

1 **PRESCRIBING INFORMATION**

2
3 **TABLOID[®]**
4 **brand Thioguanine**
5 **40-mg Scored Tablets**

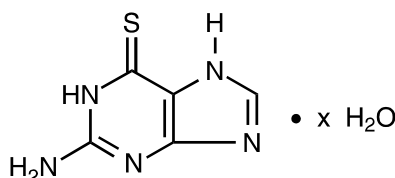
6 **CAUTION**

7 **TABLOID brand Thioguanine is a potent drug. It should not be used unless a diagnosis**
8 **of acute nonlymphocytic leukemia has been adequately established and the responsible**
9 **physician is knowledgeable in assessing response to chemotherapy.**

10 **DESCRIPTION**

11 TABLOID brand Thioguanine was synthesized and developed by Hitchings, Elion, and
12 associates at the Wellcome Research Laboratories. It is one of a large series of purine analogues
13 which interfere with nucleic acid biosynthesis, and has been found active against selected human
14 neoplastic diseases.

15 Thioguanine, known chemically as 2-amino-1,7-dihydro-6*H*-purine-6-thione, is an analogue
16 of the nucleic acid constituent guanine, and is closely related structurally and functionally to
17 PURINETHOL[®] (mercaptopurine). Its structural formula is:



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20
21 TABLOID brand Thioguanine is available in tablets for oral administration. Each scored
22 tablet contains 40 mg thioguanine and the inactive ingredients gum acacia, lactose, magnesium
23 stearate, potato starch, and stearic acid.

24 **CLINICAL PHARMACOLOGY**

25 Clinical studies have shown that the absorption of an oral dose of thioguanine in humans is
26 incomplete and variable, averaging approximately 30% of the administered dose (range: 14% to
27 46%). Following oral administration of ³⁵S-6-thioguanine, total plasma radioactivity reached a
28 maximum at 8 hours and declined slowly thereafter. Parent drug represented only a very small
29 fraction of the total plasma radioactivity at any time, being virtually undetectable throughout the
30 period of measurements.

31 The oral administration of radiolabeled thioguanine revealed only trace quantities of parent
32 drug in the urine. However, a methylated metabolite, 2-amino-6-methylthiopurine (MTG),
33 appeared very early, rose to a maximum 6 to 8 hours after drug administration, and was still
34 being excreted after 12 to 22 hours. Radiolabeled sulfate appeared somewhat later than MTG but

35 was the principal metabolite after 8 hours. Thiouric acid and some unidentified products were
36 found in the urine in small amounts. Intravenous administration of ³⁵S-6-thioguanine disclosed a
37 median plasma half-disappearance time of 80 minutes (range: 25 to 240 minutes) when the
38 compound was given in single doses of 65 to 300 mg/m². Although initial plasma levels of
39 thioguanine did correlate with the dose level, there was no correlation between the plasma
40 half-disappearance time and the dose.

41 Thioguanine is incorporated into the DNA and the RNA of human bone marrow cells. Studies
42 with intravenous ³⁵S-6-thioguanine have shown that the amount of thioguanine incorporated into
43 nucleic acids is more than 100 times higher after 5 daily doses than after a single dose. With the
44 5-dose schedule, from one-half to virtually all of the guanine in the residual DNA was replaced
45 by thioguanine. Tissue distribution studies of ³⁵S-6-thioguanine in mice showed only traces of
46 radioactivity in brain after oral administration. No measurements have been made of thioguanine
47 concentrations in human cerebrospinal fluid (CSF), but observations on tissue distribution in
48 animals, together with the lack of CNS penetration by the closely related compound,
49 mercaptopurine, suggest that thioguanine does not reach therapeutic concentrations in the CSF.

50 Monitoring of plasma levels of thioguanine during therapy is of questionable value. There is
51 technical difficulty in determining plasma concentrations, which are seldom greater than 1 to
52 2 mcg/mL after a therapeutic oral dose. More significantly, thioguanine enters rapidly into the
53 anabolic and catabolic pathways for purines, and the active intracellular metabolites have
54 appreciably longer half-lives than the parent drug. The biochemical effects of a single dose of
55 thioguanine are evident long after the parent drug has disappeared from plasma. Because of this
56 rapid metabolism of thioguanine to active intracellular derivatives, hemodialysis would not be
57 expected to appreciably reduce toxicity of the drug.

