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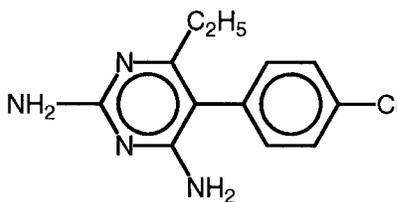
3 **DARAPRIM<sup>®</sup> (pyrimethamine)**

4 **25-mg Scored Tablets**

5

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

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



11

12 C<sub>12</sub>H<sub>13</sub>ClN<sub>4</sub>

13 Mol. Wt 248.71

14

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

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

22 Pyrimethamine possesses blood schizonticidal and some tissue schizonticidal activity against  
23 malaria parasites of humans. However, the 4-amino-quinoline compounds are more effective  
24 against the erythrocytic schizonts. It does not destroy gametocytes, but arrests sporogony in the  
25 mosquito.

## DARAPRIM<sup>®</sup> (pyrimethamine)

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

31

### 32 **INDICATIONS AND USAGE:**

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

35 **Treatment of Acute Malaria:** DARAPRIM is also indicated for the treatment of acute  
36 malaria. It should not be used alone to treat acute malaria. Fast-acting schizonticides such as  
37 chloroquine or quinine are indicated and preferable for the treatment of acute malaria. However,  
38 conjoint use of DARAPRIM with a sulfonamide (e.g., sulfadoxine) will initiate transmission  
39 control and suppression of susceptible strains of plasmodia.

40 **Chemoprophylaxis of Malaria:** DARAPRIM is indicated for the chemoprophylaxis of  
41 malaria due to susceptible strains of plasmodia. However, resistance to pyrimethamine is  
42 prevalent worldwide. It is not suitable as a prophylactic agent for travelers to most areas.

43

44 **CONTRAINDICATIONS:** Use of DARAPRIM is contraindicated in patients with known  
45 hypersensitivity to pyrimethamine. Use of the drug is also contraindicated in patients with  
46 documented megaloblastic anemia due to folate deficiency.

47

48 **WARNINGS:** The dosage of pyrimethamine required for the treatment of toxoplasmosis is 10  
49 to 20 times the recommended antimalaria dosage and approaches the toxic level. If signs of  
50 folate deficiency develop (see ADVERSE REACTIONS), reduce the dosage or discontinue  
51 the drug according to the response of the patient. Folinic acid (leucovorin) should be  
52 administered in a dosage of 5 to 15 mg daily (orally, IV, or IM) until normal hematopoiesis is  
53 restored.

## DARAPRIM<sup>®</sup> (pyrimethamine)

54 Data in two humans indicate that pyrimethamine may be carcinogenic: a 51-year-old female  
55 who developed chronic granulocytic leukemia after taking pyrimethamine for 2 years for  
56 toxoplasmosis,<sup>3</sup> and a 56-year-old patient who developed reticulum cell sarcoma after  
57 14 months of pyrimethamine for toxoplasmosis.<sup>4</sup>

58 Pyrimethamine has been reported to produce a significant increase in the number of lung  
59 tumors in mice when given intraperitoneally at doses of 25 mg/kg.<sup>5</sup>

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

63

### 64 **PRECAUTIONS:**

65 **General:** The recommended dosage for chemoprophylaxis of malaria should not be exceeded.

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

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

76 Women of childbearing potential who are taking DARAPRIM should be warned against  
77 becoming pregnant. Patients should be warned to keep DARAPRIM out of the reach of  
78 children. Patients should be advised not to exceed recommended doses. Patients should be  
79 warned that if anorexia and vomiting occur, they may be minimized by taking the drug with  
80 meals.

81 Concurrent administration of folinic acid is strongly recommended when used for the  
82 treatment of toxoplasmosis in all patients.

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83 **Laboratory Tests:** In patients receiving high dosage, as for the treatment of toxoplasmosis,  
84 semiweekly blood counts, including platelet counts, should be performed.

85 **Drug Interactions:** Pyrimethamine may be used with sulfonamides, quinine and other  
86 antimalarials, and with other antibiotics. However, the concomitant use of other antifolate drugs,  
87 such as sulfonamides or trimethoprim-sulfamethoxazole combinations, while the patient is  
88 receiving pyrimethamine, may increase the risk of bone marrow suppression. If signs of folate  
89 deficiency develop, pyrimethamine should be discontinued. Folinic acid (leucovorin) should be  
90 administered until normal hematopoiesis is restored (see WARNINGS). Mild hepatotoxicity has  
91 been reported in some patients when lorazepam and pyrimethamine were administered  
92 concomitantly.

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

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

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

102 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Pyrimethamine has been shown to  
103 be teratogenic in rats when given in oral doses 7 times the human dose for chemoprophylaxis of  
104 malaria or 2.5 times the human dose for treatment of toxoplasmosis. At these doses in rats,  
105 there was a significant increase in abnormalities such as cleft palate, brachygnathia, oligodactyly,  
106 and microphthalmia. Pyrimethamine has also been shown to produce terata, such as  
107 meningocele in hamsters and cleft palate in miniature pigs, when given in oral doses 170 and  
108 5 times the human dose, respectively, for chemoprophylaxis of malaria or for treatment of  
109 toxoplasmosis.

