

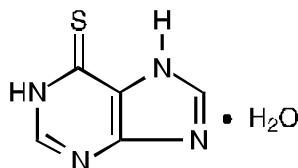
**PURINETHOL<sup>®</sup>****(mercaptopurine)****50-mg Scored Tablets****CAUTION**

**PURINETHOL (mercaptopurine) is a potent drug. It should not be used unless a diagnosis of acute lymphatic leukemia has been adequately established and the responsible physician is knowledgeable in assessing response to chemotherapy.**

**DESCRIPTION**

PURINETHOL (mercaptopurine) was synthesized and developed by Hitchings, Elion, and associates at the Wellcome Research Laboratories. It is one of a large series of purine analogues which interfere with nucleic acid biosynthesis and has been found active against human leukemias.

Mercaptopurine, known chemically as 1,7-dihydro-6*H*-purine-6-thione monohydrate, is an analogue of the purine bases adenine and hypoxanthine. Its structural formula is:



PURINETHOL is available in tablet form for oral administration. Each scored tablet contains 50 mg mercaptopurine and the inactive ingredients corn and potato starch, lactose, magnesium stearate, and stearic acid.

**CLINICAL PHARMACOLOGY**

Clinical studies have shown that the absorption of an oral dose of mercaptopurine in humans is incomplete and variable, averaging approximately 50% of the administered dose. The factors influencing absorption are unknown. Intravenous administration of an investigational preparation of

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28 mercaptopurine revealed a plasma half-disappearance time of 21 minutes in pediatric patients and  
29 47 minutes in adults. The volume of distribution usually exceeded that of the total body water.

30 Following the oral administration of <sup>35</sup>S-6-mercaptopurine in one subject, a total of 46% of the  
31 dose could be accounted for in the urine (as parent drug and metabolites) in the first 24 hours.  
32 Metabolites of mercaptopurine were found in urine within the first 2 hours after administration.  
33 Radioactivity (in the form of sulfate) could be found in the urine for weeks afterwards.

34 There is negligible entry of mercaptopurine into cerebrospinal fluid.

35 Plasma protein binding averages 19% over the concentration range 10 to 50 mcg/mL (a  
36 concentration only achieved by intravenous administration of mercaptopurine at doses exceeding 5 to  
37 10 mg/kg).

38 Monitoring of plasma levels of mercaptopurine during therapy is of questionable value. There is  
39 technical difficulty in determining plasma concentrations which are seldom greater than 1 to  
40 2 mcg/mL after a therapeutic oral dose. More significantly, mercaptopurine enters rapidly into the  
41 anabolic and catabolic pathways for purines, and the active intracellular metabolites have  
42 appreciably longer half-lives than the parent drug. The biochemical effects of a single dose of  
43 mercaptopurine are evident long after the parent drug has disappeared from plasma. Because of this  
44 rapid metabolism of mercaptopurine to active intracellular derivatives, hemodialysis would not be  
45 expected to appreciably reduce toxicity of the drug. There is no known pharmacologic antagonist to  
46 the biochemical actions of mercaptopurine in vivo.

47 Mercaptopurine competes with hypoxanthine and guanine for the enzyme hypoxanthine-guanine  
48 phosphoribosyltransferase (HGPRTase) and is itself converted to thioinosinic acid (TIMP). This  
49 intracellular nucleotide inhibits several reactions involving inosinic acid (IMP), including the  
50 conversion of IMP to xanthylic acid (XMP) and the conversion of IMP to adenylic acid (AMP) via  
51 adenylosuccinate (SAMP). In addition, 6-methylthioinosinate (MTIMP) is formed by the methylation  
52 of TIMP. Both TIMP and MTIMP have been reported to inhibit  
53 glutamine-5-phosphoribosylpyrophosphate amidotransferase, the first enzyme unique to the de novo  
54 pathway for purine ribonucleotide synthesis.

55 Experiments indicate that radiolabeled mercaptopurine may be recovered from the DNA in the  
56 form of deoxythioguanosine. Some mercaptopurine is converted to nucleotide derivatives of  
57 6-thioguanine (6-TG) by the sequential actions of inosinate (IMP) dehydrogenase and xanthylate  
58 (XMP) aminase, converting TIMP to thioguanlylic acid (TGMP).