58 Thioguanine competes with hypoxanthine and guanine for the enzyme hypoxanthine-guanine
59 phosphoribosyltransferase (HGPRTase) and is itself converted to 6-thioguanilic acid (TGMP).
60 This nucleotide reaches high intracellular concentrations at therapeutic doses. TGMP interferes
61 at several points with the synthesis of guanine nucleotides. It inhibits de novo purine
62 biosynthesis by pseudo-feedback inhibition of glutamine-5-phosphoribosylpyrophosphate
63 amidotransferase—the first enzyme unique to the de novo pathway for purine ribonucleotide
64 synthesis. TGMP also inhibits the conversion of inosinic acid (IMP) to xanthylic acid (XMP) by
65 competition for the enzyme IMP dehydrogenase. At one time TGMP was felt to be a significant
66 inhibitor of ATP:GMP phosphotransferase (guanylate kinase), but recent results have shown this
67 not to be so.

68 Thioguanilic acid is further converted to the di- and tri-phosphates, thioguanosine
69 diphosphate (TGDP) and thioguanosine triphosphate (TGTP) (as well as their 2'-deoxyribosyl
70 analogues) by the same enzymes which metabolize guanine nucleotides. Thioguanine
71 nucleotides are incorporated into both the RNA and the DNA by phosphodiester linkages and it
72 has been argued that incorporation of such fraudulent bases contributes to the cytotoxicity of
73 thioguanine.

74 Thus, thioguanine has multiple metabolic effects and at present it is not possible to designate
75 one major site of action. Its tumor inhibitory properties may be due to one or more of its effects
76 on (a) feedback inhibition of de novo purine synthesis; (b) inhibition of purine nucleotide
77 interconversions; or (c) incorporation into the DNA and the RNA. The net consequence of its
78 actions is a sequential blockade of the synthesis and utilization of the purine nucleotides.

79 The catabolism of thioguanine and its metabolites is complex and shows significant
80 differences between humans and the mouse. In both humans and mice, after oral administration
81 of ³⁵S-6-thioguanine, urine contains virtually no detectable intact thioguanine. While
82 deamination and subsequent oxidation to thiouric acid occurs only to a small extent in humans, it
83 is the main pathway in mice. The product of deamination by guanase, 6-thioxanthine is inactive,
84 having negligible antitumor activity. This pathway of thioguanine inactivation is not dependent
85 on the action of xanthine oxidase, and an inhibitor of that enzyme (such as allopurinol) will not
86 block the detoxification of thioguanine even though the inactive 6-thioxanthine is normally
87 further oxidized by xanthine oxidase to thiouric acid before it is eliminated. In humans,
88 methylation of thioguanine is much more extensive than in the mouse. The product of
89 methylation, 2-amino-6-methylthiopurine, is also substantially less active and less toxic than
90 thioguanine and its formation is likewise unaffected by the presence of allopurinol. Appreciable
91 amounts of inorganic sulfate are also found in both murine and human urine, presumably arising
92 from further metabolism of the methylated derivatives.

93 In some animal tumors, resistance to the effect of thioguanine correlates with the loss of
94 HGPRTase activity and the resulting inability to convert thioguanine to thioguanilic acid.
95 However, other resistance mechanisms, such as increased catabolism of TGMP by a nonspecific
96 phosphatase, may be operative. Although not invariable, it is usual to find cross-resistance
97 between thioguanine and its close analogue, PURINETHOL (mercaptopurine).

98 **INDICATIONS AND USAGE**

- 99 **a) Acute Nonlymphocytic Leukemias:** TABLOID brand Thioguanine is indicated for
100 remission induction, remission consolidation, and maintenance therapy of acute
101 nonlymphocytic leukemias. The response to this agent depends upon the age of the patient
102 (younger patients faring better than older) and whether thioguanine is used in previously
103 treated or previously untreated patients. Reliance upon thioguanine alone is seldom justified
104 for initial remission induction of acute nonlymphocytic leukemias because combination
105 chemotherapy including thioguanine results in more frequent remission induction and longer
106 duration of remission than thioguanine alone.
- 107 **b) Other Neoplasms:** TABLOID brand Thioguanine is not effective in chronic lymphocytic
108 leukemia, Hodgkin's lymphoma, multiple myeloma, or solid tumors. Although thioguanine is
109 one of several agents with activity in the treatment of the chronic phase of chronic
110 myelogenous leukemia, more objective responses are observed with MYLERAN[®] (busulfan),
111 and therefore busulfan is usually regarded as the preferred drug.

