pyrimethamine (Daraprim®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO234

Description

Pyrimethamine (Daraprim) is an orally administered antiparasitic agent that reversibly inhibits the protozoal enzyme dihydrofolate reductase, selectively blocking conversion of dihydrofolic acid to its functional form, tetrahydrofolic acid.

Length of Authorization

I. Initial: Six months
II. Renewal:
   i. **Congenital toxoplasmosis:** Six months, maximum one-time renewal
   ii. **All other indications:** 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit	
			Pediatric	Adult
Pyrimethamine (Daraprim)	25 mg tablets	Toxoplasmosis prophylaxis	30 tablets / 30 days	30 tablets / 30 days
		Toxoplasmosis treatment	30 tablets / 30 days	**First month:** 98 tablets / 30 days **Maintenance:** 90 tablets / 30 days
		Congenital toxoplasmosis	**First six months:** 30 tablets / 30 days **Last six months:** 10 tablets / 30 days	N/A
		Pneumocystis jiroveci pneumonia prophylaxis	N/A	30 tablets / 30 days
		Cystoisosporiasis (isosporiasis) treatment	30 tablets / 30 days	90 tablets / 30 days

Initial Evaluation

I. **Generic pyrimethamine (Daraprim)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an infectious disease specialist; **AND**
   B. Treatment with pyrimethamine compound formulation (e.g., solution, suspension, capsule) has been ineffective, contraindicated, or not tolerated; **AND**
   C. A diagnosis of one of the following:
      1. **Toxoplasmosis prophylaxis; AND**
         i. Documentation that the member is in an immunocompromised state (e.g., AIDS/HIV, transplant, cancer, or taking immunosuppressive drugs [e.g., corticosteroids, non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.), mycophenolate, biologics (e.g., adalimumab, etanercept), etc.]); **AND**
         ii. Seropositive for anti-toxoplasma immunoglobulin G (IgG); **AND**
         iii. Documentation that treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been ineffective, contraindicated, or not tolerated; **AND**
         iv. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
      2. **Toxoplasmosis treatment**
         i. Seropositive for anti-toxoplasma immunoglobulin G (IgG); **AND**
            a. Presence of active radiographic changes (one or more contrast-enhancing lesions, edema); **OR**
            b. Presence of clinical symptoms (e.g., fever, lymphadenopathy, chorioretinitis, headache, or motor weakness); **AND**
         ii. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
      3. **Congenital toxoplasmosis**; **AND**
         i. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
      4. ***Pneumocystis jiroveci* pneumonia (PCP) prophylaxis; AND**
         i. Documentation that the member is in an immunocompromised state (e.g., AIDS/HIV, transplant, cancer, or taking immunosuppressive drugs [e.g., corticosteroids, non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.), mycophenolate, biologics (e.g., adalimumab, etanercept), etc.]); **AND;**

ii. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **AND**

iii. Treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been ineffective or contraindicated; **OR**

iv. Treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been not tolerated; **AND**

a. Member has been re-challenged with trimethoprim-sulfamethoxazole (TMP-SMX) using a desensitization protocol, or and is still unable to tolerate**; OR**

5. **Cystoisosporiasis treatment; AND**

i. Treatment with pyrimethamine will be used in combination with leucovorin; **AND**

ii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:

a. Oral trimethoprim- sulfamethoxazole (TMP-SMX)**; OR**

b. IV trimethoprim- sulfamethoxazole (TMP-SMX)**; OR**

c. Ciprofloxacin

II. **Brand pyrimethamine (Daraprim)** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A)-I(C) above are met; **AND**

B. In the absence of a drug shortage, coverage of the multi-source brand drug is to be considered medically necessary when the prescriber is requesting the multi-source brand drug due to a documented adverse reaction to the generic equivalent; **AND**

C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

D. The prescriber must document one or more of the following, indicating that the reaction:

1. Was life-threatening; **OR**
2. Required hospitalization; **OR**
3. Required intervention to prevent impairment or damage; **OR**

E. The prescriber is requesting the brand name drug due to a documented allergy to the generic equivalent [i.e., skin rashes (particularly hives), itching, respiratory compilations and angioedema] that required medical intervention to prevent impairment or damage; **OR**

F. The prescriber is requesting the brand name drug due to a documented intolerance to the generic equivalent which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    1. More than one generic equivalent has been tried, or there is only one generic equivalent for the prescribed brand drug.