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59 Animal tumors that are resistant to mercaptopurine often have lost the ability to convert  
60 mercaptopurine to TIMP. However, it is clear that resistance to mercaptopurine may be acquired by  
61 other means as well, particularly in human leukemias.

62 It is not known exactly which of any one or more of the biochemical effects of mercaptopurine and  
63 its metabolites are directly or predominantly responsible for cell death.

64 The catabolism of mercaptopurine and its metabolites is complex. In humans, after oral  
65 administration of <sup>35</sup>S-6-mercaptopurine, urine contains intact mercaptopurine, thiouric acid (formed  
66 by direct oxidation by xanthine oxidase, probably via 6-mercapto-8-hydroxypurine), and a number of  
67 6-methylated thiopurines. The methylthiopurines yield appreciable amounts of inorganic sulfate. The  
68 importance of the metabolism by xanthine oxidase relates to the fact that ZYLOPRIM<sup>®</sup> (allopurinol)  
69 inhibits this enzyme and retards the catabolism of mercaptopurine and its active metabolites. A  
70 significant reduction in mercaptopurine dosage is mandatory if a potent xanthine oxidase inhibitor and  
71 mercaptopurine are used simultaneously in a patient (see PRECAUTIONS).

72

### 73 INDICATIONS AND USAGE

74 PURINETHOL (mercaptopurine) is indicated for remission induction and maintenance therapy of  
75 acute lymphatic leukemia. The response to this agent depends upon the particular subclassification of  
76 acute lymphatic leukemia and the age of the patient (pediatric patient or adult).

77 **Acute Lymphatic (Lymphocytic, Lymphoblastic) Leukemia:** Given as a single agent for  
78 remission induction, PURINETHOL induces complete remission in approximately 25% of pediatric  
79 patients and 10% of adults. However, reliance upon PURINETHOL alone is not justified for initial  
80 remission induction of acute lymphatic leukemia since combination chemotherapy with vincristine,  
81 prednisone, and L-asparaginase results in more frequent complete remission induction than with  
82 PURINETHOL alone or in combination. The duration of complete remission induced in acute  
83 lymphatic leukemia is so brief without the use of maintenance therapy that some form of drug therapy  
84 is considered essential. PURINETHOL, as a single agent, is capable of significantly prolonging  
85 complete remission duration; however, combination therapy has produced remission duration longer  
86 than that achieved with PURINETHOL alone.

87 **Acute Myelogenous (and Acute Myelomonocytic) Leukemia:** As a single agent,  
88 PURINETHOL will induce complete remission in approximately 10% of pediatric patients and adults

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89 with acute myelogenous leukemia or its subclassifications. These results are inferior to those  
90 achieved with combination chemotherapy employing optimum treatment schedules.

91 **Central Nervous System Leukemia:** PURINETHOL is not effective for prophylaxis or treatment  
92 of central nervous system leukemia.

93 **Other Neoplasms:** PURINETHOL is not effective in chronic lymphatic leukemia, the lymphomas  
94 (including Hodgkins Disease), or solid tumors.

95

### 96 **CONTRAINDICATIONS**

97 PURINETHOL should not be used unless a diagnosis of acute lymphatic leukemia has been  
98 adequately established and the responsible physician is knowledgeable in assessing response to  
99 chemotherapy.

100 PURINETHOL should not be used in patients whose disease has demonstrated prior resistance to  
101 this drug. In animals and humans, there is usually complete cross-resistance between mercaptopurine  
102 and thioguanine.

103 PURINETHOL should not be used in patients who have a hypersensitivity to mercaptopurine or  
104 any component of the formulation.

