DARAPRIM®
(pyrimethamine) 25mg tablets

ENROLLMENT FORM
PHONE: 1-844-267-3323 FAX: 1-877-241-1365

*Indicates required field. Please complete all required fields to avoid processing delays.

This form is intended for prescriber use only. Fax both pages of the completed form to 1-877-241-1365.

☐ New Patient ☐ Current Patient

PATIENT INFORMATION

*Patient Name (Last, First):

*Date of Birth: Gender: M ☐ F ☐

*Address:

*City: *State: *Zip:

*Phone #: Cell #:

Email:

Preferred Contact Method: __ Phone __ Cell __ Email

Best Time to Call: __ Morning __ Afternoon __ Evening

Parent/Guardian (if applicable): __ Principal Contact

*Deliver to: ☐ Patient's Home ☐ Physician's Office

PATIENT INSURANCE INFORMATION/PHARMACY BENEFIT PLAN

Please complete the fields below or include a copy of the front AND back of the patient's prescription benefit and insurance card(s).

*Primary Insurance: Pharmacy Help Desk #:

Policyholder Name: *Relationship to Patient:

*Member ID #: *Group ID #:

*Rx BIN #: *PCN #:

Secondary Insurance: Pharmacy Help Desk #:

Member ID #: Group ID #:

Rx BIN #: PCN #:

*Insurance: ☐ Medicaid ☐ Medicare ☐ Other _____

Special Instructions:

PRESCRIBER INFORMATION

*Prescriber Name (Last, First):

Prescriber Practice Title:

MD Specialty:

*NPI #: Physician Medicaid UPIN #:

State License #: DEA #:

*Address:

*City: *State: *Zip:

*Phone #: *Fax #:

*Staff Contact Name:

*Staff Contact Number: Staff Contact Email:

PATIENT DIAGNOSIS

*ICD-10 Code/Description:

*Please list any known allergies to medication or other substances:

PRESCRIPTION INFORMATION

*Patient Name (Last, First):

Drug: **Daraprim® (pyrimethamine) 25mg tablets**

*Quantity: *Refills:

*Directions:

*Start Date: Anticipated Duration:

Additional Prescription(s):

PROVIDER ATTESTATION

Prescriber signature must be the same as the prescriber name above

By signing below, I verify that the information being disclosed in this enrollment form is complete and accurate to the best of my knowledge. I understand that Asembia Specialty Pharmacy Network (ASPN) reserves the right at any time and for any reason, without notice, to modify this enrollment form or to modify or discontinue any services or assistance provided through this Program. I authorize ASPN as my designated agent to use and disclose my patient's protected health information as may be necessary for treatment, payment, and healthcare operations, including to verify the accuracy of any information provided, to verify patient eligibility, to provide for payment and reimbursement, and to forward the above prescription information, by fax or other mode of delivery, to a pharmacy for fulfillment.

*Prescriber's Signature: *Date:

(No Stamps) (Dispense As Written)

*Prescriber's Signature : *Date:

(No Stamps) (Substitutions Permitted)

Please see accompanying Full Prescribing Information

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PATIENT REPRESENTATIVE

By signing below, I authorize my Designee, listed below, to receive administrative information related to my treatment, such as appointment reminders, and to make decisions on my behalf—for which I will remain liable—regarding delivery of DARAPRIM® (pyrimethamine). Asembia, LLC., and its affiliates, representatives, agents and contractors is not liable for any decision(s) made by the Designee or actions taken in reliance on such Designee decisions.

Designee Name: Relationship: Phone #:

Patient's Signature: Date:

PATIENT AUTHORIZATION

I, or my authorized representative, hereby authorize the pharmacy receiving my referral or dispensing my medication, and its affiliates, representatives, agents, and contractors (collectively, "Pharmacy"), to use and disclose all of my individually identifiable health information; protected health information including but not limited to records that may contain information created by other persons or entities, including physicians and other health care providers, as well as information regarding the use of drug and alcohol treatment services, confidential HIV/AIDS treatment, mental health services (excluding psychotherapy notes), information about my medical condition, prescription, treatment, care management, and health insurance; and any other personal information, including all demographic information, email addresses, phone numbers, and other information, in the possession or control of Pharmacy (collectively "Information"), to Asembia, LLC., its affiliates, representatives, agents, and contractors, ("Asembia"); Vyera Pharmaceuticals, LLC, and, including any patient assistance program administrator(s) (collectively "Vyera") for Daraprim.