III. Pyrimethamine (Daraprim) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Prevention or treatment of malaria.

IV. Pyrimethamine (Daraprim) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., CD4 count recovery, contrast-enhancing lesions, improvement in symptoms such as fever, lymphadenopathy, chorioretinitis, or headache); **AND**
IV. Request is for compound pyrimethamine; **OR**
V. If request is for generic pyrimethamine:
    a. Provider attests that the member remains ineligible to transition to compounded pyrimethamine products (e.g., solution, suspension, or capsule); **OR**
VI. If the request is for Brand Daraprim:
    a. Provider attests that the member remains ineligible to transition to compounded pyrimethamine products (e.g., solution, suspension, or capsule) or generic pyrimethamine tablets.

Supporting Evidence

I. Pyrimethamine (Daraprim) is not considered a narrow therapeutic index drug, therefore there are no foreseeable pharmacokinetic or clinical implications in transitioning a patient from an oral generic formulation to a compounded formulation.
II. There is no universal standard scale for quantifying an immunocompromised state. The National institute of Health National Cancer Institute defines immunocompromised (also called

immunosuppressed) as having a weakened immune system and reduced ability to fight infections and other diseases. This may be caused by certain conditions, such as AIDS, cancer, diabetes, malnutrition, and certain genetic disorders. It may also be caused by certain treatments, such as biologics, corticosteroids, DMARDS, oncolytics, radiation therapy, and stem cell or organ transplant.

III. Opportunistic infections (OIs) are illnesses that occur more frequently and are more severe in people with compromised immune systems, including HIV, hematopoietic cell transplant, solid organ transplant, cancer-related immunosuppression and hematological malignancies, or taking immunosuppressive therapies. Due to the complexity of opportunistic infections, pyrimethamine needs to be prescribed by, or in consultation with, an infectious disease specialist.

IV. Initial serological screening should be performed to determine whether the member has ever been infected or is acutely or chronically infected with toxoplasmosis. *Toxoplasma*-specific IgG and IgM tests can be performed at any commercial, non-reference, or hospital-based laboratory. A positive serologic anti-toxoplasma IgG antibody test establishes that the member has been infected and is at risk of reactivation during periods of significant immunosuppression.

V. Pyrimethamine must be taken in combination with leucovorin and an antimicrobial agent due to enhanced safety and efficacy. Administration with leucovorin is recommended to reduce incidence of hematologic adverse events (myelosuppression) while taking pyrimethamine. Pyrimethamine and an antimicrobial agent act synergistically by inhibiting proliferation and survival through inhibiting the folate metabolic pathway.

VI. **Toxoplasmosis prophylaxis**

a. TMP-SMX should be considered first line therapy for toxoplasmosis prophylaxis. TMP-SMX also provides protection against other pathogens, including PCP, Nocardia, enteric pathogens, Plasmodium species, urinary pathogens, and some respiratory pathogens. The broader spectrum of activity of TMP-SMX is among the reasons this drug is preferred.

b. In adults and adolescents with HIV, toxoplasmosis prophylaxis should be discontinued in patients receiving ART whose CD4 counts increase to >200 cells/mm3 for more than 3 months. Toxoplasmosis prophylaxis should be discontinued because it adds little value in preventing toxoplasmosis and increases pill burden, potential for drug toxicity and interaction, and likelihood of development of drug-resistant pathogens.

c. There is no consensus concerning initiation and duration of toxoplasmosis prophylaxis in immunocompromised members. Regarding the incidence rate of toxoplasmosis following hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT), prophylaxis should be maintained for at least 6 months post-transplant. It should be prolonged in cases of graft-versus-host disease, prolonged neutropenia, and prolonged administration of corticosteroids.

d. In immunocompetent individuals, acute toxoplasmosis infection is usually self-limited and rarely symptomatic, although cases of severe infection due to rare Toxoplasma genotypes have been reported. Treatment for toxoplasmosis is not required for immunocompetent members who are asymptomatic or have mild, uncomplicated acute toxoplasmosis.