105

### 106 **WARNINGS**

107 **SINCE DRUGS USED IN CANCER CHEMOTHERAPY ARE POTENTIALLY**  
108 **HAZARDOUS, IT IS RECOMMENDED THAT ONLY PHYSICIANS EXPERIENCED WITH**  
109 **THE RISKS OF PURINETHOL AND KNOWLEDGEABLE IN THE NATURAL HISTORY**  
110 **OF ACUTE LEUKEMIAS ADMINISTER THIS DRUG.**

111 **Bone Marrow Toxicity:** The most consistent, dose-related toxicity is bone marrow suppression.  
112 This may be manifest by anemia, leukopenia, thrombocytopenia, or any combination of these. Any of  
113 these findings may also reflect progression of the underlying disease. Since mercaptopurine may have  
114 a delayed effect, it is important to withdraw the medication temporarily at the first sign of an  
115 abnormally large fall in any of the formed elements of the blood.

116 There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase  
117 (TPMT) who may be unusually sensitive to the myelosuppressive effects of mercaptopurine and prone  
118 to developing rapid bone marrow suppression following the initiation of treatment. Substantial

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119 dosage reductions may be required to avoid the development of life-threatening bone marrow  
120 suppression in these patients. This toxicity may be more profound in patients treated with concomitant  
121 allopurinol (see PRECAUTIONS: Drug Interactions). This problem could be exacerbated by  
122 coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine.

123 **Hepatotoxicity:** Mercaptopurine is hepatotoxic in animals and humans. A small number of deaths  
124 have been reported that may have been attributed to hepatic necrosis due to administration of  
125 mercaptopurine. Hepatic injury can occur with any dosage, but seems to occur with more frequency  
126 when doses of 2.5 mg/kg/day are exceeded. The histologic pattern of mercaptopurine hepatotoxicity  
127 includes features of both intrahepatic cholestasis and parenchymal cell necrosis, either of which may  
128 predominate. It is not clear how much of the hepatic damage is due to direct toxicity from the drug and  
129 how much may be due to a hypersensitivity reaction. In some patients jaundice has cleared following  
130 withdrawal of mercaptopurine and reappeared with its reintroduction.

131 Published reports have cited widely varying incidences of overt hepatotoxicity. In a large series of  
132 patients with various neoplastic diseases, mercaptopurine was administered orally in doses ranging  
133 from 2.5 mg/kg to 5.0 mg/kg without any evidence of hepatotoxicity. It was noted by the authors that  
134 no definite clinical evidence of liver damage could be ascribed to the drug, although an occasional  
135 case of serum hepatitis did occur in patients receiving 6-MP who previously had transfusions. In  
136 reports of smaller cohorts of adult and pediatric leukemic patients, the incidence of hepatotoxicity  
137 ranged from 0% to 6%. In an isolated report by Einhorn and Davidsohn, jaundice was observed more  
138 frequently (40%), especially when doses exceeded 2.5 mg/kg. Usually, clinically detectable jaundice  
139 appears early in the course of treatment (1 to 2 months). However, jaundice has been reported as  
140 early as 1 week and as late as 8 years after the start of treatment with mercaptopurine.

141 Monitoring of serum transaminase levels, alkaline phosphatase, and bilirubin levels may allow  
142 early detection of hepatotoxicity. It is advisable to monitor these liver function tests at weekly  
143 intervals when first beginning therapy and at monthly intervals thereafter. Liver function tests may be  
144 advisable more frequently in patients who are receiving mercaptopurine with other hepatotoxic drugs  
145 or with known pre-existing liver disease.

146 The concomitant administration of mercaptopurine with other hepatotoxic agents requires  
147 especially careful clinical and biochemical monitoring of hepatic function. Combination therapy  
148 involving mercaptopurine with other drugs not felt to be hepatotoxic should nevertheless be  
149 approached with caution. The combination of mercaptopurine with doxorubicin was reported to be

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150 hepatotoxic in 19 of 20 patients undergoing remission-induction therapy for leukemia resistant to  
151 previous therapy.

152 The hepatotoxicity has been associated in some cases with anorexia, diarrhea, jaundice, and  
153 ascites. Hepatic encephalopathy has occurred.

154 The onset of clinical jaundice, hepatomegaly, or anorexia with tenderness in the right  
155 hypochondrium are immediate indications for withholding mercaptopurine until the exact etiology can  
156 be identified. Likewise, any evidence of deterioration in liver function studies, toxic hepatitis, or  
157 biliary stasis should prompt discontinuation of the drug and a search for an etiology of the  
158 hepatotoxicity.

