

Clinical Policy: Pyrimethamine (Daraprim)

Reference Number: CP.PMN.44

Effective Date: 11.01.15

Last Review Date: 08.23

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. 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. One of the following (a or b):
 - a. Age \geq 6 years: CD4 count $<$ 100 cells/mm³;
 - b. Age $<$ 6 years: CD4 cell percentage $<$ 15%;
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. 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 (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 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. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
2. Member is HIV-infected with one of the following (a or b):
 - a. Age \geq 6 years: CD4 count \leq 200 cells/mm³ at any time in the previous 6 months;

- b. Age < 6 years: CD4 percentage has risen < 15% from baseline at any time in the previous 6 months;
3. Adherence to antiretroviral therapy as evidenced by pharmacy claims history or office notes;
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. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
2. Member is HIV-infected with one of the following (a or b):
 - a. Age ≥ 6 years: CD4 count ≤ 200 cells/mm³ at any time in the previous 3 months;
 - b. Age < 6 years: CD4 percentage has risen < 15% from baseline at any time in the previous 3 months;
3. Adherence to antiretroviral therapy as evidenced by pharmacy claims history or office notes;
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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line

of business: CP.CPA.09 for commercial, HIM.PA.154 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.PA.154 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.

- 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	<p>Administered PO in combination with a sulfonamide ± leucovorin; recommended dosing regimen varies per guideline referenced:</p> <p><u>FDA labeling</u></p> <ul style="list-style-type: none"> • 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 <p><u>HHS guidelines [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) for the remainder of treatment duration</p> <p><u>CDC guidelines</u> <i>[ocular toxoplasmosis]</i></p> <ul style="list-style-type: none"> • 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) <p><i>[congenital toxoplasmosis]</i></p> <ul style="list-style-type: none"> • 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 	300 mg/day
Primary prophylaxis of toxoplasmosis*	<p>50-75 mg/week PO in combination with a sulfonamide</p> <p>Recommended treatment regimen is Daraprim 50 mg per week plus dapsone 50 mg once daily plus</p>	75 mg/week

Indication	Dosing Regimen	Maximum Dose
	leucovorin 25 mg per week <u>or</u> Daraprim 75 mg plus dapsone 200 mg plus leucovorin 25 mg weekly	
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

Tablet: 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	P&T Approval Date
3Q 2019 annual review: no significant changes; references reviewed and updated.	04.22.19	08.19
3Q 2020 annual review: added requirement for use of generic products before brand product; for treatment of toxoplasmosis, added additional pathway to allow for higher dosing in unique cases per specialist feedback; references reviewed and updated.	04.20.20	08.20
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 to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	03.18.21	08.21
For primary prophylaxis initial criteria and for all indications continued therapy criteria, added CD4 percentage requirements for members aged < 6 years per HHS guidelines.	09.22.21	02.22
3Q 2022 annual review: no significant changes; references reviewed and updated.	03.29.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.07.22	
3Q 2023 annual review: no significant changes; references reviewed and updated.	04.13.23	08.23

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.

©2015 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene[®] and Centene Corporation[®] are registered trademarks exclusively owned by Centene Corporation.