The Information may be used and disclosed for purposes of: (1) providing, coordinating, managing, and contacting me about, my prescriptions (including medication refill and adherence reminders), treatment, patient support, and other services related to my Vyera products including providing information to the pharmacy dispensing my medication; (2) establishing my benefits eligibility, including for any financial or reimbursement support services offered by or on behalf of Vyera; (3) communicating with me and my healthcare providers, health plans, and other payers about my medical care; and (4) providing me with information about current or future products or services.

I understand that Pharmacy may receive a fee from Vyera in exchange for (1) providing me with certain materials and information described above, and (2) using or disclosing certain Information pursuant to this Authorization. I also understand that once my Information has been shared with Vyera or Asembia, it may be re-disclosed by Vyera or Asembia and no longer protected by the federal Privacy Rule. However, other state and federal laws may establish continuing protections for the disclosed information and prohibit Vyera or Asembia from disclosing specially protected information such as substance abuse treatment information, HIV/AIDS-related information, and psychiatric/mental health information.

I understand that I may revoke this Authorization at any time, in writing, by sending written notification to Asembia, LLC., 100 Campus Drive, Suite 300, Florham Park, NJ, 07931. I understand that revoking this Authorization will prohibit disclosures of my information after the date the cancellation letter is received, but will not be affected disclosures made by Pharmacy to Vyera or Asembia in reliance on this Authorization.

I understand that signing this Authorization is voluntary. I have the right to refuse to sign this Authorization and my refusal to sign will not affect my ability to obtain treatment or my eligibility for health plan benefits, and my Information will not be released. However, I understand that I will not have access to additional patient support, financial, or related services offered by Vyera. This authorization expires December 31, 2099, or at an earlier date if required by state law. I understand that I have the right to receive a copy of this Authorization.

Patient or Authorized Representative Signature: If Authorized Rep, State Basis for Authority:

Patient's Printed Name: Date:

NOTE TO RECIPIENT OF INFORMATION:

HIV Related Information: To the extent that HIV-related information has been provided to you, such information has been disclosed to you from records whose confidentiality is protected by state law. State law prohibits you from making any further disclosure of it without the specific written consent of the person to whom it pertains, or as otherwise permitted by said law. A general authorization for the release of medical or other information is NOT sufficient for this purpose. An oral disclosure shall be accompanied or followed by such notice within ten days.

VYERA PHARMACEUTICALS

Please see accompanying Full Prescribing Information

August 2017 | DAR2017032

DARAPRIM® (pyrimethamine)
25 mg tablets
Rx Only

PRESCRIBING

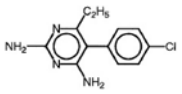
INFORMATION

DESCRIPTION

DARAPRIM (pyrimethamine) is an antiparasitic compound available in tablet form for oral administration. Each scored tablet contains 25 mg pyrimethamine and the inactive ingredients corn and potato starch, lactose, and magnesium stearate.

Pyrimethamine, known chemically as 5-(4- chlorophenyl)-6-ethyl-2, 4-pyrimidinediamine, has the following structural formula:

$C_{12}H_{13}ClN_4$
Mol. Wt. 248.71



CLINICAL PHARMACOLOGY

Pyrimethamine is well absorbed with peak levels occurring between 2 to 6 hours following administration. It is eliminated slowly and has a plasma half-life of approximately 96 hours. Pyrimethamine is 87% bound to human plasma proteins.