159 **Immunosuppression:** Mercaptopurine recipients may manifest decreased cellular  
160 hypersensitivities and impaired allograft rejection. Induction of immunity to infectious agents or  
161 vaccines will be subnormal in these patients; the degree of immunosuppression will depend on  
162 antigen dose and temporal relationship to drug. This immunosuppressive effect should be carefully  
163 considered with regard to intercurrent infections and risk of subsequent neoplasia.

164 **Pregnancy:** Pregnancy Category D. Mercaptopurine can cause fetal harm when administered to a  
165 pregnant woman. Women receiving mercaptopurine in the first trimester of pregnancy have an  
166 increased incidence of abortion; the risk of malformation in offspring surviving first trimester  
167 exposure is not accurately known. In a series of 28 women receiving mercaptopurine after the first  
168 trimester of pregnancy, 3 mothers died undelivered, 1 delivered a stillborn child, and 1 aborted; there  
169 were no cases of macroscopically abnormal fetuses. Since such experience cannot exclude the  
170 possibility of fetal damage, mercaptopurine should be used during pregnancy only if the benefit  
171 clearly justifies the possible risk to the fetus, and particular caution should be given to the use of  
172 mercaptopurine in the first trimester of pregnancy.

173 There are no adequate and well-controlled studies in pregnant women. If this drug is used during  
174 pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of  
175 the potential hazard to the fetus. Women of childbearing potential should be advised to avoid  
176 becoming pregnant.

177

## 178 PRECAUTIONS

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179 **General:** The safe and effective use of PURINETHOL demands a thorough knowledge of the natural  
180 history of the condition being treated. After selection of an initial dosage schedule, therapy will  
181 frequently need to be modified depending upon the patient's response and manifestations of toxicity.

182 The most frequent, serious, toxic effect of PURINETHOL is myelosuppression resulting in  
183 leukopenia, thrombocytopenia, and anemia. These toxic effects are often unavoidable during the  
184 induction phase of adult acute leukemia if remission induction is to be successful. Whether or not  
185 these manifestations demand modification or cessation of dosage depends both upon the response of  
186 the underlying disease and a careful consideration of supportive facilities (granulocyte and platelet  
187 transfusions) which may be available. Life-threatening infections and bleeding have been observed as  
188 a consequence of mercaptopurine-induced granulocytopenia and thrombocytopenia. Severe  
189 hematologic toxicity may require supportive therapy with platelet transfusions for bleeding, and  
190 antibiotics and granulocyte transfusions if sepsis is documented.

191 **If it is not the intent to deliberately induce bone marrow hypoplasia, it is important to**  
192 **discontinue the drug temporarily at the first evidence of an abnormally large fall in white blood**  
193 **cell count, platelet count, or hemoglobin concentration.** In many patients with severe depression of  
194 the formed elements of the blood due to PURINETHOL, the bone marrow appears hypoplastic on  
195 aspiration or biopsy, whereas in other cases it may appear normocellular. The qualitative changes in  
196 the erythroid elements toward the megaloblastic series, characteristically seen with the folic acid  
197 antagonists and some other antimetabolites, are not seen with this drug.

198 It is probably advisable to start with smaller dosages in patients with impaired renal function,  
199 since the latter might result in slower elimination of the drug and metabolites and a greater cumulative  
200 effect.

201 **Information for Patients:** Patients should be informed that the major toxicities of PURINETHOL  
202 are related to myelosuppression, hepatotoxicity, and gastrointestinal toxicity. Patients should never be  
203 allowed to take the drug without medical supervision and should be advised to consult their physician  
204 if they experience fever, sore throat, jaundice, nausea, vomiting, signs of local infection, bleeding  
205 from any site, or symptoms suggestive of anemia. Women of childbearing potential should be advised  
206 to avoid becoming pregnant.