112 **CONTRAINDICATIONS**

113 Thioguanine should not be used in patients whose disease has demonstrated prior resistance to
114 this drug. In animals and humans, there is usually complete cross-resistance between
115 PURINETHOL (mercaptopurine) and TABLOID brand Thioguanine.

116 **WARNINGS**

117 SINCE DRUGS USED IN CANCER CHEMOTHERAPY ARE POTENTIALLY
118 HAZARDOUS, IT IS RECOMMENDED THAT ONLY PHYSICIANS EXPERIENCED WITH
119 THE RISKS OF THIOGUANINE AND KNOWLEDGEABLE IN THE NATURAL HISTORY
120 OF ACUTE NONLYMPHOCYTIC LEUKEMIAS ADMINISTER THIS DRUG.

121 The most consistent, dose-related toxicity is bone marrow suppression. This may be
122 manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Any one of
123 these findings may also reflect progression of the underlying disease. Since thioguanine may
124 have a delayed effect, it is important to withdraw the medication temporarily at the first sign of
125 an abnormally large fall in any of the formed elements of the blood.

126 There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase
127 (TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine and
128 prone to developing rapid bone marrow suppression following the initiation of treatment.
129 Substantial dosage reductions may be required to avoid the development of life-threatening bone
130 marrow suppression in these patients. Prescribers should be aware that some laboratories offer
131 testing for TPMT deficiency. Since bone marrow suppression may be associated with factors
132 other than TPMT deficiency, TPMT testing may not identify all patients at risk for severe
133 toxicity. Therefore, close monitoring of clinical and hematologic parameters is important. Bone
134 marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT,
135 such as olsalazine, mesalazine, or sulphasalazine.

136 It is recommended that evaluation of the hemoglobin concentration or hematocrit, total white
137 blood cell count and differential count, and quantitative platelet count be obtained frequently
138 while the patient is on thioguanine therapy. In cases where the cause of fluctuations in the
139 formed elements in the peripheral blood is obscure, bone marrow examination may be useful for
140 the evaluation of marrow status. The decision to increase, decrease, continue, or discontinue a
141 given dosage of thioguanine must be based not only on the absolute hematologic values, but also
142 upon the rapidity with which changes are occurring. In many instances, particularly during the
143 induction phase of acute leukemia, complete blood counts will need to be done more frequently
144 in order to evaluate the effect of the therapy. The dosage of thioguanine may need to be reduced
145 when this agent is combined with other drugs whose primary toxicity is myelosuppression.

146 Myelosuppression is often unavoidable during the induction phase of adult acute
147 nonlymphocytic leukemias if remission induction is to be successful. Whether or not this
148 demands modification or cessation of dosage depends both upon the response of the underlying
149 disease and a careful consideration of supportive facilities (granulocyte and platelet transfusions)

150 which may be available. Life-threatening infections and bleeding have been observed as
151 consequences of thioguanine-induced granulocytopenia and thrombocytopenia.

152 The effect of thioguanine on the immunocompetence of patients is unknown.

153 **Pregnancy:** Pregnancy Category D. Drugs such as thioguanine are potential mutagens and
154 teratogens. Thioguanine may cause fetal harm when administered to a pregnant woman.

155 Thioguanine has been shown to be teratogenic in rats when given in doses 5 times the human
156 dose. When given to the rat on the 4th and 5th days of gestation, 13% of surviving placentas did
157 not contain fetuses, and 19% of offspring were malformed or stunted. The malformations noted
158 included generalized edema, cranial defects, and general skeletal hypoplasia, hydrocephalus,
159 ventral hernia, situs inversus, and incomplete development of the limbs. There are no adequate
160 and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the
161 patient becomes pregnant while taking the drug, the patient should be apprised of the potential
162 hazard to the fetus. Women of childbearing potential should be advised to avoid becoming
163 pregnant.

164 **PRECAUTIONS**

165 **General:** Although the primary toxicity of thioguanine is myelosuppression, other toxicities
166 have occasionally been observed, particularly when thioguanine is used in combination with
167 other cancer chemotherapeutic agents.

