Clinical Policy: Pyrimethamine (Daraprim)

Reference Number: ERX.NPA.44
Effective Date: 12.01.15
Last Review Date: 08.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Pyrimethamine (Daraprim®) is a folic acid antagonist.

FDA Approved Indication(s)
Daraprim is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Daraprim is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Initial Therapy for Toxoplasmosis Infection – Active Disease (must meet all)**:**

1. Diagnosis of toxoplasmosis;
2. Prescribed by or in consultation with an infectious disease or HIV specialist;
3. Member meets one of the following (a or b):
   a. Age < 18 years;
   b. Failure of ≥ 10 days, or radiological deterioration within 7 days, of trimethoprim/ sulfamethoxazole (TMP/SMX), unless contraindicated or clinically significant adverse effects are experienced;
4. Daraprim is prescribed with sulfadiazine or clindamycin, and leucovorin;
5. If request is for the brand product, member must use the generic product, unless contraindicated or clinically significant adverse effects are experienced;
6. Request meets one of the following (a, b, or c):
   a. Immunocompromised member: Dose does not exceed an initial loading dose of 200 mg, followed by ≤ 75 mg per day for treatment duration;
   b. Immunocompetent member: Dose does not exceed an initial loading dose of 100 mg, followed by ≤ 50 mg per day for treatment duration;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

Approval duration:
Congenital toxoplasmosis in newborns – 12 months
All other requests – Duration of request or 8 weeks (whichever is less)

B. Primary Prophylaxis for Toxoplasmosis – Preventing 1st Episode (off-label) (must meet all)**:**

1. Diagnosis of HIV infection;
2. Prescribed by or in consultation with an infectious disease or HIV specialist;
3. Request is for prevention for toxoplasmosis;
4. One of the following (a or b):
   a. Age ≥ 6 years: CD4 count < 100 cells/mm^3;
   b. Age < 6 years: CD4 cell percentage < 15%;

5. Seropositive for *Toxoplasma gondii* IgG;
6. Member is contraindicated or has experienced clinically significant adverse effects to TMP/SMX;
7. Daraprim is prescribed with leucovorin and dapsone;
8. If request is for the brand product, member must use the generic product, unless contraindicated or clinically significant adverse effects are experienced;
9. Dose does not exceed 75 mg per week.

Approval duration: 6 months

C. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Chronic Maintenance – Following Initial Therapy for Active Disease (off-label) (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is HIV-infected with one of the following (a or b):
   a. Age ≥ 6 years: CD4 count ≤ 200 cells/mm^3 at any time in the previous 6 months;
   b. Age < 6 years: CD4 percentage has risen < 15% from baseline at any time in the previous 6 months;
3. Adherence to antiretroviral therapy as evidenced by pharmacy claims history or office notes;
4. If request is for the brand product, member must use the generic product, unless contraindicated or clinically significant adverse effects are experienced;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 50 mg per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

B. Primary Prophylaxis for Toxoplasmosis – Preventing 1st Episode (off-label) (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is HIV-infected with one of the following (a or b):
   a. Age ≥ 6 years: CD4 count ≤ 200 cells/mm^3 at any time in the previous 3 months;
   b. Age < 6 years: CD4 percentage has risen < 15% from baseline at any time in the previous 3 months;
3. Adherence to antiretroviral therapy as evidenced by pharmacy claims history or office notes;
4. If request is for the brand product, member must use the generic product, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 75 mg per week.

Approval duration: 3 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;

B. Malaria.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
HHS: Department of Health and Human Services
HIV: human immunodeficiency virus
TMP/SMX: trimethoprim/sulfamethoxazole

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
trimethoprim/ sulfamethoxazole (Bactrim®, Bactrim® DS)*	Treatment: TMP 5 mg/kg and SMX 25 mg/kg IV or PO BID Primary prophylaxis: 1 DS PO QD (preferred) or 1 DS TIW or 1 SS QD Chronic maintenance: 1 DS PO QD or BID	See regimen

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label uses; dosing recommendations per HHS guidelines*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): documented megaloblastic anemia due to folate deficiency, known hypersensitivity to pyrimethamine or to any component of the formulation
- Boxed warning(s): none reported

