

PRESCRIBING INFORMATION

TABLOID[®] brand Thioguanine 40-mg Scored Tablets

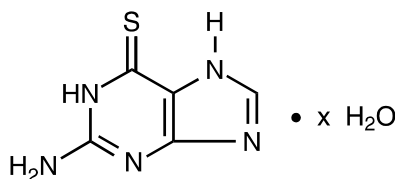
CAUTION

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

DESCRIPTION

TABLOID brand Thioguanine 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 selected human neoplastic diseases.

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



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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

73 Thus, thioguanine has multiple metabolic effects and at present it is not possible to designate
74 one major site of action. Its tumor inhibitory properties may be due to one or more of its effects

75 on (a) feedback inhibition of de novo purine synthesis; (b) inhibition of purine nucleotide
76 interconversions; or (c) incorporation into the DNA and the RNA. The net consequence of its
77 actions is a sequential blockade of the synthesis and utilization of the purine nucleotides.

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

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

97 **INDICATIONS AND USAGE**

98 **a) Acute Nonlymphocytic Leukemias:** TABLOID brand Thioguanine is indicated for
99 remission induction and remission consolidation treatment of acute nonlymphocytic
100 leukemias. However, it is not recommended for use during maintenance therapy or similar
101 long term continuous treatments due to the high risk of liver toxicity (see WARNINGS and
102 ADVERSE REACTIONS).

103 The response to this agent depends upon the age of the patient (younger patients faring
104 better than older) and whether thioguanine is used in previously treated or previously
105 untreated patients. Reliance upon thioguanine alone is seldom justified for initial remission
106 induction of acute nonlymphocytic leukemias because combination chemotherapy including
107 thioguanine results in more frequent remission induction and longer duration of remission
108 than thioguanine alone.

109 **b) Other Neoplasms:** TABLOID brand Thioguanine is not effective in chronic lymphocytic
110 leukemia, Hodgkin's lymphoma, multiple myeloma, or solid tumors. Although thioguanine is
111 one of several agents with activity in the treatment of the chronic phase of chronic
112 myelogenous leukemia, more objective responses are observed with MYLERAN[®] (busulfan),
113 and therefore busulfan is usually regarded as the preferred drug.

114 **CONTRAINDICATIONS**

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

118 **WARNINGS**

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

123 THIOGUANINE IS NOT RECOMMENDED FOR MAINTENANCE THERAPY OR
124 SIMILAR LONG TERM CONTINUOUS TREATMENTS DUE TO THE HIGH RISK OF
125 LIVER TOXICITY ASSOCIATED WITH VASCULAR ENDOTHELIAL DAMAGE (see
126 DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS). This liver toxicity has
127 been observed in a high proportion of children receiving thioguanine as part of maintenance
128 therapy for acute lymphoblastic leukaemia and in other conditions associated with continuous
129 use of thioguanine. This liver toxicity is particularly prevalent in males. Liver toxicity usually
130 presents as the clinical syndrome of hepatic veno-occlusive disease (hyperbilirubinaemia, tender
131 hepatomegaly, weight gain due to fluid retention, and ascites) or with signs of portal
132 hypertension (splenomegaly, thrombocytopenia, and oesophageal varices). Histopathological
133 features associated with this toxicity include hepatoportal sclerosis, nodular regenerative
134 hyperplasia, peliosis hepatis, and periportal fibrosis.

135 Thioguanine therapy should be discontinued in patients with evidence of liver toxicity as
136 reversal of signs and symptoms of liver toxicity have been reported upon withdrawal.

137 Patients must be carefully monitored (see PRECAUTIONS, Laboratory Tests). Early
138 indications of liver toxicity are signs associated with portal hypertension such as
139 thrombocytopenia out of proportion with neutropenia and splenomegaly. Elevations of liver
140 enzymes have also been reported in association with liver toxicity but do not always occur.