207 **Laboratory Tests:** It is recommended that evaluation of the hemoglobin or hematocrit, total white  
208 blood cell count and differential count, and quantitative platelet count be obtained weekly while the

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209 patient is on therapy with PURINETHOL. In cases where the cause of fluctuations in the formed  
210 elements in the peripheral blood is obscure, bone marrow examination may be useful for the  
211 evaluation of marrow status. The decision to increase, decrease, continue, or discontinue a given  
212 dosage of PURINETHOL must be based not only on the absolute hematologic values, but also upon  
213 the rapidity with which changes are occurring. In many instances, particularly during the induction  
214 phase of acute leukemia, complete blood counts will need to be done more frequently than once  
215 weekly in order to evaluate the effect of the therapy.

216 **Drug Interactions:** When allopurinol and mercaptopurine are administered concomitantly, it is  
217 imperative that the dose of mercaptopurine be reduced to one third to one quarter of the usual dose.  
218 Failure to observe this dosage reduction will result in a delayed catabolism of mercaptopurine and  
219 the strong likelihood of inducing severe toxicity.

220 There is usually complete cross-resistance between mercaptopurine and thioguanine.

221 The dosage of mercaptopurine may need to be reduced when this agent is combined with other  
222 drugs whose primary or secondary toxicity is myelosuppression. Enhanced marrow suppression has  
223 been noted in some patients also receiving trimethoprim-sulfamethoxazole.

224 Inhibition of the anticoagulant effect of warfarin, when given with mercaptopurine, has been  
225 reported.

226 As there is in vitro evidence that aminosalicylate derivatives (e.g., olsalazine, mesalazine, or  
227 sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients  
228 receiving concurrent mercaptopurine therapy (see WARNINGS).

229 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Mercaptopurine causes chromosomal  
230 aberrations in animals and humans and induces dominant-lethal mutations in male mice. In mice,  
231 surviving female offspring of mothers who received chronic low doses of mercaptopurine during  
232 pregnancy were found sterile, or if they became pregnant, had smaller litters and more dead fetuses as  
233 compared to control animals. Carcinogenic potential exists in humans, but the extent of the risk is  
234 unknown.

235 The effect of mercaptopurine on human fertility is unknown for either males or females.

236 **Pregnancy: Teratogenic Effects:** Pregnancy Category D. See WARNINGS section.

237 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs  
238 are excreted in human milk, and because of the potential for serious adverse reactions in nursing



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239 infants from mercaptopurine, a decision should be made whether to discontinue nursing or to  
240 discontinue the drug, taking into account the importance of the drug to the mother.

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

242

### 243 **ADVERSE REACTIONS**

244 The principal and potentially serious toxic effects of PURINETHOL are bone marrow toxicity and  
245 hepatotoxicity (see WARNINGS).

246 **Hematologic:** The most frequent adverse reaction to PURINETHOL is myelosuppression. The  
247 induction of complete remission of acute lymphatic leukemia frequently is associated with marrow  
248 hypoplasia. Maintenance of remission generally involves multiple-drug regimens whose component  
249 agents cause myelosuppression. Anemia, leukopenia, and thrombocytopenia are frequently observed.  
250 Dosages and schedules are adjusted to prevent life-threatening cytopenias.

251 **Renal:** Hyperuricemia and/or hyperuricosuria may occur in patients receiving PURINETHOL as a  
252 consequence of rapid cell lysis accompanying the antineoplastic effect. Adverse effects can be  
253 minimized by increased hydration, urine alkalization, and the prophylactic administration of a  
254 xanthine oxidase inhibitor such as allopurinol. The dosage of PURINETHOL should be reduced to  
255 one third to one quarter of the usual dose if allopurinol is given concurrently.

256 **Gastrointestinal:** Intestinal ulceration has been reported. Nausea, vomiting, and anorexia are  
257 uncommon during initial administration. Mild diarrhea and sprue-like symptoms have been noted  
258 occasionally, but it is difficult at present to attribute these to the medication. Oral lesions are rarely  
259 seen, and when they occur they resemble thrush rather than antifolic ulcerations.

260 An increased risk of pancreatitis may be associated with the investigational use of PURINETHOL  
261 in inflammatory bowel disease.

262 **Miscellaneous:** While dermatologic reactions can occur as a consequence of disease, the  
263 administration of PURINETHOL has been associated with skin rashes and hyperpigmentation.  
264 Alopecia has been reported.