Microbiology: Pyrimethamine is a folic acid antagonist and the rationale for its therapeutic action is based on the differential requirement between host and parasite for nucleic acid precursors involved in growth. This activity is highly selective against *Toxoplasma gondii.*

The action of pyrimethamine against *Toxoplasma gondii* is greatly enhanced when used in conjunction with sulfonamides. This was demonstrated by Eyles and Coleman[1] in the treatment of experimental toxoplasmosis in the mouse. Jacobs et al[2] demonstrated that combination of the 2 drugs effectively prevented the development of severe uveitis in most rabbits following the inoculation of the anterior chamber of the eye with toxoplasma.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Use of DARAPRIM is contraindicated in patients with known hypersensitivity to pyrimethamine or to any component of the formulation. Use of the drug is also contraindicated in patients with documented megaloblastic anemia due to folate deficiency.

WARNINGS

The dosage of pyrimethamine required for the treatment of toxoplasmosis has a narrow therapeutic window. If signs of folate deficiency develop (see ADVERSE REACTIONS), 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.

Data in 2 humans indicate that pyrimethamine may be carcinogenic; a 51-year-old female who developed chronic granulocytic leukemia after taking pyrimethamine for 2 years for toxoplasmosis[3] and a 56-year-old patient who developed reticulum cell sarcoma after 14 months of pyrimethamine for toxoplasmosis.[4]

Pyrimethamine has been reported to produce a significant increase in the number of lung tumors in mice when given intraperitoneally at doses of 25 mg/kg.[5]

DARAPRIM should be kept out of the reach of infants and children as they are extremely susceptible to adverse effects from an overdose. Deaths in pediatric patients have been reported after accidental ingestion.

PRECAUTIONS

General: A small "starting" dose for toxoplasmosis is recommended in patients with convulsive disorders to avoid the potential nervous system toxicity of pyrimethamine. DARAPRIM should be used with caution in patients with impaired renal or hepatic function or in patients with possible folate deficiency, such as individuals with malabsorption syndrome, alcoholism, or pregnancy, and those receiving therapy, such as phenytoin, affecting folate levels (see Pregnancy subsection).

Information for Patients: Patients should be warned that at the first appearance of a skin rash they should stop use of DARAPRIM and seek medical attention immediately. Patients should also be warned that the appearance of sore throat, pallor, purpura, or glossitis may be early indications of serious disorders which require treatment with DARAPRIM to be stopped and medical treatment to be sought.

Women of childbearing potential who are taking DARAPRIM should be warned against becoming pregnant. Patients should be warned to keep DARAPRIM out of the reach of children. Patients should be advised not to exceed recommended doses. Patients should be warned that if anorexia and vomiting occur, they may be minimized by taking the drug with meals. Concurrent administration of folinic acid is strongly recommended when used for the treatment of toxoplasmosis in all patients.

Laboratory Tests: In patients receiving high dosage, semiweekly blood counts, including platelet counts, should be performed.

Drug Interactions: Pyrimethamine may be used with sulfonamides, quinine and other antimalarials, and with other antibiotics. However, the concomitant use of other antifolic drugs or agents associated with myelosuppression including sulfonamides or trimethoprim-sulfamethoxazole combinations, proguanil, zidovudine, or cytostatic agents (e.g., methotrexate), while the patient is receiving pyrimethamine, may increase the risk of bone marrow suppression. If signs of folate deficiency develop, pyrimethamine should be discontinued. Folinic acid (leucovorin) should be administered until normal hematopoiesis is restored (see WARNINGS). Mild hepatotoxicity has been reported in some patients when lorazepam and pyrimethamine were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS section for information on carcinogenesis.

Mutagenesis: Pyrimethamine has been shown to be nonmutagenic in the following *in vitro* assays: the Ames point mutation assay, the Rec assay, and the *E. coli* WP2 assay. It was positive in the L5178Y/TK +/- mouse lymphoma assay in the absence of exogenous metabolic activation.[6] Human blood lymphocytes cultured *in vitro* had structural chromosome aberrations induced by pyrimethamine.

In vivo, chromosomes analyzed from the bone marrow of rats dosed with pyrimethamine showed an increased number of structural and numerical aberrations.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Pyrimethamine has been shown to be teratogenic in rats when given in oral doses 2.5 times the human dose for treatment of toxoplasmosis. At these doses in rats, there was a significant increase in abnormalities such as cleft palate, brachygnathia, oligodactyly, and microphthalmia. Pyrimethamine has also been shown to produce terata such as meningocele in hamsters and cleft palate in miniature pigs when given in oral doses 5 times the human dose for the treatment of toxoplasmosis.

