Original Effective Date: 10/01/2015
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Last P&T Approval/Version: 01/31/2024
Next Review Due By: 01/2025
Policy Number: C8631-A

Daraprim (pyrimethamine)

PRODUCTS AFFECTED

Daraprim (pyrimethamine), pyrimethamine

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Treatment of toxoplasmosis, Prophylaxis of pneumocystis pneumonia in HIV patients, treatment of toxoplasmosis in HIV patients, Prophylaxis of toxoplasmosis in HIV patients, Cystoisosporiasis (formerly Isosporiasis) in patients with HIV

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PRIMARY PROPHYLAXIS OF TOXOPLASMOSIS:
1. Documentation of a confirmed positive test for toxoplasmosis gondii IgG antibodies
AND

2. Documentation that member has a diagnosis of HIV/AIDS
   AND
3. Documentation that member has a CD4 count <100 cell/µL
   AND
4. Documentation that member has tried/failed or absolute contraindication to the recommended first line agent trimethoprim-sulfamethoxazole (TMP-SMX)
   AND
5. Documentation providing rationale that member is not an appropriate candidate for atovaquone 1500mg once daily
   AND
6. Prescriber attestation pyrimethamine will be used as part of combination therapy regimen (See Appendix)

B. AIDS ASSOCIATED CNS TOXOPLASMOSIS:

1. Documentation of confirmed positive serum test for toxoplasmosis gondii IgG antibodies
   AND
2. Documentation that member has a diagnosis of HIV/AIDS
   AND
3. Documentation that member has a CD4 count <100cell/µL
   AND
4. Documentation that member has clinical syndrome of headache, fever and neurological symptoms present AND brain imaging (CT or MRI) demonstrates typical radiographic ring-enhancing lesions
   AND
5. Prescriber attestation that pyrimethamine will be used in combination with sulfadiazine and leucovorin per FDA label or guideline recommended combination therapy

C. AIDS RELATED CHRONIC MAINTENANCE THERAPY OF TOXOPLASMOSIS:

1. Documentation member completed six weeks of active treatment for AIDS-related toxoplasmosis
   AND
2. Documentation that a CT scan or MRI showed improvement in the ring-enhancing lesions prior to initiating maintenance therapy AND documented improvement in clinical symptoms in physical exam
   AND
3. Documentation that pyrimethamine will be used in combination with sulfadiazine and leucovorin per FDA label or guideline recommended combination therapy

D. NON-AIDS RELATED TOXOPLASMOSIS:

1. Documented diagnosis of acquired or congenital toxoplasmosis
   AND
2. Documentation that pyrimethamine is being used in combination with sulfadiazine and leucovorin

E. PNEUMOCYSTIS PNEUMONIA PROPHYLAXIS:

1. (a) Documentation that member has a diagnosis of HIV/AIDS AND Documentation that member has a CD4 count <200 cell/µL
   OR
   (b) Prescriber attests member is at high risk of infectious complication due to hematopoietic cell transplant or chemotherapy regimen
   AND
2. Documentation of inadequate treatment response, serious side effects, contraindication, or non-susceptibility to a first-line agent trimethoprim-sulfamethoxazole (TMP-SMX)
   AND
3. Prescriber attestation pyrimethamine will be used as part of combination therapy regimen

F. CYSTOISOSPORIASIS (FORMERLY ISOSPORIASIS) TREATMENT AND SECONDARY PREVENTION:
1. Documentation that member has a diagnosis of Cystoisosporiasis confirmed by fecal specimen
AND
2. Documentation that member has a contraindication to use of TMP-SMX AND ciprofloxacin

CONTINUATION OF THERAPY:

A. PRIMARY PROPHYLAXIS OF TOXOPLASMOSIS:
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Documentation that CD4 counts have NOT been greater than 200 cells/µL for at least 3 months
AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

B. AIDS ASSOCIATED CNS TOXOPLASMOSIS:
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Documentation of improvement on brain imagining (CT or MRI) and of clinical symptoms
AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

C. AIDS RELATED CHRONIC MAINTENANCE THERAPY OF TOXOPLASMOSIS:
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Documentation that CD4 counts have NOT been greater than 200 cells/µL for at least 3 months
AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

D. ALL OTHER INDICATIONS:
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition’s signs and symptoms
AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

PRIMARY PROPHYLAXIS OF TOXOPLASMOSIS: Initial authorization: 6 months, Continuation of Therapy: 6 months
AIDS ASSOCIATED CNS TOXOPLASMOSIS: Initial authorization: 3 months, Continuation of Therapy: 3 months
AIDS RELATED CHRONIC MAINTENANCE THERAPY OF TOXOPLASMOSIS: Initial authorization: 12 months, Continuation of Therapy: 12 months

NON-AIDS RELATED TOXOPLASMOSIS: Initial authorization: 3 months, Continuation of Therapy: 3 months
PNEUMOCYSTIS PNEUMONIA PROPHYLAXIS: Initial authorization: 12 months, Continuation of Therapy:12 months
CYSTOISOSPORIASIS (FORMERLY ISOSPORIASIS) TREATMENT AND SECONDARY PROPHYLAXIS: Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with an infectious disease specialist, neurologist or HIV specialist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
None

QUANTITY:
Dosage, frequency, and total treatment duration must be supported by FDA label or compendia supported dosing for prescribed indication

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Antimalarial

FDA-APPROVED USES:
DARAPRIM is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination.

