# Clinical Policy: Pyrimethamine (Daraprim)

Reference Number: PA.CP.PMN.44
Effective Date: 01/2018
Last Review Date: 07/2023

Coding Implications
Revision Log

**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.

**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 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. Daraprim is prescribed with sulfadiazine, clindamycin, atovaquone, or azithromycin and leucovorin;
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, 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 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** – 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.LTSS.PHAR.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. 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 PA Health & Wellness benefit or member has previously met initial approval criteria, or the Continuity of Care policy applies (*see PA.LTSS.PHAR.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. 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 PA Health & Wellness benefit and documentation supports positive response to therapy, or the Continuity of Care policy applies (*see PA.LTSS.PHAR.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
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 for all relevant lines of business 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<br><br>Primary prophylaxis: 1 DS PO QD (preferred) or 1 DS TIW or 1 SS QD<br><br>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:<br><br><u>FDA labeling</u><br>• 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<br>• 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<br><br><u>HHS guidelines</u> [*HIV-infected patients*]<br>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<br><br><u>CDC guidelines</u> [*immunocompetent patients*]<br>[*ocular toxoplasmosis*]<br>• Adult: Initial loading dose of 100 mg, followed by 25-50 mg/day for the remainder of treatment duration (usually 4-6 weeks)<br>• Pediatric: Initial loading dose of 2 mg/kg, followed by 1 mg/kg/day for the remainder of treatment duration (usually 4-6 weeks)<br>[*congenital toxoplasmosis*] | 300 mg/day |

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| | • 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<br><br>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 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

Tablets: 25 mg

## VII. References

1. Daraprim Prescribing Information. Raleigh, NC: Salix Pharmaceuticals, Inc.; August 2017. Available at: www.daraprimdirect.com. Accessed April 13, 2023.
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 May 8, 2023.
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 May 8, 2023.
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 February 14, 2023. Accessed May 8, 2023.

5. Sulfamethoxazole/trimethoprim. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed May 8, 2023.
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 July 13, 2022. Accessed May 8, 2023.

| Reviews, Revisions, and Approvals | Date | Approval 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 | |