VII. **Toxoplasmosis treatment**

a. Toxoplasmosis therapy requires serologic anti-toxoplasma IgG detection, radiographic changes (CT or MRI with multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated edema), and/or presence of clinical symptoms. Common clinical manifestations include lymphadenopathy, chorioretinitis (a type of posterior uveitis), headache, confusion, and motor weakness. The radiologic goals for treatment include resolution of the lesion(s) in terms of size, contrast enhancement, and associated edema, although residual contrast-enhancing lesions may persist for prolonged periods
b. In members with HIV, acute therapy for toxoplasmosis must be continued for at least 6 weeks. Longer courses may be necessary if clinical or radiologic disease is extensive, or response is incomplete at 6 weeks. After completion of the acute therapy, guidelines recommend members who have completed a 6-week treatment course for acute toxoplasmosis therapy should be given chronic maintenance therapy to suppress infection until immune reconstitution occurs as a consequence of antiretroviral therapy (ART). Members receiving chronic maintenance therapy for toxoplasmosis are at low risk for recurrence if they have successfully completed initial therapy, remain asymptomatic regarding signs and symptoms of toxoplasmosis, and have an increase in their CD4 counts to >200 cells/mm3 after ART that is sustained for more than 6 months.

VIII. **Congenital toxoplasmosis**

a. Pregnant women with suspected or confirmed primary toxoplasmosis and newborns with possible or documented congenital toxoplasmosis should be managed in consultation with an appropriate infectious disease specialist. Empiric therapy should be strongly considered for newborns of HIV-infected mothers who had symptomatic or asymptomatic primary Toxoplasma infection during pregnancy, regardless of whether treatment was administered during pregnancy. The recommended duration of treatment for congenital toxoplasmosis in infants is 12 months (continuously throughout the first year of life).

IX. ***Pneumocystis jiroveci* pneumonia (PCP) prophylaxis**

a. The preferred PCP prophylaxis regimen for HIV and immunocompromised non-HIV infected patients is TMP-SMX, because of its superior efficacy compared with aerosolized pentamidine, oral dapsone, or oral atovaquone. TMP-SMX chemoprophylaxis should be continued, when clinically feasible, in patients who have non-life-threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction, re-institution of the drug should be considered after the reaction has resolved. Oral desensitization regimens have been used successfully for HIV-infected patients with fever and rash, and similar protocols have been used in HCT recipients with a success rate of approximately 80%. Therapy should be permanently discontinued (with no rechallenge) in patients with life-threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis.
b. PCP prophylaxis should be discontinued in adult and adolescent members who have responded to ART with an increase in CD4 counts from 200 cells/mm3 for >3 months.

Discontinuation of primary PCP prophylaxis in patients with CD4 count increase to >200 cells/mm3 as a result of ART is recommended because its preventive benefits against PCP, toxoplasmosis, and bacterial infections are limited; stopping the drugs reduces pill burden, cost, and the potential for drug toxicity, drug interactions, and selection of drug-resistant pathogens.

c. PCP prophylaxis and treatment with pyrimethamine is not indicated for pediatric members. TMP–SMX is a first line prophylaxis agent due to its high efficacy, relative safety, low cost, and broad antimicrobial spectrum. Dapsone or atovaquone are second line effective and safe prophylaxis regimens available for pediatric patients unable to take TMP-SMX.

X. **Cystoisosporiasis treatment**

a. Cystoisosporiasis (also known as isosporiasis) should not be confused with Cryptosporidiosis. Cystoisosporiasis has also been reported immunocompromised as well as in immunocompetent individuals. In adults and adolescents with HIV, chemoprophylaxis with oral trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with a lower incidence or prevalence of isosporiasis. Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption. Ciprofloxacin is considered a second-line alternative.

b. In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment). In an observational study, incidence of isosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in patients with CD4 counts <50 cells/mm^3. After adjustment for the CD4 T lymphocyte (CD4) cell count, the risk of isosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine.

