PRIOR AUTHORIZATION CRITERIA

BRAND NAME*
(generic)

DARAPRIM
(pyrimethamine)

Status: CVS Caremark Criteria ***REG***
Type: Initial Prior Authorization ***Ref# 3404-A***

** Drugs that are listed in the target drug box include both brand and generic and all dosage forms and strengths unless otherwise stated. OTC products are not included unless otherwise stated.*

FDA-APPROVED INDICATIONS

Treatment of Toxoplasmosis
Daraprim is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination.

Compendial Uses
Toxoplasmosis; Prophylaxis[2,3,4,5]
Pneumocystis jiroveci pneumonia; Prophylaxis[2,3,4]
Cystoisosporiasis: treatment and secondary prophylaxis [2,4,5]

COVERAGE CRITERIA

The requested drug will be covered with prior authorization when the following criteria are met:

- The requested drug is being prescribed for the treatment of congenital toxoplasmosis in a pediatric patient

OR

- The requested drug is being prescribed for the treatment of toxoplasmosis

OR

- The requested drug is being prescribed for secondary prophylaxis of toxoplasmosis
  - **AND**
  - The patient has had a CD4 cell count of less than 200/mm3 within the past 6 months

OR

- The requested drug is being prescribed for any of the following: A) primary prophylaxis of toxoplasmosis, B) pneumocystis jiroveci pneumonia prophylaxis
  - **AND**
  - The patient has had a CD4 cell count of less than 200/mm3 within the past 3 months

OR

- The requested drug is being prescribed for the treatment of cystoisosporiasis

OR

- The requested drug is being prescribed for secondary prophylaxis of cystoisosporiasis
  - **AND**
  - The patient has had a CD4 cell count less than 200/mm3 within the past 6 months

RATIONALE

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Daraprim is indicated for the treatment of toxoplasmosis when used conjointly with a sulfonamide, since synergism exists with this combination.[1]

The CDC, National Institutes of Health (NIH), HIV Medicine Association of the Infectious Diseases Society of America (IDSA), American Academy of Pediatrics (AAP), and others state that a regimen of pyrimethamine (and leucovorin) in conjunction with sulfadiazine is the regimen of choice for initial treatment of toxoplasmosis, including toxoplasmosis in HIV infected adults, adolescents, and children.[2]

The dosage of Daraprim for the treatment of toxoplasmosis must be carefully adjusted so as to provide maximum therapeutic effect and a minimum of side effects. At the dosage required, there is a marked variation in the tolerance to the drug. Young patients may tolerate higher doses than older individuals. Concurrent administration of folinic acid is strongly recommended in all patients.

- The pediatric dosage of Daraprim is 1 mg/kg/day divided into 2 equal daily doses; after 2 to 4 days this dose may be reduced to one half and continued for approximately 1 month. The usual pediatric sulfonamide dosage is used in conjunction with Daraprim.[1]
    - The preferred treatment for congenital toxoplasmosis is a combination of pyrimethamine and sulfadiazine, with supplemental leucovorin to minimize hematologic toxicity associated with pyrimethamine. Duration of treatment of congenital toxoplasmosis in infants without HIV infection is 12 months. In the absence of definitive data, the same duration is recommended for treating congenital toxoplasmosis in HIV-infected children.[2,3,5]
- The adult *starting* dose is 50 to 75 mg of the drug daily, together with 1 to 4 g daily of a sulfonamide of the sulfapyrimidine type, e.g. sulfadoxine. This dosage is ordinarily continued for 1 to 3 weeks, depending on the response of the patient and tolerance to therapy. The dosage may then be reduced to about one half that previously given for each drug and continued for an additional 4 to 5 weeks.[1]

Toxoplasmosis; Prophylaxis[2-5]: *Toxoplasma*-seropositive patients who have a CD4+ count of <100 cells/μL should receive prophylaxis against Toxoplasmic encephalitis (TE). A regimen of pyrimethamine (and leucovorin) used in conjunction with dapsone is the recommended alternative for primary prophylaxis against toxoplasmosis in HIV-infected adults or adolescents who cannot tolerate co-trimoxazole (trimethoprim-sulfamethoxazole (TMP-SMX)). A regimen of pyrimethamine (and leucovorin) in conjunction with sulfadiazine usually is the regimen of choice for secondary prophylaxis of toxoplasmosis in HIV-infected adults, adolescents, and children since it provides coverage against both toxoplasmosis and Pneumocystis jiroveci (formerly Pneumocystis carinii) pneumonia (PCP).

The CDC, NIH, and IDSA guidelines state that primary prophylaxis against toxoplasmosis generally can be discontinued in HIV-infected adults and adolescents who have CD4 T-cell counts that have remained greater than 200/mm for longer than 3 months in response to antiretroviral therapy. Guidelines also state that secondary prophylaxis against toxoplasmosis generally can be discontinued in HIV-infected adults and adolescents who have successfully completed initial therapy for toxoplasmic encephalitis, remain asymptomatic with respect to toxoplasmic encephalitis, and have CD4 T-cell counts that have remained greater than 200/mm for more than 6 months in response to antiretroviral therapy since limited data indicate such individuals are at low risk for recurrence of toxoplasmic encephalitis. [2-5]

Pneumocystis jiroveci Pneumonia; Prevention[2-4]: TMP-SMX is the drug of choice for prevention of initial episodes (primary prophylaxis) of PCP in HIV-infected adults, adolescents, and children and for chronic maintenance therapy to prevent recurrence following an initial PCP episode in these individuals (secondary prophylaxis). Dapsone plus pyrimethamine plus leucovorin is considered an alternative therapy. The CDC, NIH, and IDSA state that primary or secondary PCP prophylaxis generally can be discontinued in HIV infected adults and adolescents if CD4+ Tcell counts have remained at 200/mm3 or greater for at least 3 months.

