PRODUCT MONOGRAPH

Pr Mercaptopurine Tablets USP

Tablet 50 mg

Antileukemic

SteriMax Inc.
2735 Matheson Boulevard East, Suite 1
Mississauga, Ontario
L4W 4M8

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[Pr]Mercaptopurine Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 50 mg	lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

MERCAPTOPURINE TABLETS USP is indicated for:

- Maintenance therapy of the acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen.

MERCAPTOPURINE TABLETS USP (mercaptopurine) should not be used unless a diagnosis of acute lymphatic leukemia has been adequately established and the responsible physician is experienced with the risks of MERCAPTOPURINE TABLETS USP and knowledgeable in assessing response to chemotherapy.

The response to this agent depends upon the particular subclassification of the acute lymphatic leukemia and the age of the patient (child or adult).

Leukemia

Acute lymphatic leukemia occurring in children responds, in general, more favorably to mercaptopurine than the same disorder occurring in adults. Combination therapy with multiple agents has produced results superior to that achieved with mercaptopurine alone. The effectiveness of mercaptopurine in maintenance programs in adult lymphatic leukemia has not been established.

Central Nervous System Leukemia

Mercaptopurine is not effective for prophylaxis or treatment of central nervous system leukemia.

Other Neoplasms

Mercaptopurine is not effective in acute myelogenous leukemia, chronic lymphocytic leukemia, the lymphomas (including Hodgkin's Disease), or solid tumors.

Geriatrics:
No data is available.

Pediatrics:
Acute lymphatic leukemia occurring in children responds, in general, more favorably to mercaptopurine than the same disorder occurring in adults.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- MERCAPTOPURINE TABLETS USP (mercaptopurine) should not be used unless a diagnosis of acute leukemia has been adequately established and the responsible physician is knowledgeable in assessing response to chemotherapy. Mercaptopurine should not be used in patients whose disease has demonstrated prior resistance to this drug. In animals and man there is usually complete cross-resistance between mercaptopurine and thioguanine.

Immunization
Immunization using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunizations with live organism vaccines is contraindicated in patients treated with MERCAPTOPURINE TABLETS USP.

WARNINGS AND PRECAUTIONS

General
The safe and effective use of MERCAPTOPURINE TABLETS USP (mercaptopurine) demands a thorough knowledge of the natural history of the condition being treated. After selection of an initial dosage schedule, therapy will frequently need to be modified depending upon the patient's response and manifestations of toxicity.

The most frequent, serious, toxic effect of mercaptopurine is myelosuppression resulting in leukopenia, thrombocytopenia and anemia. Whether or not these manifestations demand modification or cessation of treatment and/or dosage depends both upon the response of the underlying disease and a careful consideration of supportive facilities (granulocyte and platelet transfusions) which may be available. Life-threatening infections and bleeding have been observed as a consequence of mercaptopurine-induced granulocytopenia and thrombocytopenia. Severe hematologic toxicity may require supportive therapy with platelet transfusions for bleeding, and antibiotics and granulocyte transfusions if sepsis is documented.

It is important to discontinue the drug temporarily at the first evidence of an abnormally large fall in white blood cell count, platelet count or hemoglobin concentration, as leukocyte and platelet counts continue to fall after treatment is stopped. In many patients with severe

depression of the formed elements of the blood due to mercaptopurine, the bone marrow appears hypoplastic on aspiration or biopsy, whereas in other cases it may appear normocellular. The qualitative changes in the erythroid elements towards the megaloblastic series, characteristically seen with the folic acid antagonists and some other antimetabolites, are not seen with this drug.

It is recommended that evaluation of the hemoglobin or hematocrit, total white blood cell count and differential count, and quantitative platelet count be obtained weekly while the patient is on mercaptopurine therapy. In cases where the cause of fluctuations in the formed elements in the peripheral blood is obscure, bone marrow examination may be useful for the evaluation of marrow status. The decision to increase, decrease, continue or discontinue a given dosage of mercaptopurine must be based not only on the absolute hematologic values, but also upon the rapidity with which changes are occurring. In many instancescomplete blood counts will need to be done more frequently than once weekly (often daily) in order to evaluate the effect of the therapy. The dosage of mercaptopurine may need to be reduced when this agent is combined with other drugs whose primary toxicity is myelosuppression.

Carcinogenesis and Mutagenesis

MERCAPTOPURINE TABLETS USP in common with other anti-metabolites causes chromosomal aberrations in mice, rats and man and induces dominant-lethal mutations in male mice. Carcinogenic potential exists in man, as post-marketing surveys have documented the occurrence of acute nonlyphocytic leukemia, acute myelogenous leukemia and chronic myeloid leukemia in patients treated with 6-MP. These data include patients who received 6-mercaptopurine for non-neoplastic disorders.

In addition, post marketing cases of the rare, very aggressive and usually fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with mercaptopurine (see ADVERSE REACTIONS).