168 A few cases of jaundice have been reported in patients with leukemia receiving thioguanine.
169 Among these were 2 adult male patients and 4 pediatric patients with acute myelogenous
170 leukemia and an adult male with acute lymphocytic leukemia who developed veno-occlusive
171 hepatic disease while receiving chemotherapy for their leukemia. Six patients had received
172 cytarabine prior to treatment with thioguanine, and some were receiving other chemotherapy in
173 addition to thioguanine when they became symptomatic. While veno-occlusive hepatic disease
174 has not been reported in patients treated with thioguanine alone, it is recommended that
175 thioguanine be withheld if there is evidence of toxic hepatitis or biliary stasis, and that
176 appropriate clinical and laboratory investigations be initiated to establish the etiology of the
177 hepatic dysfunction. Deterioration in liver function studies during thioguanine therapy should
178 prompt discontinuation of treatment and a search for an explanation of the hepatotoxicity.

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

185 **Laboratory Tests:** Prescribers should be aware that some laboratories offer testing for TPMT
186 deficiency (see WARNINGS).

187 It is advisable to monitor liver function tests (serum transaminases, alkaline phosphatase,
188 bilirubin) at weekly intervals when first beginning therapy and at monthly intervals thereafter. It

189 may be advisable to perform liver function tests more frequently in patients with known
190 pre-existing liver disease or in patients who are receiving thioguanine and other hepatotoxic
191 drugs. Patients should be instructed to discontinue thioguanine immediately if clinical jaundice is
192 detected (see WARNINGS).

193 **Drug Interactions:** There is usually complete cross-resistance between PURINETHOL
194 (mercaptopurine) and TABLOID brand Thioguanine.

195 In one study, 12 of approximately 330 patients receiving continuous busulfan and thioguanine
196 therapy for treatment of chronic myelogenous leukemia were found to have esophageal varices
197 associated with abnormal liver function tests. Subsequent liver biopsies were performed in 4 of
198 these patients, all of which showed evidence of nodular regenerative hyperplasia. Duration of
199 combination therapy prior to the appearance of esophageal varices ranged from 6 to 45 months.
200 With the present analysis of the data, no cases of hepatotoxicity have appeared in the
201 busulfan-alone arm of the study. Long-term continuous therapy with thioguanine and busulfan
202 should be used with caution.

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

206 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In view of its action on cellular
207 DNA, thioguanine is potentially mutagenic and carcinogenic, and consideration should be given
208 to the theoretical risk of carcinogenesis when thioguanine is administered (see WARNINGS).

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

210 **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because of the
211 potential for tumorigenicity shown for thioguanine, a decision should be made whether to
212 discontinue nursing or to discontinue the drug, taking into account the importance of the drug to
213 the mother.

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

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

221 **ADVERSE REACTIONS**

222 The most frequent adverse reaction to thioguanine is myelosuppression. The induction of
223 complete remission of acute myelogenous leukemia usually requires combination chemotherapy
224 in dosages which produce marrow hypoplasia. Since consolidation and maintenance of remission
225 are also effected by multiple-drug regimens whose component agents cause myelosuppression,
226 pancytopenia is observed in nearly all patients. Dosages and schedules must be adjusted to
227 prevent life-threatening cytopenias whenever these adverse reactions are observed.

228 Hyperuricemia frequently occurs in patients receiving thioguanine as a consequence of rapid
229 cell lysis accompanying the antineoplastic effect. Adverse effects can be minimized by increased
230 hydration, urine alkalinization, and the prophylactic administration of a xanthine oxidase
231 inhibitor such as ZYLOPRIM[®] (allopurinol). Unlike PURINETHOL (mercaptopurine) and
232 IMURAN[®] (azathioprine), thioguanine may be continued in the usual dosage when allopurinol
233 is used conjointly to inhibit uric acid formation.

234 Less frequent adverse reactions include nausea, vomiting, anorexia, and stomatitis. Intestinal
235 necrosis and perforation have been reported in patients who received multiple-drug
236 chemotherapy including thioguanine.