XI. In the United States, the Office of Generic Drugs at the Food and Drug Administration (FDA) follows a rigorous review process to make sure that, compared to the brand name (or innovator) medications, the proposed generic medications:

a. Contain the same active/key ingredient
b. Have the same strength
c. Use the same dosage form (for instance, a table, capsule, or liquid) and
d. Use the same route of administration (for instance, oral, topical, or injectable)

XII. The FDA's review process also ensures that generic medications perform the same way in the human body and have the same intended use as the name brand medication. Healthcare professionals and consumers can be assured that FDA-approved generic drug products have met the same rigid manufacturing standards as the innovator drug. In addition, FDA inspects facilities to make certain the generic manufacturing, packaging, and testing sites pass the same quality standards as those of brand-name drugs.

a. Thus, when an adverse reaction or allergy occurs to any medication (brand or generic), it is important to report to MedWatch.

b. In order to keep effective medical products available on the market, the FDA relies on the voluntary reporting of these events. This information is used to maintain safety surveillance and to monitor if modifications in use or design of the product are warranted to increase patient safety.

XIII. It can be difficult to distinguish an allergy from a distinct adverse event related to the generic, therefore any event thought to be related to the medication should be reported to MedWatch.

a. As defined by the American Academy of Allergy, Asthma, and Immunology, an allergic reaction occurs when the immune system overreacts to a substance, triggering an allergic reaction. Sensitivities to drugs may produce similar symptoms, but do not involve the immune system. Only 5-20% of adverse reactions to drugs are considered true allergic reactions. The chances of developing an allergy are higher when you take the medication frequently or when it is rubbed on the skin or given by injection, rather than taken by mouth. The most frequent types of allergic symptoms to medications include skin rashes (particularly hives), itching, respiratory complications and angioedema. The most severe form of immediate allergic reactions is anaphylaxis, and symptoms include hives, facial or throat swelling, wheezing, light-headedness, vomiting and shock.

Investigational or Not Medically Necessary Uses

I. The use of pyrimethamine for prophylaxis or treatment of malaria in adults is no longer recommended in the CDC Guidelines for the Treatment of Malaria in the United States.

Appendix

Please note, specific doses vary among non-HIV conditions. Dosing regimens listed below are not all inclusive. Please cross-reference compendia for member-specific dose.

I. Table 1: Recommendations for Preventing and Treating Toxoplasmosis in Adults and Adolescents with HIV[2]

Indication	Preferred regimen	Alternative regimens	Treatment duration
Toxoplasmosis Prophylaxis	TMP-SMX 1 DS PO daily	• TMP-SMX 1 DS PO three times weekly, or • TMP-SMX SS PO daily, or • Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, or • (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly, or • Atovaquone 1500 mg PO daily, or • (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily	• CD4 count >200 cells/ mm^3 for >3 months in response to ART; or • Can consider if CD4 count is 100-200 cells/ mm^3 and HIV RNA levels remain below limits of detection for at least 3-6 months **Indication for Restarting Primary Prophylaxis:** • CD4 count < 100 – 200 cells/ mm^3
Treating acute Toxoplasmosis*	**Induction: 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)	Preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine-sulfadiazine: • Pyrimethamine (leucovorin)‡ plus clindamycin 600 mg IV or PO q6h + must add additional agent for PCP prophylaxis, or • TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID, or • Atovaquone 1500 mg PO BID + pyrimethamine (leucovorin)‡, or • Atovaquone 1500 mg PO BID + sulfadiazine, or • Atovaquone 1500 mg PO BID	• At least 6 weeks; 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
Toxoplasmosis Chronic Maintenance Therapy	Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily	• Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily; or • TMP-SMX DS 1 tablet BID, or • TMP-SMX DS 1 tablet daily, 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), or • Atovaquone 750–1500 mg PO BID	• Successfully completed initial therapy, remain asymptomatic of signs and symptoms of toxoplasmosis, and CD4 count >200 cells/mm^3 for >6 months in response to ART **Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance** • CD4 count <200 cells/ mm^3

* Acute toxoplasma treatment: if pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine. For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies. Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved.