Appendix D: General Information

- On June 21, 2017, Daraprim's FDA labeling was updated to exclude the previously approved indications for treatment and chemoprophylaxis of malaria. These uses are not recommended per the CDC malaria treatment guidelines due to prevalent worldwide resistance to pyrimethamine.
- For the treatment of toxoplasmosis, higher doses than what is recommended by the FDA, HHS, and CDC may be required for severe cases or cases affecting sequestered sites such as chorioretinitis.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Treatment of toxoplasmosis	Administered PO in combination with a sulfonamide ± leucovorin; recommended dosing regimen varies per guideline referenced: <u>FDA labeling</u> Adults: 50-75 mg daily for 1-3 weeks depending on the response of the patient and tolerance to therapy, followed by one-half of the initial dose continued for an additional 4 to 5 weeks Pediatrics: 1 mg/kg/day divided into 2 equal daily doses for 2-4 days, followed by one-half of the initial dose continued for approximately 1 month <u>HHS guidelines</u> [*HIV-infected patients*] Initial loading dose of 200 mg, followed by 50 mg/day (if body weight ≤ 60 kg) or 75 mg/day (if body weight > 60 kg) for the remainder of treatment duration	300 mg/day

Indication	Dosing Regimen	Maximum Dose
	CDC guidelines [*ocular toxoplasmosis*] Adult: Initial loading dose of 100 mg, followed by 25-50 mg/day for the remainder of treatment duration (usually 4-6 weeks) Pediatric: Initial loading dose of 2 mg/kg, followed by 1 mg/kg/day for the remainder of treatment duration (usually 4-6 weeks) [*congenital toxoplasmosis*] Newborns: 2 mg/kg per day, divided twice per day for the first 2 days; then from day 3 to 2 months (or 6 months if symptomatic) 1 mg/kg per day, every day; then 1 mg/kg per day 3 times per week for a total of 12 months	
Primary prophylaxis of toxoplasmosis*	50-75 mg/week PO in combination with a sulfonamide Recommended treatment regimen is Daraprim 50 mg per week plus dapsone 50 mg once daily plus leucovorin 25 mg per week or Daraprim 75 mg plus dapsone 200 mg plus plus leucovorin 25 mg weekly	75 mg/week
Chronic maintenance therapy (secondary prophylaxis of toxoplasmosis)*	25-50 mg/day PO in combination with a sulfonamide	50 mg/day

**Off-label uses recommended by the HHS guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents*

VI. Product Availability

Tablet: 25 mg

VII. References

1. Daraprim Prescribing Information. Raleigh, NC: Salix Pharmaceuticals, Inc.; August 2017. Available at: www.daraprimdirect.com. Accessed March 29, 2022.
2. Panel on Opportunistic Infections in HIV-infected Adults and Adolescents. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents - Toxoplasma gondii encephalitis: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Department of Health and Human Services. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/toxoplasma-gondii-encephalitis. Updated July 25, 2017. Accessed March 29, 2022.
3. Panel on Opportunistic Infections in HIV-exposed and HIV-infected Children. Guidelines for prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children – Toxoplasmosis: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection/toxoplasmosis?view=full. Updated October 29, 2015. Accessed March 29, 2022.
4. Global Health - Division of Parasitic Diseases and Malaria. Treatment of malaria: guidelines for clinicians (United States). Centers for Disease Control and Prevention. http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html. Updated November 2, 2020. Accessed March 29, 2022.
5. Sulfamethoxazole/trimethoprim. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed March 29, 2022.

6. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. Antimicrob Agents Chemother. 1998; 42(6): 1346-1349.
7. Global Health - Division of Parasitic Diseases and Malaria. Resources for health professionals: toxoplasmosis. Centers for Disease Control and Prevention. Available at http://www.cdc.gov/parasites/toxoplasmosis/health_professionals/index.html. Updated January 19, 2022. Accessed March 29, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2018 annual review: no significant changes; HIV specialist added as prescriber option; removed recommended regimens from continued criteria and moved to Section V Dosage and Administration; references reviewed and updated.	04.02.18	08.18
3Q 2019 annual review: no significant changes; references reviewed and updated.	04.22.19	08.19
3Q 2020 annual review: added requirement for use of generic products before brand product; for treatment of toxoplasmosis, added additional pathway to allow for higher dosing in unique cases per specialist feedback; references reviewed and updated.	04.20.20	08.20
3Q 2021 annual review: added initial approval duration of 12 months for treatment of congenital toxoplasmosis in newborns per CDC guidelines; revised “medical justification” to “must use” language; added requirement for use of generic to continued criteria; references reviewed and updated.	03.18.21	08.21
For primary prophylaxis initial criteria and for all indications continued therapy criteria, added CD4 percentage requirements for members aged < 6 years per HHS guidelines.	09.22.21	02.22
3Q 2022 annual review: no significant changes; references reviewed and updated.	03.29.22	08.22

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.