Clinical Policy: Pyrimethamine (Daraprim)

Reference Number: PA.CP.PMN.44
Effective Date: 01/2018
Last Review Date: 07/2025

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

FDA approved indication
Daraprim is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination.

Policy/Criteria
** Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria **

It is the policy of PA Health & Wellness® that pyrimethamine 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. Pyrimethamine is prescribed concurrently with sulfadiazine, clindamycin, atovaquone, or azithromycin and leucovorin;
4. For Daraprim requests, member must use pyrimethamine, unless contraindicated or clinically significant adverse effects are experienced;
5. 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 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 or IgM;
6. Member must use TMP-SMX, unless contraindicated or clinically significant adverse effects are experienced;
7. Pyrimethamine is prescribed with leucovorin and dapsone;
8. For Daraprim requests, member must use pyrimethamine, 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 – Refer to PA.CP.PMN.53 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 PA Health & Wellness benefit or member has previously met initial approval criteria, or the Continuity of Care policy applies (*see* PA. PHARM.01);
2. Member is HIV-infected with one of the following (a or b):
   a. Age ≥ 6 years: CD4 counts ≤ 200 cells/mm^3 at any time in the previous 6 months;
   b. Age < 6 years: CD4 counts have risen < 15% from baseline at any time in the previous 6 months;
3. Adherence to antiretroviral therapy (ART) as evidenced by pharmacy claims history or office notes, or medical justification as to why the member is not being treated with ART;
4. For Daraprim requests, member must use pyrimethamine, 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: 12 months

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

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met initial approval criteria, or the Continuity of Care policy applies (*see* PA.PHARM.01);
2. Member is HIV-infected with one of the following (a or b):
   a. Age ≥ 6 years: CD4 counts ≤ 200 cells/mm^3 at any time in the previous 6 months;
   b. Age < 6 years: CD4 counts have risen < 15% from baseline at any time in the previous 6 months;

3. Adherence to antiretroviral therapy (ART) as evidenced by pharmacy claims history or office notes, or medical justification as to why the member is not being treated with ART;
4. For Daraprim requests, member must use pyrimethamine, 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 PA Health & Wellness benefit and documentation supports positive response to therapy, or the Continuity of Care policy applies (*see* PA.PHARM.01); or
2. Refer to PA.CP.PMN.53 if requested indication is NOT listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

Approval duration: duration of request or 6 months (whichever is shorter)

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 – PA.CP.PMN.53 or evidence of coverage documents

B. Malaria

IV. Appendices/General Information

Appendix A: Abbreviation Key

ART: antiretroviral therapy
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 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 <u>CDC guidelines</u> [*immunocompetent patients*] [*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	300 mg/day

Indication	Dosing Regimen	Maximum Dose
	remainder of treatment duration (usually 4-6 weeks) [*congenital toxoplasmosis*] • Infants: 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 dapsone and leucovorin Recommended treatment regimen is pyrimethamine 50 mg per week plus dapsone 50 mg once daily plus leucovorin 25 mg per week or pyrimethamine 75 mg plus dapsone 200 mg plus leucovorin 25 mg weekly	75 mg/week
Chronic maintenance therapy (secondary prophylaxis of toxoplasmosis) †*	25-50 mg/day PO in combination with leucovorin and sulfadiazine (preferred), clindamycin, or atovaquone. Recommended treatment regimen is pyrimethamine 250 – 50 mg PO daily plus sulfadiazine 2,000 – 4,000 mg PO daily (in 2 to 4 divided doses) plus leucovorin 10 – 25 mg PO daily	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

Tablets: 25 mg

VII. References

1. Daraprim Prescribing Information. Jersey City, NJ: Tilde Sciences LLC; October 2023. Available at: www.daraprimdirect.com. Accessed May 9, 2025.
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 September 16, 2024. Accessed May 9, 2025.
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. Updated October 29, 2015. Accessed May 9, 2025.
4. Centers for Disease Control and Prevention. Clinical Guidance: Malaria Diagnosis & Treatment in the U.S. Available at: https://www.cdc.gov/malaria/hcp/clinical-guidanceUpdated June 5, 2024. Accessed May 9, 2025.
5. Merative™ Micromedex® Alternative Medicine (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com. Accessed May 9, 2025.
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. Centers for Disease Control and Prevention. Clinical Care of Toxoplasmosis. Available at: https://www.cdc.gov/toxoplasmosis/hcp/clinical-care/index.html. Updated January 22, 2024. Accessed May 9, 2025.

Reviews, Revisions, and Approvals	Date
3Q 2018 annual review: no significant changes; HIV specialist added as prescriber option; removed recommended regimens from continued criteria; references reviewed and updated.	08/2018
3Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	07/2019
3Q 2020 annual review: added requirement for use of generic products before brand product; references reviewed and updated.	07/2020
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.	07/2021
3Q 2022 annual review: For primary prophylaxis initial criteria and for all indications continued therapy criteria, added CD4 percentage requirements for members aged < 6 years per HHS guidelines; references reviewed and updated.	07/2022
3Q 2023 annual review: added requirement for use of generic to continued criteria for Primary Prophylaxis for Toxoplasmosis and removed prescribed with leucovorin and dapsone; references reviewed and updated.	07/2023
3Q 2024 annual review: no significant changes; references reviewed and updated	07/2024
3Q 2025 annual review: for toxoplasmosis prophylaxis, clarified member must use TMP-SMX unless contraindicated or clinically significant adverse effects are experienced; in continued therapy for chronic maintenance following initial therapy for active disease, increased duration of approval from 6 months to 12 months; in Appendix B, clarified dosing regimen per guideline; updated Section V per guidelines; references reviewed and updated.	07/2025