Clinical Policy Title:	pyrimethamine
Policy Number:	RxA.88
Drug(s) Applied:	Daraprim®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All Line of Business

Background

Daraprim® is a folic acid antagonist. It is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
pyrimethamine (Daraprim®)	Treatment of toxoplasmosis	Administered in combination with a sulfonamide; recommended dosing regimen varies per guideline referenced: <u>FDA labeling</u> Adults: 50-75 mg daily in combination with a sulfonamide 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>HIV-infected patients</u> 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) in combination with sulfadiazine plus leucovorin	300 mg/day

		Ocular toxoplasmosis Adult: Initial loading dose of 100 mg, followed by 25-50 mg/day plus sulfadiazine and leucovorin Pediatric: Initial loading dose of 2 mg/kg, followed by 1 mg/kg/day plus sulfadiazine and leucovorin	
pyrimethamine (Daraprim®)	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 leucovorin 25 mg weekly	75 mg/week
pyrimethamine (Daraprim®)	Chronic maintenance therapy (secondary prophylaxis of toxoplasmosis) *	25-50 mg/day PO with leucovorin plus sulfadiazine	50 mg/day

Dosage Forms

- Tablet: 25 mg

Clinical Policy

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

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 contraindicated or clinically significant adverse effects are experienced;
4. Daraprim® is prescribed with (a or b)
   a. sulfadiazine or clindamycin or atovaquone or azithromycin, and leucovorin (HIV members)
   b. a sulfonamide (non-HIV members)
5. Doses does not exceed (a or b)
   a. Immunocompromised member: initial loading dose of 200 mg, followed by ≤ 75 mg per day for treatment duration;

b. Immunocompetent member: initial loading dose of 100 mg, followed by ≤ 50 mg per day for treatment duration.

Approval Duration
Commercial: 56 days
Medicaid: 56 days

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/mm3;
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 or atovaquone;
8. Dose does not exceed 75 mg per week.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Chronic Maintenance – Following Initial Therapy for Active Disease (off-label) (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is HIV-infected with CD4 count ≤ 200 cells/mm3 at any time in the previous 6 months;
3. For non-HIV member dose may reduce dose by 50% and continue for 4 to 5 weeks; use with a sulfonamide in combination with leucovorin calcium;
4. Adherence to antiretroviral therapy as evidenced by pharmacy claims history or office notes;
5. Dose does not exceed 50 mg per day.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Primary Prophylaxis for Toxoplasmosis – Preventing 1st Episode (off-label) (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is HIV-infected with CD4 count ≤ 200 cells/mm3 at any time in the previous 3 months;
3. Adherence to antiretroviral therapy as evidenced by pharmacy claims history or office notes;
4. Dose does not exceed 75 mg per week.

Approval Duration
Commercial: 3 months
Medicaid: 3 months

III. Appendices

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

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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 once daily (preferred) or 1 DS TIW or 1 SS once daily Chronic maintenance: 1 DS PO once daily 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):
  - Daraprim® is contraindicated in patients with known hypersensitivity to pyrimethamine or to any component of the formulation. Use of the drug is also contraindicated in patients with documented megaloblastic anemia due to folate deficiency.

- 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.
- The concomitant use of other antifolic drugs or agents associated with myelosuppression including sulfonamides or trimethoprim- sulfamethoxazole combinations, proguanil, zidovudine, or cytostatic agents (e.g., methotrexate), while the patient is receiving pyrimethamine, may increase the risk of bone marrow suppression.
- If signs of folate deficiency develop, pyrimethamine should be discontinued. Folinic acid (leucovorin) should be administered until normal hematopoiesis is restored.
- Mild hepatotoxicity has been reported in some patients when lorazepam and pyrimethamine were administered concomitantly.

References

1. Daraprim® Prescribing Information. Raleigh, NC: Salix Pharmaceuticals, Inc.; August 2017. Available at: https://www.daraprimdirect.com/. Accessed February 02, 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/introduction. Updated May 29, 2018. Accessed February 02, 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 April 2019. Accessed February 02, 2021.
4. Sulfamethoxazole/trimethoprim. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed February 02, 2021.
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): 13461349.
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 October 26, 2018. Accessed February 02, 2021.
7. Pyrimethamine. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed February 02, 2021.
8. Daraprim®, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed March 05, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy was established	01/2020	02/07/2020
Updated dosing regimens, availability, and formatting	04/2020	
Policy was reviewed: 1. Clinical policy title table was updated. 2. Drug(s) applied was updated. 3. Line of Business Policy Applies to was update to all lines of business. 4. Dosing information was updated for indication. 5. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 6. Initial approval criteria updated for toxoplasmosis infection for 56 days instead of “whichever is less….” 7. Appendix B: "Therapeutic alternatives verbiage was updated to below are suggested therapeutic alternatives based on clinical	02/05/2021	03/09/2021

guidance...." 8. Appendix C contraindication updated. 9. Appendix D updated. 10. References were reviewed and updated. 11. HIV dosing regimen updated to: 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) in combination with sulfadiazine plus leucovorin.		