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

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112 Concurrent administration of folic acid is strongly recommended when used for the  
113 treatment of toxoplasmosis during pregnancy.

114 **Nursing Mothers:** Pyrimethamine is excreted in human milk. Because of the potential for  
115 serious adverse reactions in nursing infants from pyrimethamine, a decision should be made  
116 whether to discontinue nursing or to discontinue the drug, taking into account the importance of  
117 the drug to the mother (see WARNINGS and PRECAUTIONS: Pregnancy).

118 **Pediatric Use:** See DOSAGE AND ADMINISTRATION section.

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

125

126 **ADVERSE REACTIONS:** Hypersensitivity reactions, occasionally severe (such as Stevens-  
127 Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and anaphylaxis), and  
128 hyperphenylalaninemia can occur particularly when pyrimethamine is administered concomitantly  
129 with a sulfonamide. With doses of pyrimethamine used for the treatment of toxoplasmosis,  
130 anorexia and vomiting may occur. Vomiting may be minimized by giving the medication with  
131 meals; it usually disappears promptly upon reduction of dosage. Doses used in toxoplasmosis  
132 may produce megaloblastic anemia, leukopenia, thrombocytopenia, pancytopenia, atrophic  
133 glossitis, hematuria, and disorders of cardiac rhythm. Hematologic effects, however, may also  
134 occur at low doses in certain individuals (see PRECAUTIONS: General).

135 Pulmonary eosinophilia has been reported rarely.

136

137 **OVERDOSAGE:** Following the ingestion of 300 mg or more of pyrimethamine,  
138 gastrointestinal and/or central nervous system signs may be present, including convulsions. The  
139 initial symptoms are usually gastrointestinal and may include abdominal pain, nausea, severe and  
140 repeated vomiting, possibly including hematemesis. Central nervous system toxicity may be

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141 manifest by initial excitability, generalized and prolonged convulsions which may be followed by  
142 respiratory depression, circulatory collapse, and death within a few hours. Neurological  
143 symptoms appear rapidly (30 minutes to 2 hours after drug ingestion), suggesting that in gross  
144 overdose pyrimethamine has a direct toxic effect on the central nervous system.

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

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

155

### 156 **DOSAGE AND ADMINISTRATION:**

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

162 The adult *starting* dose is 50 to 75 mg of the drug daily, together with 1 to 4 g daily of a  
163 sulfonamide of the sulfapyrimidine type, e.g., sulfadoxine. This dosage is ordinarily continued for  
164 1 to 3 weeks, depending on the response of the patient and tolerance to therapy. The dosage  
165 may then be reduced to about one-half that previously given for each drug and continued for an  
166 additional 4 to 5 weeks.

167 The pediatric dosage of DARAPRIM is 1 mg/kg per day divided into two equal daily doses;  
168 after 2 to 4 days this dose may be reduced to one-half and continued for approximately  
169 1 month. The usual pediatric sulfonamide dosage is used in conjunction with DARAPRIM.

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170 **For Treatment of Acute Malaria:** DARAPRIM is NOT recommended alone in the  
171 treatment of acute malaria. Fast-acting schizonticides, such as chloroquine or quinine, are  
172 indicated for treatment of acute malaria. However, DARAPRIM at a dosage of 25 mg daily for  
173 2 days with a sulfonamide will initiate transmission control and suppression of non-*falciparum*  
174 malaria. DARAPRIM is only recommended for patients infected in areas where susceptible  
175 plasmodia exist. Should circumstances arise wherein DARAPRIM must be used alone in semi-  
176 immune persons, the adult dosage for acute malaria is 50 mg for 2 days; children 4 through  
177 10 years old may be given 25 mg daily for 2 days. In any event, clinical cure should be followed  
178 by the once-weekly regimen described below for chemoprophylaxis. Regimens which include  
179 suppression should be extended through any characteristic periods of early recrudescence and  
180 late relapse, i.e., for at least 10 weeks in each case.

### 181 **For Chemoprophylaxis of Malaria:**

182 Adults and pediatric patients over 10 years — 25 mg (1 tablet) once weekly

183 Children 4 through 10 years — 12.5 mg (1/2 tablet) once weekly

184 Infants and children under 4 years — 6.25 mg (1/4 tablet) once weekly

185

186 **HOW SUPPLIED:** White, scored tablets containing 25 mg pyrimethamine, imprinted with  
187 “DARAPRIM” and “A3A” in bottles of 100 (NDC 0173-0201-55).

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

189

### 190 **REFERENCES:**

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200 L5178Y/TK +/- mouse lymphoma mutagen assay system. *Mut Res.* 1979;59:61-108.

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205 Catalytica Pharmaceuticals, Inc.

206 Greenville, NC 27834

207 for

208 Glaxo Wellcome Inc.

209 Research Triangle Park, NC 27709

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