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

146 There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase
147 (TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine and
148 prone to developing rapid bone marrow suppression following the initiation of treatment.
149 Substantial dosage reductions may be required to avoid the development of life-threatening bone
150 marrow suppression in these patients. Prescribers should be aware that some laboratories offer
151 testing for TPMT deficiency. Since bone marrow suppression may be associated with factors
152 other than TPMT deficiency, TPMT testing may not identify all patients at risk for severe

153 toxicity. Therefore, close monitoring of clinical and hematologic parameters is important. Bone
154 marrow suppression could be exacerbated by coadministration with drugs that inhibit TPMT,
155 such as olsalazine, mesalazine, or sulphasalazine.

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

166 Myelosuppression is often unavoidable during the induction phase of adult acute
167 nonlymphocytic leukemias if remission induction is to be successful. Whether or not this
168 demands modification or cessation of dosage depends both upon the response of the underlying
169 disease and a careful consideration of supportive facilities (granulocyte and platelet transfusions)
170 which may be available. Life-threatening infections and bleeding have been observed as
171 consequences of thioguanine-induced granulocytopenia and thrombocytopenia.

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

173 **Pregnancy:** Pregnancy Category D. Drugs such as thioguanine are potential mutagens and
174 teratogens. Thioguanine may cause fetal harm when administered to a pregnant woman.
175 Thioguanine has been shown to be teratogenic in rats when given in doses 5 times the human
176 dose. When given to the rat on the 4th and 5th days of gestation, 13% of surviving placentas did
177 not contain fetuses, and 19% of offspring were malformed or stunted. The malformations noted
178 included generalized edema, cranial defects, and general skeletal hypoplasia, hydrocephalus,
179 ventral hernia, situs inversus, and incomplete development of the limbs. There are no adequate
180 and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the
181 patient becomes pregnant while taking the drug, the patient should be apprised of the potential
182 hazard to the fetus. Women of childbearing potential should be advised to avoid becoming
183 pregnant.

184 **PRECAUTIONS**

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

188 A few cases of jaundice have been reported in patients with leukemia receiving thioguanine.
189 Among these were 2 adult male patients and 4 pediatric patients with acute myelogenous
190 leukemia and an adult male with acute lymphocytic leukemia who developed hepatic
191 veno-occlusive disease while receiving chemotherapy for their leukemia. Six patients had

192 received cytarabine prior to treatment with thioguanine, and some were receiving other
193 chemotherapy in addition to thioguanine when they became symptomatic. While hepatic
194 veno-occlusive disease has not been reported in patients treated with thioguanine alone, it is
195 recommended that thioguanine be withheld if there is evidence of toxic hepatitis or biliary stasis,
196 and that appropriate clinical and laboratory investigations be initiated to establish the etiology of
197 the hepatic dysfunction. Deterioration in liver function studies during thioguanine therapy should
198 prompt discontinuation of treatment and a search for an explanation of the hepatotoxicity.

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

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

207 It is advisable to monitor liver function tests (serum transaminases, alkaline phosphatase,
208 bilirubin) at weekly intervals when first beginning therapy and at monthly intervals thereafter. It
209 may be advisable to perform liver function tests more frequently in patients with known
210 pre-existing liver disease or in patients who are receiving thioguanine and other hepatotoxic
211 drugs. Patients should be instructed to discontinue thioguanine immediately if clinical jaundice is
212 detected (see WARNINGS).

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

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

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

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

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

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

227 **Geriatric Use:** Clinical studies of thioguanine did not include sufficient numbers of subjects
228 aged 65 and over to determine whether they respond differently from younger subjects. Other
229 reported clinical experience has not identified differences in responses between the elderly and
230 younger patients. In general, dose selection for an elderly patient should be cautious, usually

231 starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic,
232 renal, or cardiac function, and of concomitant disease or other drug therapy.

233 **ADVERSE REACTIONS**

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

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

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

249 **Hepatic Effects:** Liver toxicity associated with vascular endothelial damage has been reported
250 when thioguanine is used in maintenance or similar long term continuous therapy which is not
251 recommended (see WARNINGS and DOSAGE AND ADMINISTRATION). This usually
252 presents as the clinical syndrome of hepatic veno-occlusive disease (hyperbilirubinaemia, tender
253 hepatomegaly, weight gain due to fluid retention, and ascites) or signs and symptoms of portal
254 hypertension (splenomegaly, thrombocytopenia, and esophageal varices). Elevation of liver
255 transaminases, alkaline phosphatase, and gamma glutamyl transferase and jaundice may also
256 occur. Histopathological features associated with this toxicity include hepatoportal sclerosis,
257 nodular regenerative hyperplasia, peliosis hepatis, and periportal fibrosis.

