PRIOR AUTHORIZATION CRITERIA

BRAND NAME*
(generic)

DARAPRIM
(pyrimethamine)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization ***Ref # 1341-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[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 patient has an intolerance or contraindication to sulfamethoxazole/trimethoprim AND the requested drug is being prescribed for any of the following: A) Toxoplasmosis prophylaxis B) Pneumocystis jiroveci pneumonia prophylaxis C) Cystoisosporiasis

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

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
    - 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.

Toxoplasmosis; Prophylaxis[2-5]: *Toxoplasma*-seropositive patients who have a CD4+ count of <100 cells/μL should receive prophylaxis against Toxoplasmic encephalitis (TE). The double-strength tablet daily dose of trimethoprim-sulfamethoxazole (TMP-SMX), recommended as the preferred regimen for Pneumocystis carinii pneumonia (PCP) prophylaxis, also is effective against TE and is recommended. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against PCP. Primary prophylaxis should be discontinued among patients who have responded to highly active antiretroviral therapy with an increase in CD4 T-lymphocyte counts to >200 cells/μL for at least 3 months.

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+ T-cell counts have remained at 200/mm3 or greater for at least 3 months.

Cystoisosporiasis[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. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. 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. 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.

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 2019.
3. Micromedex (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. http://www.micromedexsolutions.com/. Accessed December 2019.
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 http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed December 2019.
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 2019.

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 2019.

Written by: UM Development (RP)
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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	Does the patient have an intolerance or contraindication to sulfamethoxazole/trimethoprim AND is the requested drug being prescribed for any of the following: A) Toxoplasmosis prophylaxis B) Pneumocystis jiroveci pneumonia prophylaxis C) Cystoisosporiasis?	Yes	No

Guidelines for Approval			
Duration of Approval 12 Months			
Set 1			
Yes to question(s)		**No to question(s)**	
1		None	
Duration of Approval 3 Months		**Duration of Approval 3 Months**	
Set 2		**Set 3**	
Yes to question(s)	**No to question(s)**	**Yes to question(s)**	**No to question(s)**
2	1	3	1
			2

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.	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 are using Daraprim for the treatment of toxoplasmosis - You have either tried or are unable to take sulfamethoxazole/trimethoprim and Daraprim is being prescribed for any of the following conditions: toxoplasmosis prophylaxis; pneumocystis jiroveci pneumonia prophylaxis; or cystoisosporiasis Your request has been denied based on the information we have. [Short Description: No approvable diagnosis, No intolerance or contraindication to sulfamethoxazole/trimethoprim]