Drug Coverage Policy

Effective Date.....6/15/2024
Coverage Policy Number.....IP0348
Policy Title.....Pyrimethamine

Infectious Disease – Pyrimethamine

- Daraprim® (pyrimethamine tablets – Vyera, generic)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

OVERVIEW

Pyrimethamine tablets (Daraprim, generic), a folic acid antagonist, are indicated for the treatment of **toxoplasmosis** when used conjointly with a sulfonamide, since synergism exists with this combination.[1]

Pyrimethamine tablets are considered to be the most effective drug against toxoplasmosis and are a standard component of therapy.[2] Leucovorin, a folinic acid, protects the bone marrow from the toxic effects of pyrimethamine and is prescribed in conjunction with pyrimethamine.

Guidelines

The Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with Human Immunodeficiency (HIV) [last updated September 2023] recommend pyrimethamine tablets as the drug of choice for treatment and chronic maintenance treatment (secondary prophylaxis) of *Toxoplasma gondii* encephalitis.[3] Pyrimethamine tablets are recommended as an option for: primary prophylaxis of *Toxoplasma gondii* encephalitis; primary prophylaxis and secondary prophylaxis (chronic maintenance treatment) of *Pneumocystis* pneumonia; and secondary prophylaxis (chronic maintenance treatment) and treatment of cystoisosporiasis (formerly isosporiasis). The drug of choice for these conditions is trimethoprim-sulfamethoxazole.

Medical Necessity Criteria

Pyrimethamine tablets (Daraprim, generic) are considered medically necessary when ONE of the following is met (1, 2, 3, 4, 5, 6, or 7):

FDA-Approved Indication

1. **Toxoplasmosis – Treatment.** Approve for 1 year if the patient meets the following (A, B, C and D):
   - **A)** The medication is prescribed in combination with leucovorin; AND
   - **B)** Patient meets one of the following (i or ii):
     - **i.** The medication is prescribed in combination with sulfadiazine; OR
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Patient is unable to take sulfadiazine; AND
       - **b)** Patient meets one of the following (1 or 2):
         - **(1)**The medication is prescribed in combination with systemic clindamycin; OR
         - **(2)**The medication is prescribed in combination with atovaquone; AND
   - **C)** The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.
   - **D)** Preferred product criteria is met for the product(s) as listed in the below table(s)

Other Uses with Supportive Evidence

2. **Cystoisosporiasis (formerly known as isosporiasis) – Secondary Prophylaxis (Chronic Maintenance Treatment).** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient has tried at least one other therapy for this condition; AND
     Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole and systemic ciprofloxacin.
   - **B)** The medication is prescribed in combination with leucovorin; AND
   - **C)** The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.
   - **D)** Preferred product criteria is met for the product(s) as listed in the below table(s)

3. **Cystoisosporiasis (formerly known as isosporiasis) – Treatment.** Approve for 1 year if the patient meets the following (A, B, C, and D):
   - **A)** Patient has tried at least one other therapy for this condition; AND
     Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole and systemic ciprofloxacin.

B) The medication is prescribed in combination with leucovorin; AND
C) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.
D) Preferred product criteria is met for the product(s) as listed in the below table(s)

4. ***Pneumocystis*** **Pneumonia – Primary Prophylaxis.** Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient has tried at least one other therapy for this condition; AND
Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole, systemic dapsone, aerosolized pentamidine (via Respigard II™ nebulizer), and atovaquone.
B) The medication is prescribed in combination with leucovorin; AND
C) Patient meets one of the following (i or ii):
i. The medication is prescribed in combination with systemic dapsone; OR
ii. The medication is prescribed in combination with atovaquone; AND
D. The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.
E. Preferred product criteria is met for the product(s) as listed in the below table(s)

5. ***Pneumocystis*** **Pneumonia – Secondary Prophylaxis (Chronic Maintenance Therapy).** Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient has tried at least one other therapy for this condition; AND
Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole, systemic dapsone, aerosolized pentamidine (via Respigard II™ nebulizer), and atovaquone.
B) The medication is prescribed in combination with leucovorin; AND
C) Patient meets one of the following (i or ii):
i. The medication is prescribed in combination with systemic dapsone; OR
ii. The medication is prescribed in combination with atovaquone; AND
D) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.
E) Preferred product criteria is met for the product(s) as listed in the below table(s)

