Clinical Policy: Pyrimethamine (Daraprim)

Reference Number: PA.CP.PMN.44
Effective Date: 01/18
Last Review Date: 11/16
Line of Business: Medicaid

Coding Implications
Revision Log

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

FDA approved indication
- Treatment of toxoplasmosis when used conjointly with a sulfonamide
- Treatment of acute malaria when used conjointly with a sulfonamide
- Chemoprophylaxis of malaria due to susceptible strains of plasmodia
  Limitation of use: Resistance to pyrimethamine is prevalent worldwide. It is not suitable as a prophylactic agent for travelers to most areas.

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 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. Doses should not exceed the following recommendations:
   - Immunocompromised member: initial loading dose should NOT exceed 200mg, followed by ≤ 75mg per day for treatment duration;
   - Immunocompetent member: initial loading dose should NOT exceed 100mg, followed by ≤ 50mg per day for treatment duration.

Approval duration: duration of request or 8 weeks (whichever is shorter)

B. Primary Prophylaxis for Toxoplasmosis – Preventing 1st Episode (must meet all)**:**
1. Diagnosis of HIV infection and both of the following:
   a. CD4 counts < 100 cells/mm^3 (*for age ≥ 6 years*) or CD4 cell percentage < 15% (*for age < 6 years*);
   b. Seropositive for *Toxoplasma gondii* IgG;

2. Prescribed by or in consultation with an infectious disease specialist;
3. Request is for prevention for toxoplasmosis;
4. Member experiences clinically significant adverse effects or has contraindication(s) to TMP/SMX;
5. Daraprim is prescribed with leucovorin and dapsone;
6. Requested dose is ≤ 75 mg per week along with leucovorin and dapsone.
   *Recommended treatment regimen is dapsone (50 mg once daily) plus pyrimethamine (Daraprim) (50 mg per week) plus leucovorin (25 mg per week) *or* dapsone 200 mg plus pyrimethamine (Daraprim) 75 mg plus leucovorin 25 mg weekly.

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 (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 CD4 counts < 200 cells/mm^3 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 sulfadiazine or clindamycin, and leucovorin;
5. Request does not exceed 50 mg per day.

Approval duration: 6 months

B. Primary Prophylaxis for Toxoplasmosis – Preventing 1st Episode (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 CD4 counts < 200 cells/mm^3 at any time in the previous 3 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.
   Recommended treatment regimen is dapsone (50 mg once daily) plus pyrimethamine (Daraprim) (50 mg per week) plus leucovorin (25 mg per week) or dapsone 200 mg plus pyrimethamine (Daraprim) 75 mg plus leucovorin 25 mg weekly.

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 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. Treatment and chemoprophylaxis of malaria†

†*Although FDA approved indications, these uses are not recommended per the CDC malaria treatment guidelines due to prevalent worldwide resistance to pyrimethamine.*

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

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

V. Dosage and Administration

Daraprim should be administered orally in combination with a sulfonamide.

Per the FDA labeling for Daraprim, dosing recommendations are:

Indication	Population	Recommended Dose
Treatment	Adult	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
	Pediatric	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

Although the FDA labeling does not distinguish treatment of immunocompromised versus immunocompetent patients, the recommended dosing for these populations can vary per practice guidelines. Alternative acceptable dosing regimens are as follows:

- Per the HHS guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents, Daraprim dosing recommendations in *HIV-infected patients* are:

Indication	Population	Recommended Dose
Primary prophylaxis	Adults, adolescents	50-75 mg/week
Treatment		Initial loading dose of 200 mg, followed by 50-75 mg/day for the remainder of treatment duration

Chronic maintenance therapy (secondary prophylaxis)		25-50 mg/day

- Per the CDC guidelines for toxoplasmosis, Daraprim dosing recommendations in *immunocompetent patients* are:

Indication	Population	Recommended Dose
Treatment	Adult	Initial loading dose of 100 mg, followed by 25-50 mg/day for the remainder of treatment duration
	Pediatric	Initial loading dose of 2 mg/kg, followed by 1 mg/kg/day for the remainder of treatment duration

VI. Product Availability

Tablets: 25 mg

VII. References

1. Daraprim Prescribing Information. Raleigh, NC: Salix Pharmaceuticals, Inc.; October 2015. Available at: www.daraprimdirect.com. Accessed September 7, 2016.
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: 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://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/0. Updated August 17, 2016. Accessed September 7, 2016.
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 July 2013. Accessed September 7, 2016.
4. Sulfamethoxazole/trimethoprim. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed September 7, 2016.
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 16, 2016. Accessed September 7, 2016.

Reviews, Revisions, and Approvals	Date	Approval Date