Prior Authorization Protocol
DARAPRIM® (pyrimethamine)

NATL

Coverage of drugs is first determined by the member's pharmacy or medical benefit. Please consult with or refer to the Evidence of Coverage document.

I. FDA Approved Indications:

- Treatment of Toxoplasmosis: for the treatment of toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination.
- Treatment of Acute Malaria: 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.
- Chemoprophylaxis of Malaria: 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.

II. Health Net Approved Indications and Usage Guidelines:

Toxoplasmosis

- Diagnosis of Toxoplasmosis

  AND

- Prescribed or in consultation with an infectious disease specialist

Toxoplasmosis Prophylaxis

- Patient has a diagnosis of HIV/AIDS

  AND

- Patient is *Toxoplasma*-seropositive

  AND

- Patient has a $CD4^+$ count of <100 cells/μL

  AND

- Failure or clinically significant adverse effects to trimethoprim-sulfamethoxazole (TMP-SMX)

Treatment of Acute Malaria

- Prescribed by an infectious disease specialist or prescriber specializes in travel medicine

  AND

- Patient infected in area(s) where susceptible plasmodia exist or parasite susceptibility has been confirmed

  AND

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- Failure or clinically significant adverse effects to atovaquone/proguanil and hydroxychloroquine unless lack of susceptibility is documented

  OR

- There is an attestation that the CDC has been contacted and supports the use of pyrimethamine

Prophylaxis for Malaria:

- Patient is traveling to area(s) susceptible to pyrimethamine

  AND

- Clinical justification as to why formulary alternatives cannot be used (e.g. atovaquone/proguanil and hydroxychloroquine)

  OR

- There is an attestation that the CDC has been contacted and supports the use of pyrimethamine

III. Coverage is Not Authorized For:

- Non-FDA approved indications, which are not listed in the Health Net Approved Indications and Usage Guidelines section, unless there is sufficient documentation of efficacy and safety in the published literature

IV. General Information:

- Although FDA approved for the prophylaxis and treatment of malaria, CDC (Center of Disease Control and Prevention) does not recommend the use of pyrimethamine for these indications:
  - http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria#4904
  - http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf
- Resistance to pyrimethamine is prevalent worldwide. It is not suitable as a prophylactic agent for travelers to most areas
  - http://www.cdc.gov/malaria/travelers/country_table/a.html
- Pyrimethamine is no longer available in retail pharmacies as of June, 2015. It is only available through a special access program http://www.daraprimdirect.com/how-to-prescribe.
- The dosage of pyrimethamine required for the treatment of toxoplasmosis is 10 to 20 times the recommended antimalaria dosage and approaches the toxic level. If signs of folate deficiency develop, reduce the dosage or discontinue the drug according to the response of the patient. Folinic acid (leucovorin) should be administered in a dosage of 5 to 15 mg daily (orally, IV, or IM) until normal hematopoiesis is restored.

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V. Therapeutic Alternatives:

Drug	Dosing Regimen	Dose/Limit/Maximum Dose
atovaquone-proguanil (Malarone®)	**Treatment (malaria):** 4 tablets PO QD x 3 days **Prophylaxis (malaria):** 1 tablet PO QD- begin 1 to 2 days before entering the endemic area; continue daily during the stay and for 7 days after leaving the area.	**Treatment (malaria):** total of atovaquone 1000 mg/400 mg proguanil (4 tablets) per day **Prophylaxis (malaria):** atovaquone 250 mg/100 mg proguanil (1 tablet) per day
hydroxychloroquine (Plaquenil®)	**Treatment (malaria):** 800 mg PO initially, followed by 400 mg 6, 24, and 48 hours later **Prophylaxis (malaria):** 400 mg PO weekly on the same day each week; begin 2 weeks before exposure; continue for 4 weeks after leaving endemic area	**Treatment (malaria):** Total dose: 2 g **Prophylaxis (malaria):** If dosing is not begun prior to the exposure, double the initial dose and give in 2 doses, 6 hours apart and continue treatment for 8 weeks.

*Requires Prior Authorization

VI. Recommended Dosing Regimen and Authorization Limit:

Drug	Dosing Regimen	Authorization Limit
Daraprim	**Toxoplasmosis-non-AIDS related** *Starting dose:* 50 to 75 mg PO QD for 1 to 3 week Use with a sulfonamide in combination with leucovorin *Maintenance dose:* 50% of starting dose for an additional 4 to 5 weeks Use with a sulfonamide in combination with leucovorin	12 Weeks
Daraprim	**Toxoplasmosis-AIDS-related** 200 mg PO for one dose, then If less than 60kg: pyrimethamine 50 mg PO daily with sulfadiazine 1,000 mg Q6H and leucovorin 10 mg-50 mg QD If 60kg or greater: pyrimethamine 75 mg PO daily with sulfadiazine 1,500 mg Q6H and leucovorin 10mg -50 mg QD Treatment should be given daily for six weeks	12 Weeks
Daraprim	**Toxoplasmosis prophylaxis in HIV positive patients** 50 mg PO once weekly plus leucovorin 25 mg	12 Weeks Reauthorization: Patient receiving

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Drug	Dosing Regimen	Authorization Limit
	PO once weekly plus dapsone 50 mg PO QD	antiretroviral therapy (ART) whose $CD4^+$ count is not increased to >200 cells/μL for more than 3 months. Reauthorization requests will be approved for an additional 12 weeks.
Daraprim	**Treatment of Acute Malaria** *Starting dose:* With a sulfonamide, 25 mg PO QD for 2 days OR If Daraprim must be used alone, Adults: 50 mg PO QD for 2 days Children 4 – 10 years: 25 mg PO QD for 2 days *Maintenance Dose:* Adults and patients over 10 years: 25 mg PO once weekly for at least 10 weeks Children 4 – 10 years: 12.5 mg PO once weekly for at least 10 weeks Infants and children under 4 years: 6.25 mg PO once weekly for at least 10 weeks	10 Weeks
Daraprim	**Chemoprophylaxis of Malaria** *Adults and pediatric patients over 10 years:* 25 mg PO once weekly *Children 4 through 10 years:* 12.5 mg PO once weekly *Infants and children under 4 years:* 6.25 mg PO once weekly	Length of travel

VII. Product Availability:

Tablets: 25 mg

VIII. References:

1. Daraprim [Prescribing Information]. New York, NY: Turing Pharmaceuticals; October 2015
2. AIDS info: Notice of Availability of Pyrimethamine. AIDSinfo. Rockville, MD. 2015. Available at https://aidsinfo.nih.gov/news/1604/notice-of-availability-of-pyrimethamine. Accessed: July 5, 2016.
3. Micromedex® Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed: July 5, 2016.
4. Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America, et al: Guidelines for Prevention

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and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009; 58 (RR4):1-207. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5804a1.htm. Accessed: July 5, 2016

The materials provided to you are guidelines used by this health plan to authorize, modify, or determine coverage for persons with similar illnesses or conditions. Specific care and treatment may vary depending on individual needs and the benefits covered under your contract.

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