Clinical Policy: Pyrimethamine (Daraprim)

Reference Number: CP.PMN.44
Effective Date: 11.01.15
Last Review Date: 08.19
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Pyrimethamine (Daraprim®) is a folic acid antagonist.

FDA Approved Indication(s)

Daraprim is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide.

Policy/Criteria

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

It is the policy of health plans affiliated with Centene Corporation® 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 contraindicated or clinically significant adverse effects are experienced;
4. Daraprim is prescribed with sulfadiazine or clindamycin, and leucovorin;
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: 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;

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;
8. Dose does not exceed 75 mg per week.

Approval duration: 6 months

C. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Chronic Maintenance – Following Initial Therapy for Active Disease (off-label) (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is HIV-infected with CD4 count ≤ 200 cells/mm^3 at any time in the previous 6 months;
3. Adherence to antiretroviral therapy as evidenced by pharmacy claims history or office notes;
4. Dose does not exceed 50 mg per day.

Approval duration: 6 months

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is HIV-infected with CD4 count ≤ 200 cells/mm^3 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: 3 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents;

B. Malaria.

IV. Appendices/General Information

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

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 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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Treatment of toxoplasmosis	Administered in combination with a sulfonamide; recommended dosing regimen varies per guideline referenced: FDA labeling 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 HHS guidelines [*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 CDC guidelines [*ocular toxoplasmosis*] 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	300 mg/day
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 April 22, 2019.
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://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/322/toxo. Updated July 25, 2017. Accessed April 22, 2019.
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 April 22, 2019.
4. Sulfamethoxazole/trimethoprim. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed April 22, 2019.
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 October 26, 2018. Accessed April 22, 2019.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Guideline created.	11.15	11.15
Converted to new integrated template. Updated verbiage and references. -Initial therapy for active disease: Modified TMP/SMX trial duration to be at least 10 days (vs range of 10-14 days) for failure (i.e., lack of clinical improvement) and within 7 days for radiological deterioration. Modified approval duration to up to 8 weeks for all members (vs 6 weeks for immunocompromised and 4 weeks for immunocompetent) per FDA labeling as well as literature review that indicates treatment duration may take longer than 6 and 4 weeks for these populations. -Primary prophylaxis: For initial criteria, modified to allow coverage for members who have experienced clinically significant adverse effects (vs only contraindications) to TMP/SMX. For continued criteria, added requirement of adherence to ART. -Chronic maintenance: Removed criteria requiring patient to be < 18 years or have documented failure/contraindication to TMP/SMX as	09.16	11.16

Reviews, Revisions, and Approvals	Date	P&T Approval Date
this is already assessed in the initial criteria, and the continued criteria requires member to be currently receiving Daraprim through Centene benefit.		
Converted to new template. Daraprim is no longer indicated for malaria as of 06/2017; updated policy to reflect this. Continued therapy: Corrected CD4 requirement from < 200 cells/mm^3 to ≤ 200 cells/mm^3 per guidelines.	07.05.17	11.17
3Q 2018 annual review: policies combined for Centene Medicaid, HIM and Commercial lines of business; no significant changes from previously approved corporate policy; all: HIV specialist added as prescriber option; Medicaid/HIM: removed recommended regimens from continued criteria; Commercial: added trial of TMP/SMX (unless age < 18 years) for treatment of toxoplasmosis, added recommended regimens to initial criteria, off-label coverage for chronic maintenance treatment added and max doses modified per guidelines, modified approval durations from 12 weeks to 8 weeks/6 months and 6 months/3 months per guidelines; references reviewed and updated.	04.02.18	08.18
3Q 2019 annual review: no significant changes; references reviewed and updated.	04.22.19	08.19

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

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