Cystoisosporiasis; treatment and secondary prophylaxis [2,4,5]: TMP-SMX is the antimicrobial agent of choice for treatment of cystoisosporiasis (formerly isosporiasis). It is the only agent whose use is supported by substantial published data and clinical experience. Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50–75 mg/day) plus leucovorin (10–25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients. Insufficient evidence is available, however, to support a general recommendation for primary prophylaxis for isosporiasis per se, especially for U.S. travelers in isosporiasis-endemic areas. Patients with CD4 cell counts <200 cells/mm3 should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX, which is also protective against *Pneumocystis jiroveci* and *Toxoplasma gondii* infections. In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used. The issue of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in patients without evidence of active *I. belli* infection who have a sustained increase in the CD4 cell count to levels >200 cells/mm3 for >6 months after initiation of anti-retroviral therapy (ART).[5]

CD4 counts should be monitored every 3 to 6 months to assess the need for opportunistic infections (OIs) prophylaxis. The CD4 count is used to assess a patient's immunologic response to ART. It is also used to determine whether prophylaxis for OIs can be discontinued.[7]

Malaria; Treatment[2,3,6]: Pyrimethamine is NOT recommended alone in the treatment of acute malarial attacks and is no longer included in the CDC Guidelines for the treatment of malaria.

Malaria; Prophylaxis[2,3,6]: Pyrimethamine is NOT the drug of choice for malaria prophylaxis. Depending on the resistance patterns, drugs such as chloroquine or mefloquine are preferred.

REFERENCES

1. Daraprim [package insert]. New York, NY: Vyera Pharmaceuticals, LLC; August 2017.
2. Lexicomp Online, AHFS DI (Adult and Pediatric) Online. Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc. http://online.lexi.com/. Accessed December 2020.
3. Micromedex (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. http://www.micromedexsolutions.com/. Accessed December 2020.
4. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: 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/sites/default/files/inline-files/adult_oi.pdf. Accessed December 2020.
5. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Department of Health and Human Services. Recommendations from the National Institutes of Health, Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf. Accessed December 2020.
6. Guidelines for the Treatment of Malaria in the United States. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/malaria/resources/pdf/Malaria_Treatment_Table_120419.pdf. Accessed December 2020.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed December 2020.

Written by:	UM Development (JK)
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CRITERIA FOR APPROVAL

1	Is the requested drug being prescribed for the treatment of congenital toxoplasmosis in a pediatric patient? [If yes, then no further questions.]	Yes	No
2	Is the requested drug being prescribed for the treatment of toxoplasmosis? [If yes, then no further questions.]	Yes	No
3	Is the requested drug being prescribed for secondary prophylaxis of toxoplasmosis? [If yes, then skip to question 8.]	Yes	No
4	Is the requested drug being prescribed for any of the following: A) primary prophylaxis of toxoplasmosis, B) pneumocystis jiroveci pneumonia prophylaxis? [If no, then skip to question 6.]	Yes	No

5	Has the patient had a CD4 cell count less than 200/mm3 for within the past 3 months? [No further questions.]	Yes	No
6	Is the requested drug being prescribed for the treatment of cystoisosporiasis? [If yes, then no further questions.]	Yes	No
7	Is the requested drug being prescribed for secondary prophylaxis of cystoisoporiasis? [If no, then no further questions.]	Yes	No
8	Has the patient had a CD4 cell count less than 200/mm3 within the past 6 months?	Yes	No

Mapping Instructions			
	Yes	**No**	**DENIAL REASONS – DO NOT USE FOR MEDICARE PART D**
1.	Approve, 12 months	Go to 2	
2.	Approve, 3 months	Go to 3	
3.	Go to 8	Go to 4	
4.	Go to 5	Go to 6	
5.	Approve, 3 months	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet any of these conditions: - You have had a CD4 count less than 200/mm3 within the past 3 months Your request has been denied based on the information we have. [Short Description: CD4 counts not above appropriate level]
6.	Approve, 6 months	Go to 7	
7.	Go to 8	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet any of these conditions: - The requested drug is being prescribed for any of the following conditions: treatment of toxoplasmosis; toxoplasmosis prophylaxis; pneumocystis jiroveci pneumonia prophylaxis; treatment of cystoisosporiasis; secondary prophylaxis of cystoisosporiasis Your request has been denied based on the information we have. [Short Description: No approvable diagnosis]
8.	Approve, 6 months	Deny	You do not meet the requirements of your plan. Your plan covers this drug when you meet one these conditions: - You are using the requested drug for secondary prophylaxis of cystoisosporiasis AND you have had a CD4 count less than 200/mm3 within the past 6 months - You are using the requested drug for secondary prophylaxis of toxoplasmosis AND you have had a CD4 count less than 200/mm3 within the past 6 months Your request has been denied based on the information we have. [Short Description: No approvable diagnosis, CD4 counts not above appropriate level]