265 Drug fever has been very rarely reported with PURINETHOL. Before attributing fever to  
266 PURINETHOL, every attempt should be made to exclude more common causes of pyrexia, such as  
267 sepsis, in patients with acute leukemia.

268 Oligospermia has been reported.

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### 270 **OVERDOSAGE**

271 Signs and symptoms of overdosage may be immediate such as anorexia, nausea, vomiting, and  
272 diarrhea; or delayed such as myelosuppression, liver dysfunction, and gastroenteritis. Dialysis cannot  
273 be expected to clear mercaptopurine. Hemodialysis is thought to be of marginal use due to the rapid  
274 intracellular incorporation of mercaptopurine into active metabolites with long persistence. The oral  
275 LD<sub>50</sub> of mercaptopurine was determined to be 480 mg/kg in the mouse and 425 mg/kg in the rat.

276 There is no known pharmacologic antagonist of mercaptopurine. The drug should be discontinued  
277 immediately if unintended toxicity occurs during treatment. If a patient is seen immediately following  
278 an accidental overdosage of the drug, it may be useful to induce emesis.

### 279 **DOSAGE AND ADMINISTRATION**

280 **Induction Therapy:** PURINETHOL is administered orally. The dosage which will be tolerated  
281 and be effective varies from patient to patient, and therefore careful titration is necessary to obtain the  
282 optimum therapeutic effect without incurring excessive, unintended toxicity. The usual initial dosage  
283 for pediatric patients and adults is 2.5 mg/kg of body weight per day (100 to 200 mg in the average  
284 adult and 50 mg in an average 5-year-old child). Pediatric patients with acute leukemia have tolerated  
285 this dose without difficulty in most cases; it may be continued daily for several weeks or more in  
286 some patients. If, after 4 weeks at this dosage, there is no clinical improvement and no definite  
287 evidence of leukocyte or platelet depression, the dosage may be increased up to 5 mg/kg daily. A  
288 dosage of 2.5 mg/kg/day may result in a rapid fall in leukocyte count within 1 to 2 weeks in some  
289 adults with acute lymphatic leukemia and high total leukocyte counts.

290 The total daily dosage may be given at one time. It is calculated to the nearest multiple of 25 mg.

291 The dosage of PURINETHOL should be reduced to one third to one quarter of the usual dose if  
292 allopurinol is given concurrently. Because the drug may have a delayed action, it should be  
293 discontinued at the first sign of an abnormally large or rapid fall in the leukocyte or platelet count. If  
294 subsequently the leukocyte count or platelet count remains constant for 2 or 3 days, or rises, treatment  
295 may be resumed.

296 **Maintenance Therapy:** Once a complete hematologic remission is obtained, maintenance therapy  
297 is considered essential. Maintenance doses will vary from patient to patient. A usual daily  
298 maintenance dose of PURINETHOL is 1.5 to 2.5 mg/kg/day as a single dose. It is to be emphasized

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299 that in pediatric patients with acute lymphatic leukemia in remission, superior results have been  
300 obtained when PURINETHOL has been combined with other agents (most frequently with  
301 methotrexate) for remission maintenance. PURINETHOL should rarely be relied upon as a single  
302 agent for the maintenance of remissions induced in acute leukemia.

303 Procedures for proper handling and disposal of anticancer drugs should be considered. Several  
304 guidelines on this subject have been published.<sup>1-8</sup>

305 There is no general agreement that all of the procedures recommended in the guidelines are  
306 necessary or appropriate.

307 **Dosage in Renal Impairment:** Consideration should be given to reducing the dosage in patients  
308 with impaired renal function.

309 **Dosage in Hepatic Impairment:** Consideration should be given to reducing the dosage in patients  
310 with impaired hepatic function.

311

### 312 HOW SUPPLIED

313 Pale yellow to buff, scored tablets containing 50 mg mercaptopurine, imprinted with  
314 "PURINETHOL" and "04A"; bottles of 25 (NDC 0173-0807-25) and 250 (NDC 0173-0807-65).

315 **Store at 15° to 25°C (59° to 77°F) in a dry place.**

316

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