There are no adequate and well-controlled studies in pregnant women. DARAPRIM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Concurrent administration of folinic acid is strongly recommended when used during pregnancy.

Nursing Mothers: Pyrimethamine is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pyrimethamine and from concurrent use of a sulfonamide with DARAPRIM for treatment of some patients with toxoplasmosis, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS and PRECAUTIONS: Pregnancy).

Pediatric Use: See DOSAGE AND ADMINISTRATION section.

Geriatric Use: Clinical studies of DARAPRIM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Hypersensitivity reactions, occasionally severe (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and anaphylaxis), and hyperphenylalaninemia, can occur particularly when pyrimethamine is administered concomitantly with a sulfonamide. Consult the complete prescribing information for the relevant sulfonamide for sulfonamide-associated adverse events. With doses of pyrimethamine used for the treatment of toxoplasmosis, anorexia and vomiting may occur. Vomiting may be minimized by giving the medication with meals; it usually disappears promptly upon reduction of dosage. Doses used in toxoplasmosis may produce megaloblastic anemia, leukopenia, thrombocytopenia, pancytopenia, neutropenia, atrophic glossitis, hematuria, and disorders of cardiac rhythm.

Hematologic effects, however, may also occur at low doses in certain individuals (see PRECAUTIONS; General).

Pulmonary eosinophilia has been reported rarely.

OVERDOSAGE

Following the ingestion of 300 mg or more of pyrimethamine, gastrointestinal and/or central nervous system signs may be present, including convulsions. The initial symptoms are usually gastrointestinal and may include abdominal pain, nausea, severe and repeated vomiting, possibly including hematemesis. Central nervous system toxicity may be manifest by initial excitability, generalized and prolonged convulsions which may be followed by respiratory depression, circulatory collapse, and death within a few hours. Neurological symptoms appear rapidly (30 minutes to 2 hours after drug ingestion), suggesting that in gross overdosage pyrimethamine has a direct toxic effect on the central nervous system.

The fatal dose is variable, with the smallest reported fatal single dose being 375 mg. There are, however, reports of pediatric patients who have recovered after taking 375 to 625 mg.

There is no specific antidote to acute pyrimethamine poisoning. In the event of overdosage, symptomatic and supportive measures should be employed. Gastric lavage is recommended and is effective if carried out very soon after drug ingestion. Parenteral diazepam may be used to control convulsions. Folinic acid should be administered within 2 hours of drug ingestion to be most effective in counteracting the effects on the hematopoietic system (see WARNINGS). Due to the long half-life of pyrimethamine, daily monitoring of peripheral blood counts is recommended for up to several weeks after the overdose until normal hematologic values are restored.

DOSAGE AND ADMINISTRATION

For Treatment of Toxoplasmosis: 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 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.

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.

HOW SUPPLIED:

White, scored tablets containing 25 mg pyrimethamine, imprinted with "DARAPRIM" and "A3A" in bottles of 100 (NDC 69413-330-10) and bottles of 30 (NDC 69413-330-30).

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

REFERENCES

1. Eyles DE, Coleman N. Synergistic effect of sulfadiazine and Daraprim against experimental toxoplasmosis in the mouse. *Antibiot Chemother* 1953;3:483-490.
2. Jacobs L, Melton ML, Kaufman HE. Treatment of experimental ocular toxoplasmosis. *Arch Ophthalmol.* 1964;71:111-118.
3. Jim RTS, Elizaga FV. Development of chronic granulocytic leukemia in a patient treated with pyrimethamine. *Hawaii Med J.* 1977;36:173-176.
4. Sadoff L. Antimalarial drugs and Burkitt's lymphoma. *Lancet.* 1973;2:1262-1263.
5. Bahna L. Pyrimethamine. *LARC Monogr Eval Carcinog Risk Chem.* 1977;13:233-242.
6. Clive D, Johnson KO, Spector JKS, et al. Validation and characterization of the L5178Y/TK +/- mouse lymphoma mutagen assay system. *Mut Res.* 1979;59:61-108.

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