ǂ Pyrimethamine and leucovorin doses: Same as doses listed in Preferred Regimen for treating acute toxoplasmosis

Acronyms: ART = antiretroviral therapy; BID = twice daily; CD4 = CD4 T lymphocyte cell; DS = double strength; IV = intravenous; PCP = *Pneumocystis* Pneumonia; PO = orally; q(n)h = every "n" hour; SS = single strength; TMP-SMX = trimethoprim-sulfamethoxazole

II. Table 2. Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis in HIV-Exposed and HIV-Infected Children[3]

Indication	Preferred regimen	Alternative regimens	Treatment Duration / Comments
Primary Prophylaxis	TMP-SMX 150/750 mg/m^2 body surface area once daily by mouth	**For Children Aged ≥1 Month:** • Dapsone 2 mg/kg body weight or 15 mg/ m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Pyrimethamine 1 mg/kg body weight (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth every 3 days **For Children Aged 1–3 Months and >24 Months:** • Atovaquone 30 mg/kg body weight by mouth once daily **Children Aged 4–24 Months:** • Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth every 3 days **Acceptable Alternative Dosage Schedules for TMP-SMX:** • TMP-SMX 150/750 mg/ m^2 body surface area per dose once daily by mouth 3 times weekly on 3 consecutive days per week • TMP-SMX 75/375 mg/ m^2 body surface area per dose twice daily by mouth every day • TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily by mouth TIW on alternate days	**Primary Prophylaxis Indicated for:** *IgG Antibody to Toxoplasma and Severe Immunosuppression:* • HIV-infected children aged <6 years with CD4 percentage <15%; HIV infected children aged ≥6 years with CD4 count <100 cells/mm^3 **Criteria for Discontinuing Primary Prophylaxis:** Note: Do not discontinue in children aged <1 year • After ≥6 months of cART, and • Aged 1 to <6 years; CD4 percentage is ≥15% for >3 consecutive months • Aged ≥6 years; CD4 count >200 cells/mm^3 for >3 consecutive months **Criteria for Restarting Primary Prophylaxis:** • Aged 1 to <6 years with CD4 percentage <15% • Aged ≥6 years with CD4 count <100 to 200 cells/mm^3
Secondary Prophylaxis (Suppressive Therapy)	• Sulfadiazine 42.5–60 mg/ kg body weight per dose twice daily* (maximum 2–4 g per day) by mouth, plus • Pyrimethamine 1 mg/kg body weight or 15 mg/ m^2 body surface area (maximum	• Clindamycin 7–10 mg/kg body weight per dose by mouth 3 times daily, plus • Pyrimethamine 1 mg/kg body weight or 15 mg/ m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth once every 3 days **Children Aged 1–3 Months and >24 Months:**	**Secondary Prophylaxis Indicated:** • Prior toxoplasmic encephalitis Note: Alternate regimens with very limited data in children. TMP-SMX only to be used if patient intolerant to other regimens

	25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth once every 3 days	• Atovaquone 30 mg/kg body weight by mouth once daily • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX, 150/750 mg/ m^2 body surface area once daily by mouth **Children Aged 4–24 Months:** • Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/ m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX, 150/750 mg/ m^2 body surface area once daily by mouth	**Criteria for Discontinuing Secondary Prophylaxis If All of the Following Criteria are Fulfilled:** • Completed ≥6 months of cART, completed initial therapy for TE, asymptomatic for TE, **and** • Aged 1 to < 6 years; CD4 percentage ≥15% for >6 consecutive months • Aged ≥6 years; CD4 cell count >200 cells/ mm^3 for >6 consecutive months **Criteria For Restarting Secondary Prophylaxis:** • Aged 1 to <6 years with CD4 percentage <15% • Aged ≥6 years with CD4 cell count <200 cells/mm^3
Treatment	**Congenital Toxoplasmosis:** • Pyrimethamine loading dose—2 mg/kg body weight by mouth once daily for 2 days, then 1 mg/kg body weight by mouth once daily for 2–6 months, then 1 mg/kg body weight by mouth 3 times weekly, plus • Leucovorin (folinic acid) 10 mg by mouth or IM with each dose of pyrimethamine, plus • Sulfadiazine 50 mg/kg body weight by mouth twice daily **Acquired Toxoplasmosis Acute Induction Therapy (Followed by Chronic Suppressive Therapy):** • Pyrimethamine: loading dose—2 mg/kg body weight (maximum 50 mg) by mouth once daily for 3 days, then 1 mg/kg body weight (maximum 25 mg) by mouth once daily, plus • Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) by mouth per dose 4 times daily, plus • Leucovorin 10–25 mg by mouth once daily, followed by chronic suppressive therapy	**For Sulfonamide-Intolerant Patients:** • Clindamycin 5–7.5 mg/kg body weight (maximum 600 mg/dose) by mouth or IV per dose given 4 times a day can be substituted for sulfadiazine combined with pyrimethamine and leucovorin	**Treatment Duration:** • 12 months **Congenital Toxoplasmosis:** • For infants born to mothers with symptomatic Toxoplasma infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mother's treatment during pregnancy. **Acquired Toxoplasmosis:** • Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less than daily dosing. • TMP-SMX—TMP 5 mg/kg body weight plus SMX 25 mg/kg body weight per dose IV or by mouth given twice daily has been used as an alternative to pyrimethamine-sulfadiazine in adults but has not been studied in children. • Atovaquone (for adults, 1.5 g by mouth twice daily—double the prophylaxis dose) in regimens combined with pyrimethamine/ leucovorin, with sulfadiazine alone, or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine, has been used in adults, but these regimens have not been studied in children. • Azithromycin (for adults, 900– 1,200 mg/day, corresponding to 20 mg/ kg/day in children) has also been used in adults combined with pyrimethamine-sulfadiazine, but has not been studied in children. • Corticosteroids (e.g., prednisone, dexamethasone) have been used in children