258 Liver toxicity during short term cyclical therapy presents as veno-occlusive disease. Reversal
259 of signs and symptoms of this liver toxicity has been reported upon withdrawal of short term or
260 long term continuous therapy.

261 Centrilobular hepatic necrosis has been reported in a few cases; however, the reports are
262 confounded by the use of high doses of thioguanine, other chemotherapeutic agents, and oral
263 contraceptives and chronic alcohol abuse.

264 **OVERDOSAGE**

265 Signs and symptoms of overdosage may be immediate, such as nausea, vomiting, malaise,
266 hypotension, and diaphoresis; or delayed, such as myelosuppression and azotemia. It is not
267 known whether thioguanine is dialyzable. Hemodialysis is thought to be of marginal use due to
268 the rapid intracellular incorporation of thioguanine into active metabolites with long persistence.
269 The oral LD₅₀ of thioguanine was determined to be 823 mg/kg ± 50.73 mg/kg and

270 740 mg/kg \pm 45.24 mg/kg for male and female rats, respectively. Symptoms of overdose may
271 occur after a single dose of as little as 2.0 to 3.0 mg/kg thioguanine. As much as 35 mg/kg has
272 been given in a single oral dose with reversible myelosuppression observed. There is no known
273 pharmacologic antagonist of thioguanine. The drug should be discontinued immediately if
274 unintended toxicity occurs during treatment. Severe hematologic toxicity may require supportive
275 therapy with platelet transfusions for bleeding, and granulocyte transfusions and antibiotics if
276 sepsis is documented. If a patient is seen immediately following an accidental overdose of the
277 drug, it may be useful to induce emesis.

278 **DOSAGE AND ADMINISTRATION**

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

284 There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase
285 (TPMT) who may be unusually sensitive to the myelosuppressive effects of thioguanine and
286 prone to developing rapid bone marrow suppression following the initiation of treatment.
287 Substantial dosage reductions may be required to avoid the development of life-threatening bone
288 marrow suppression in these patients (see WARNINGS). Prescribers should be aware that some
289 laboratories offer testing for TPMT deficiency.

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

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

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

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

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

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

313 **HOW SUPPLIED**

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

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

317 **REFERENCES**

- 318 1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations
319 for Practice. Pittsburgh, PA: Oncology Nursing Society; 1999:32-41.
- 320 2. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC:
321 Division of Safety, Clinical Center Pharmacy Department and Cancer Nursing Services,
322 National Institutes of Health and Human Services, 1992, US Dept of Health and Human
323 Services, Public Health Service publication NIH 92-2621.
- 324 3. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics.
325 *JAMA*. 1985;253:1590-1591.
- 326 4. National Study Commission on Cytotoxic Exposure. Recommendations for handling
327 cytotoxic agents. 1987. Available from Louis P. Jeffrey, Chairman, National Study
328 Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health
329 Sciences, 179 Longwood Avenue, Boston, MA 02115.
- 330 5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling
331 of antineoplastic agents. *Med J Australia*. 1983;1:426-428.
- 332 6. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: a report from the
333 Mount Sinai Medical Center. *CA-A Cancer J for Clin*. 1983;33:258-263.
- 334 7. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling
335 cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990;47:1033-1049.
- 336 8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines.)
337 *Am J Health-Syst Pharm*. 1996;53:1669-1685.

338
339



340
341 Manufactured by
342 DSM Pharmaceuticals, Inc.
343 Greenville, NC 27834
344 for GlaxoSmithKline
345 Research Triangle Park, NC 27709

346

347 ©YEAR, GlaxoSmithKline. All rights reserved.

348

349 Month YEAR

RL-XXX