Prior Authorization Review Panel

Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 08/01/2021**
Policy Number: PA.CP.PMN.44	**Effective Date: 01/2018** **Revision Date: 07/2021**
Policy Name: Pyrimethamine (Daraprim)	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ✓ **Revised Policy***
- ☐ **Annual Review - No Revisions**
- ☐ **Statewide PDL** - *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

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.

Name of Authorized Individual (Please type or print): **Venkateswara R. Davuluri, MD**	**Signature of Authorized Individual:**

Clinical Policy: Pyrimethamine (Daraprim)

Reference Number: PA.CP.PMN.44
Effective Date: 01/2018
Last Review Date: 07/2021

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 Pennsylvania Health and 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. 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) at maximum indicated doses, unless member experiences clinically significant adverse effects or has contraindication(s) to TMP/SMX;
4. Daraprim is prescribed with sulfadiazine, clindamycin, atovaquone, or azithromycin 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 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. CD4 count < 100 cells/mm^3 (*for age ≥ 6 years*) or CD4 cell percentage < 15% (*for age < 6 years*);
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 Pennsylvania Health and 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 Pennsylvania Health and 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. Daraprim is prescribed with leucovorin and dapsone;
5. Requested dose is ≤ 75 mg per week.

Approval duration: 3 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and 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 Primary prophylaxis: 1 DS PO QD (preferred) or 1 DS TIW or 1 SS QD	See regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Chronic maintenance: 1 DS PO QD or BID	

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*]	300 mg/day

Indication	Dosing Regimen	Maximum Dose
	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

Tablets: 25 mg

VII. References

1. Daraprim Prescribing Information. Raleigh, NC: Salix Pharmaceuticals, Inc.; August 2017. Available at: www.daraprimdirect.com. Accessed March 18, 2021.
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 18, 2021.
3. 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 18, 2021.

4. Sulfamethoxazole/trimethoprim. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed April 21, 2020.
5. 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.
6. 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 May 26, 2020. Accessed March 18, 2021.

Reviews, Revisions, and Approvals	Date	Approval Date
4Q 2018 annual review: no significant changes; HIV specialist added as prescriber option; removed recommended regimens from continued criteria; references reviewed and updated.	08/18	
3Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	07/17/19	
3Q 2020 annual review: added requirement for use of generic products before brand product; references reviewed and updated.	07/20	
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.	07/2021	