237 **Hepatic Effects:** Liver enzyme and other liver function studies are occasionally abnormal. If
238 jaundice, hepatomegaly, or anorexia with tenderness in the right hypochondrium occurs,
239 thioguanine should be withheld until the exact etiology can be determined. There have been
240 reports of veno-occlusive liver disease occurring in patients who received combination
241 chemotherapy including thioguanine. Esophageal varices have been reported in patients
242 receiving continuous busulfan and thioguanine therapy for treatment of chronic myelogenous
243 leukemia (see PRECAUTIONS: Drug Interactions).

244 **OVERDOSAGE**

245 Signs and symptoms of overdose may be immediate, such as nausea, vomiting, malaise,
246 hypotension, and diaphoresis; or delayed, such as myelosuppression and azotemia. It is not
247 known whether thioguanine is dialyzable. Hemodialysis is thought to be of marginal use due to
248 the rapid intracellular incorporation of thioguanine into active metabolites with long persistence.
249 The oral LD₅₀ of thioguanine was determined to be 823 mg/kg ± 50.73 mg/kg and
250 740 mg/kg ± 45.24 mg/kg for male and female rats, respectively. Symptoms of overdose may
251 occur after a single dose of as little as 2.0 to 3.0 mg/kg thioguanine. As much as 35 mg/kg has
252 been given in a single oral dose with reversible myelosuppression observed. There is no known
253 pharmacologic antagonist of thioguanine. The drug should be discontinued immediately if
254 unintended toxicity occurs during treatment. Severe hematologic toxicity may require supportive
255 therapy with platelet transfusions for bleeding, and granulocyte transfusions and antibiotics if
256 sepsis is documented. If a patient is seen immediately following an accidental overdose of the
257 drug, it may be useful to induce emesis.

258 **DOSAGE AND ADMINISTRATION**

259 TABLOID brand Thioguanine is administered orally. The dosage which will be tolerated and
260 effective varies according to the stage and type of neoplastic process being treated. Because the
261 usual therapies for adult and pediatric acute nonlymphocytic leukemias involve the use of
262 thioguanine with other agents in combination, physicians responsible for administering these
263 therapies should be experienced in the use of cancer chemotherapy and in the chosen protocol.

264 There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase
265 (TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine and

266 prone to developing rapid bone marrow suppression following the initiation of treatment.
267 Substantial dosage reductions may be required to avoid the development of life-threatening bone
268 marrow suppression in these patients (see WARNINGS). Prescribers should be aware that some
269 laboratories offer testing for TPMT deficiency.

270 Ninety-six (59%) of 163 pediatric patients with previously untreated acute nonlymphocytic
271 leukemia obtained complete remission with a multiple-drug protocol including thioguanine,
272 prednisone, cytarabine, cyclophosphamide, and vincristine. Remission was maintained with daily
273 thioguanine, 4-day pulses of cytarabine and cyclophosphamide, and a single dose of vincristine
274 every 28 days. The median duration of remission was 11.5 months.⁸

275 Fifty-three percent of previously untreated adults with acute nonlymphocytic leukemias
276 attained remission following use of the combination of thioguanine and cytarabine according to a
277 protocol developed at The Memorial Sloan-Kettering Cancer Center. A median duration of
278 remission of 8.8 months was achieved with the multiple-drug maintenance regimen which
279 included thioguanine.

280 On those occasions when single-agent chemotherapy with thioguanine may be appropriate,
281 the usual initial dosage for pediatric patients and adults is approximately 2 mg/kg of body weight
282 per day. If, after 4 weeks on this dosage, there is no clinical improvement and no leukocyte or
283 platelet depression, the dosage may be cautiously increased to 3 mg/kg/day. The total daily dose
284 may be given at one time.

285 The dosage of thioguanine used does not depend on whether or not the patient is receiving
286 ZYLOPRIM (allopurinol); **this is in contradistinction to the dosage reduction which is**
287 **mandatory when PURINETHOL (mercaptopurine) or IMURAN (azathioprine) is given**
288 **simultaneously with allopurinol.**

289 Procedures for proper handling and disposal of anticancer drugs should be considered. Several
290 guidelines on this subject have been published.¹⁻⁸

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

293 **HOW SUPPLIED**

294 Greenish-yellow, scored tablets containing 40 mg thioguanine, imprinted with
295 "WELLCOME" and "U3B" on each tablet; in bottles of 25 (NDC 0173-0880-25).

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

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