6. ***Toxoplasma gondii*** **Encephalitis – Primary Prophylaxis.** Approve for 1 year if the patient meets the following (A, B, C, D, and E):
A) Patient has tried at least one other therapy for this condition; AND
Note: Examples of other therapies used for this condition include trimethoprim-sulfamethoxazole and atovaquone.
B) The medication is prescribed in combination with leucovorin; AND
C) Patient meets one of the following (i or ii):
i. The medication is prescribed in combination with systemic dapsone; OR
ii. The medication is prescribed in combination with atovaquone; AND
D) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.
E) Preferred product criteria is met for the product(s) as listed in the below table(s)

7. ***Toxoplasma gondii*** **Encephalitis – Secondary Prophylaxis (Chronic Maintenance Therapy).** Approve for 1 year if the patient meets the following (A, B, C, and D):
A) The medication is prescribed in combination with leucovorin; AND
B) Patient meets one of the following (i or ii):
i. The medication is prescribed in combination with sulfadiazine; OR
ii. Patient meets both of the following (a and b):
a) Patient is unable to take sulfadiazine; AND

b) Patient meets one of the following (1 or 2):
(1) The medication is prescribed in combination with systemic clindamycin; OR
(2) The medication is prescribed in combination with atovaquone; AND

C) The medication is prescribed by or in consultation with an infectious diseases specialist or a physician specializing in the treatment of human immunodeficiency virus (HIV) infection.

D) Preferred product criteria is met for the product(s) as listed in the below table(s)

Employer Plans:

Product	Criteria
Daraprim tablets (pyrimethamine)	The patient has tried the bioequivalent generic product, **pyrimethamine tablets**, AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

Individual and Family Plans:

Product	Criteria
Daraprim tablets (pyrimethamine)	The patient has tried the bioequivalent generic product, **pyrimethamine tablets**, AND cannot take due to a formulation difference in the inactive ingredient(s) [for example, difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which, per the prescriber, would result in a significant allergy or serious adverse reaction.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Malaria – Chemoprophylaxis or Treatment.** Pyrimethamine is no longer indicated for the treatment of acute malaria or for chemoprophylaxis of malaria.[1]

References

1. Daraprim® tablets [prescribing information]. New York, NY: Vyera; August 2017.
2. Centers for Disease Control and Prevention – Toxoplasmosis. Available at: https://www.cdc.gov/parasites/toxoplasmosis/index.html. Accessed on December 1, 2023.
3. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: 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. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines. Accessed on December 1, 2023.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	Updated the title of the policy **For All Indications:** Added "medication is prescribed in combination with leucovorin" and relocated requirement for step through generic pyrimethamine to preferred product tables and updated language. **Cystoisosporiasis (formerly known as isosporiasis) – Secondary Prophylaxis (Chronic Maintenance Treatment):** "Failure, contraindication, or intolerance to ONE of the following: trimethoprim-sulfamethoxazole or systemic ciprofloxacin" was changed to "patient has tried at least one other therapy for this condition" with examples moved to a "Note". **Cystoisosporiasis (formerly known as isosporiasis) – Treatment:** "Failure, contraindication or intolerance to ONE of the following: trimethoprim-sulfamethoxazole or systemic ciprofloxacin" was changed to "patient has tried at least one other therapy for this condition" with examples moved to a "Note". **Pneumocystis Pneumonia – Primary Prophylaxis:** "Failure, contraindication or intolerance to ONE of the following: trimethoprim-sulfamethoxazole, systemic dapsone, aerosolized pentamidine (via Respigard II™ nebulizer) or atovaquone" was changed to "patient has tried at least one other therapy for this condition" with examples moved to a "Note". Added a requirement the medication is prescribed in combination with systemic dapsone OR atovaquone. **Pneumocystis Pneumonia – Secondary Prophylaxis (Chronic Maintenance Therapy)**: "Failure, contraindication or intolerance to ONE of the following: trimethoprim-sulfamethoxazole, systemic dapsone, aerosolized pentamidine (via Respigard II™ nebulizer) or atovaquone" was changed to "patient has tried at least one other therapy for this condition" with examples moved to a "Note". Added a requirement the medication is	6/15/2024

	prescribed in combination with systemic dapsone OR atovaquone. ***Toxoplasma gondii* Encephalitis – Primary Prophylaxis.** "Failure, contraindication or intolerance to ONE of the following: trimethoprim-sulfamethoxazole or atovaquone was changed to "patient has tried at least one other therapy for this condition" with examples moved to a "Note". Added a requirement the medication is prescribed in combination with systemic dapsone OR atovaquone. ***Toxoplasma gondii* Encephalitis – Secondary Prophylaxis (Chronic Maintenance Therapy).** Added a requirement the medication is prescribed in combination with systemic clindamycin OR atovaquone, if unable to take sulfadiazine.	

The policy effective date is in force until updated or retired.