Treatment of folate deficiency involves use of folinic acid (leucovorin) doses of 5-15 mg daily (oral, IV, or IM) until normal hematopoiesis is restored
- Discontinue for sore throat, pallor, purpura, or glossitis
- Discontinue if skin rash develops
- Woman of child bearing potential should be warned against becoming pregnant
- When used during pregnancy, simultaneous use of folinic acid is strongly recommended
- Simultaneous use with other anti-folate drugs or agents associated with myelosuppression, such as phenytoin, trimethoprim-sulfamethoxazole, proguanil, zidovudine, or methotrexate increases risk of bone marrow suppression

Criteria:

- **Criteria for initial therapy:** Daraprim (pyrimethamine) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. A confirmed diagnosis of Toxoplasmosis

  2. When approved, will be used simultaneously with a sulfonamide

DARAPRIM® (pyrimethamine) oral tablet (cont.)

3. Individual has failure, contraindication, intolerance or the organism is proven to be resistant to **ALL** the following preferred step therapy agents:
    - Atovaquone
    - Sulfamethoxazole-trimethoprim
    - A compound prescription with pyrimethamine

4. There are **NO** contraindications:
    - Contraindications include:
        - Known hypersensitivity to pyrimethamine or to any component of the formulation
        - Documented megaloblastic anemia due to folate deficiency

Initial approval duration: 2 months

- **Criteria for continuation of coverage (renewal request):** Daraprim (pyrimethamine) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual's condition has not worsened while on therapy
    - Worsening is defined as:
        - Continues to have fever, chills, sweats or
        - Confusion, headache, other neurologic deficits or
        - Ocular inflammation has not improved or
        - Dyspnea, cough

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

3. Individual has been adherent with the medication **and** sulfonamide

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse effect such as:
        - Hypersensitivity (SJS, TEN, EM, anaphylaxis)
            - Signs and symptoms may include: progressive skin rash, hives, blistering, oral ulcers, difficulty breathing, edema of throat, swelling of lips, mouth or tongue
        - Bone marrow suppression
            - Signs and symptoms may include: fever, chills, infection, unexplained bleeding or bruising, or unexplained weakness or shortness of breath

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- Cardiac arrhythmia
  - Signs and symptoms may include: abnormal heart beat, feeling light-headed, faint or experiencing an irregular heartbeat

5. There are no significant interacting drugs

Renewal duration: 8 months

Resources:

Daraprim. Package Insert. Revised by manufacturer 08/2017. Accessed 11-09-17.

Daraprim. Package Insert. Revised by manufacturer 10/2014. Accessed 11-25-2015.

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

Daraprim. Package Insert. Revised by manufacturer 10/2015. Accessed 11-28-2016.

UpToDate: Toxoplasmosis in immunocompetent hosts. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/toxoplasmosis-in-immunocompetent-hosts?source=search_result&search=toxoplasmosis&selectedTitle=2~150#H28186575

UpToDate: Toxoplasmosis in HIV-infected patients. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/toxoplasmosis-in-hiv-infected-patients?source=search_result&search=toxoplasmosis&selectedTitle=1~150

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.