	Treatment Duration (Followed by Chronic Suppressive Therapy): • ≥6 weeks (longer duration if clinical or radiologic disease is extensive or response in incomplete at 6 weeks)		with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or there are focal lesions with significant mass effects, with discontinuation as soon as clinically feasible. • Anticonvulsants should be administered to patients with a history of seizures and continued through the acute treatment; but should not be used prophylactically.

*Note: Sulfadiazine may be given as 2–4 equal doses per day as long as the total daily dose is 85–120 mg/kg body weight.

Key to Acronyms: cART = combination antiretroviral therapy; CBC = complete blood count; CD4 = CD4 T lymphocyte; CNS = central nervous system; CSF = cerebrospinal fluid; IgG = Immunoglobulin G; IM = intramuscular; IV = intravenous; TE = toxoplasmic encephalitis; TMP-SMX = trimethoprim-sulfamethoxazole

III. Table 3. Recommendations for prevention (prophylaxis) of *Pneumocystis jiroveci* pneumonia in adults and adolescents with HIV[2]

Indication	Preferred regimen	Alternative regimens	Treatment duration
Preventing First Episode of PCP (Primary Prophylaxis)	• TMP-SMX 1 DS tablet PO daily, or • TMP-SMX 1 SS tablet daily	• TMP-SMX 1 DS PO three times weekly, or • Dapsone 100 mg PO daily or 50 mg PO BID, or • Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or • (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly; or • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month, or • Atovaquone 1500 mg PO daily, or • (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10mg) PO daily	• CD4 count increased from <200 cells/ mm^3 to ≥200 cells/mm3 for ≥3 months in response to ART • Can consider when CD4 count is 100–200 cells/ mm^3 and HIV RNA remains below limit of detection of the assay used for ≥3 months to 6 months **Indication for Restarting Primary Prophylaxis:** • CD4 count <100 cells/ mm^3 regardless of HIV RNA • CD4 count 100–200 cells/mm^3 and HIV RNA above detection limit of the assay used
Preventing Subsequent Episode of PCP (Secondary Prophylaxis)	• TMP-SMX 1 DS tablet PO daily, or • TMP-SMX 1 SS tablet daily	• TMP-SMX 1 DS tablet PO three times weekly, or • Dapsone 100 mg PO daily, or • Dapsone 50 mg PO twice daily, or • Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or • (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly, or • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month, or • Atovaquone 1500 mg PO daily with food, or • (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily	• CD4 count increased from 200 cells/ mm^3 for >3 months as a result of ART, or • Can consider if CD4 count is 100–200 cells/ mm^3 and HIV RNA remains below limits of detection of assay used for ≥3 months to 6 months • For patients in whom PCP occurs at a CD4 count >200 cells/ mm^3 while not on ART, discontinuation of prophylaxis can be considered once HIV RNA levels are suppressed to below limits of detection of the assay used for ≥3 months to 6 months, although there are no data to support recommendations in this setting. Note: If an episode of PCP occurs at a CD4 count >200 cells/ mm^3 while a patient is on ART, it would be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART. **Indications for Restarting Secondary Prophylaxis:** • CD4 count <100 cells/ mm^{3}regardless of HIV RNA • CD4 count 100-200 cells/ mm^3 and HIV RNA above detection limit of the assay used
Note: Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis Key to acronyms = ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; DS = double strength; IV = intravenously; PCP = Pneumocystis pneumonia; PO = orally; SS = single strength; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole			