COMPENDIAL APPROVED OFF-LABELED USES:
Prophylaxis of pneumocystis pneumonia in HIV patients, Treatment of toxoplasmosis in HIV patients, Prophylaxis of toxoplasmosis in HIV patients, Cystoisosporiasis (formerly Isosporiasis) in patients with HIV

APPENDIX

APPENDIX:
National Institutes of Health, the Centers for Disease Control and Prevention, and the HIV Medicine Association of the Infectious Diseases Society of America Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV
Preventing 1st Episode of Toxoplasma gondii Encephalitis (Primary Prophylaxis)
Indications for Initiating Primary Prophylaxis:
• Toxoplasma IgG positive patients with CD4 count <100 cells/mm3 (AIII)
NOTE: All the recommended regimens for preventing 1st episode of toxoplasmosis are also effective in preventing PCP
Preferred Regimen:

• TMP-SMX 1 DS PO daily (AII)

Alternative Regimens:

• TMP-SMX 1 DS PO three times weekly (BIII), or
• TMP-SMX SS PO daily (BIII), or
• Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly (BI), or
• (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly (BI), or
• Atovaquone 1500 mg PO daily (CIII), or
• (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily (CIII)

Indication for Discontinuing Primary Prophylaxis:

• CD4 count >200 cells/mm3 for >3 months in response to ART (AI); or
• Can consider if CD4 count is 100-200 cells/mm3 and HIV RNA levels remain below limits of detection for at least 3-6 months (BII).

Indication for Restarting Primary Prophylaxis:

• CD4 count <100-200 cells/mm3 (AIII)

Treating Toxoplasma gondii Encephalitis

Preferred Regimen (AI):

• Pyrimethamine 200 mg PO once, followed by dose based on body weight:
  Body weight ≤60 kg:
    • pyrimethamine 50 mg PO daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)
  Body weight >60 kg:
    • pyrimethamine 75 mg PO daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)
  Note: if pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (BI). For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies (BI) Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved (CIII).

Alternative Regimens:

• Pyrimethamine (leucovorin) plus clindamycin 600 mg IV or PO q6h (AI); preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine-sulfadiazine; must add additional agent for PCP prophylaxis, or
• TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID (BI), or
• Atovaquone 1500 mg PO BID + pyrimethamine (leucovorin) (BII), or
• Atovaquone 1500 mg PO BID + sulfadiazine (BII), or
• Atovaquone 1500 mg PO BID (BII), or

Total Duration for Treating Acute Infection:

• At least 6 weeks (BII); longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks
• After completion of the acute therapy, all patients should be continued on chronic maintenance therapy as outlined below

Chronic Maintenance Therapy for Toxoplasma gondii Encephalitis

Preferred Regimen:

• Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily (AI)

Alternative Regimen:

• Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily (BI); must add additional agent to prevent PCP (AII), or
• TMP-SMX DS 1 tablet BID (BII), or
• TMP-SMX DS 1 tablet daily (BII), or
• Atovaquone 750–1500 mg PO BID + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily, or
• Atovaquone 750–1500 mg PO BID + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) (BII), or
• Atovaquone 750–1500 mg PO BID (BII)

Discontinuing Chronic Maintenance Therapy:

• Successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and CD4

count >200 cells/mm3 for >6 months in response to ART (BI)

Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance

• CD4 count <200 cells/mm3 (AIII)

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Daraprim® (pyrimethamine) is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination. Daraprim is also indicated for the treatment of acute malaria. It should not be used alone to treat acute malaria. Fast-acting schizonticides such as chloroquine or quinine are indicated and preferable for the treatment of acute malaria. However, conjoint use of Daraprim with a sulfonamide (e.g., sulfadoxine) will initiate transmission control and suppression of susceptible strains of plasmodia. In addition, Daraprim is indicated for the chemoprophylaxis of malaria due to susceptible strains of plasmodia. However, resistance to pyrimethamine is prevalent worldwide. It is not suitable as a prophylactic agent for travelers to most areas. The use of Daraprim for the treatment or prophylaxis of malaria is no longer recommended in the CDC Guidelines for the Treatment of Malaria in the United States. For the treatment of malaria, contact the CDC Malaria Hotline: (770) 488-7788 or (855) 856-4713 toll-free Monday-Friday 9 am to 5 pm EST.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Daraprim (pyrimethamine) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Daraprim (pyrimethamine) include: 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.

OTHER SPECIAL CONSIDERATIONS:

Daraprim is available through the Daraprim Direct Program. See daraprimdirect.com for details.
If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (BI). For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies (BI). Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved (CIII).

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:

Daraprim TABS 25MG
Pyrimethamine TABS 25MG

REFERENCES

1. Daraprim [Package Insert]. New York, NY: Vyera Pharmaceuticals; August 2017.
2. Centers for Disease Control and Prevention. Treatment of Malaria (Guidelines For Clinicians): http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf
3. Centers for Disease Control and Prevention. CDC Health Information for International Travel 2016. New York: Oxford University Press; 2016. Accessed January 9, 2018:

http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-totravel/malaria#4904
4. Daraprim How to Prescribe Information. Accessed January 9,2018:http://www.daraprimdirect.com/how-to-prescribe
5. Department of Health and Human Services. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.: https://aidsinfo.nih.gov/guidelines/html/4/adult-and- adolescent-oi-prevention-and- treatment guidelines/322/toxo
6. Department of Health and Human Services. Guidelines for the Prevention and treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children.: https://aidsinfo.nih.gov/guidelines/html/5/pediatric-oi-prevention-and- treatment guidelines/418/toxoplasmosis
7. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. National Institutes of Health, Centers for Disease Control and Prevention, and the HIV Medicine Association of the Infectious Disease Society of America. Toxoplasma gondii Encephalitis. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-oi/toxoplasma- gondii-encephalitis-adult-adolescent-oi.pdf. Accessed 23 December 2022.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy	Q1 2024
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy Appendix Other Special Considerations References	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file