IV. Table 4. Dose recommendations for the prevention and treatment of cystoisoporiasis in adults and adolescents with HIV[2]

Indication	Preferred regimen	Alternative regimens	Treatment duration
Acute cystoisoporiasis therapy infection	• TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days, or • TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days • One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist • IV therapy for patients with potential or documented malabsorption	For Patients with Sulfa Intolerance: • Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily, or • Ciprofloxacin 500 mg PO BID for 7 days	7- 10 days
Chronic Maintenance Therapy (Secondary Prophylaxis)	In Patients with CD4 Count <200/mm3: • TMP-SMX (160 mg/800 mg) PO 3 times weekly	• TMP-SMX (160 mg/800 mg) PO daily, or • TMP-SMX (320 mg/1600 mg) PO 3 times weekly, or • Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily, or • Ciprofloxacin 500 mg PO 3 times weekly as a second line alternative	Sustained increase in CD4 count >200 cells/mm3 for >6 months in response to ART and without evidence of active infection
Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intravenous; PO = orally; QID = four times a day; TMP-SMX = trimethoprim-sulfamethoxazole			

V. Table 5. Dose recommendations for the prevention and treatment of cystoisoporiasis in HIV-Exposed and HIV-Infected Children[3]

Indication	Preferred regimen	Alternative regimens	Treatment duration / Comments
Primary prophylaxis	There are no U.S. recommendations for primary prophylaxis of isosporiasis.		
Secondary prophylaxis	If Severe Immunosuppression: • Administer TMP-SMX 2.5 mg/kg body weight of TMP component twice daily by mouth 3 times per week	Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid, 10–25 mg by mouth once daily. Second-Line Alternative: • Ciprofloxacin, 10–20 mg/kg body weight given twice daily by mouth 3 times per week	Consider discontinuing secondary prophylaxis in a patient receiving cART after sustained improvement from severe immunosuppression (from CDC immunologic category 3 to CD4 values that fall within category 1 or 2) for longer than 6 months. In adults, the dose of pyrimethamine for secondary prophylaxis (25 mg daily) is lower than the dose for treatment (50–75 mg daily), but no similar data exist for children. Thus, the recommended dosing for secondary prophylaxis in children is 1 mg/kg per dose (maximum 25 mg) once daily. Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.
Treatment	TMP-SMX 5 mg/kg body weight of TMP component given twice daily by mouth for 10 days	Pyrimethamine 1 mg/kg body weight plus folinic acid 10-25 mg by mouth once daily for 14 days Second-Line Alternatives: • Ciprofloxacin 10–20 mg/kg body weight/day twice daily by mouth for 7 days • Nitazoxanide for 3 consecutive days	If symptoms worsen or persist, the TMPSMX dose may be increased to 5 mg/kg/day given 3–4 times daily by mouth for 10 days or the duration of treatment may be lengthened. Duration of treatment with pyrimethamine has not been well established. Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.

Key to Acronyms: CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; cART = combination antiretroviral therapy; TMP-SMX = trimethoprim-sulfamethoxazole

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to policy format; Added initial and renewal length of authorization; Added toxoplasmosis prophylaxis, toxoplasmosis treatment, congenital toxoplasmosis, *Pneumocystis jiroveci* pneumonia prophylaxis, and cystoisoporiasis treatment intervention criteria for compound, generic, and brand product; Added brand Daraprim requirement; Added supporting evidence and dosing appendix.	06/2021
Policy created	02/2016