Hematologic

Bone Marrow Toxicity

The most consistent dose-related toxicity is bone marrow suppression. This may be manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Any of these findings may also indicate progression of the underlying disease. It is imperative that patients be instructed to report promptly the development of fever, sore throat, signs of local infection, bleeding from any site, or symptoms suggestive of anemia. Since mercaptopurine may have a delayed effect, it is important to withdraw the medication temporarily at the first sign of an abnormally large fall in any of the formed elements of the blood. Full blood counts must be taken daily during remission induction and careful monitoring of haematological parameters should be conducted during maintenance therapy.

6-MP is primarily inactivated by metabolism through the enzyme thiopurine S-methyltransferase (TPMT), whose activity can be highly variable due to polymorphisms in the TPMT gene. Approximately 0.3% of Caucasians and African Americans have little to no enzyme due to 2 non-functional TPMT alleles (homozygous deficient). 10% of patients have only one functional allele (heterozygotes) resulting in intermediate TPMT activity, whereas approximately 90% of

individuals have normal TPMT activity with two functional alleles. Patients with low or intermediate TPMT activity accumulate higher concentrations of 6-MP cytotoxic metabolites than those with normal TPMT activity. Although available, phenotypic or genetic screening tests for TPMT deficiency are not currently uniform for patient care in Canada.

Individuals who are homozygous for an inherited defect in the TPMT (thiopurine-Smethyltransferase) gene are unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment. Laboratory tests are available, both genotypic and phenotypic, to determine the TPMT status. Substantial dose reductions are generally required for homozygous-TPMT deficiency patients (two non-functional alleles) to avoid the development of life threatening bone marrow suppression (See Pharmacokinetics). Although heterozygous patients with intermediate TPMT activity may have increased mercaptopurine toxicity, this is variable, and the majority of patients tolerate normal doses of MERCAPTOPURINE TABLETS USP. If a patient has clinical or laboratory evidence of severe toxicity, particularly myelosuppression, TPMT testing should be considered. In patients who exhibit excessive myelosuppression due to 6-mercaptopurine, it may be possible to adjust the mercaptopurine dose and administer the usual dosage of other myelosuppressive chemotherapy as required for treatment (see **DOSAGE AND ADMINISTRATION**). Bone marrow toxicity may be more profound in patients treated with concomitant allopurinol (see **DRUG INTERACTIONS** and **DOSAGE AND ADMINISTRATION**). This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine,
mesalazine, or sulphasalazine.

A possible association between decreased TPMT activity and secondary leukemias and myelodysplasia has also been reported in individuals receiving 6-mercaptopurine in combination with other cytotoxics.

Hepatic/Biliary/Pancreatic

MERCAPTOPURINE TABLETS USP (mercaptopurine) is hepatotoxic in animals and man; deaths have been reported from hepatic necrosis. Hepatic injury can occur with any dosage, but seems to occur with greatest frequency when doses of 2.5mg/kg/day are exceeded. The histologic pattern of mercaptopurine hepatotoxicity includes features of both intrahepatic cholestasis and parenchymal cell necrosis, either of which may predominate. It is not clear how much of the hepatic damage is due to direct toxicity from the drug and how much may be due to a hypersensitivity reaction. In some patients jaundice has cleared following withdrawal of mercaptopurine and reappeared with its reintroduction.

Published reports have cited widely varying incidences of overt hepatotoxicity; several reports have indicated that as many as 10 to 40% of patients with acute leukemia develop jaundice while receiving treatment with mercaptopurine.

Usually, clinically detectable jaundice appears early in the course of treatment (1 or 2 months). However, jaundice has been reported as early as 1 week and as late as 8 years after the start of treatment with mercaptopurine.

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

The concomitant administration of mercaptopurine with other hepatotoxic agents requires especially careful clinical and biochemical monitoring of hepatic function. Combination therapy involving mercaptopurine with other drugs not felt to be hepatotoxic should nevertheless be approached with caution. The combination of mercaptopurine with doxorubicin was reported to be hepatotoxic in 19 of 20 patients undergoing remission-induction therapy (an unauthorized indication) for leukemia resistant to previous therapy.

The hepatotoxicity has been associated in some cases with anorexia, diarrhea, jaundice, and ascites. Hepatic encephalopathy has occurred. The onset of clinical jaundice, hepatomegaly, or anorexia with tenderness in the right hypochondrium are immediate indications for withholding mercaptopurine until the exact etiology can be identified. Likewise, any evidence of deterioration in liver function studies, toxic hepatitis, or biliary stasis should prompt discontinuation of the drug and lead to a search for an etiology of the hepatotoxicity.

Immune

Immunization

Immunization using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunizations with live organism vaccines are contraindicated in patients treated with MP-6.

Immunosuppresion

Mercaptopurine recipients may manifest decreased cellular hypersensitivities and impaired allograft rejection. Induction of immunity to infectious agents or vaccines will be subnormal in these patients; the degree of immunosuppression will depend on antigen dose and temporal relationship to drug. This drug effect is similar to that of azathioprine and should be carefully considered with regard to intercurrent infections and risk of subsequent neoplasia.

Renal

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

Sexual Function/Reproduction

Teratogenesis

Mercaptopurine has been shown to be embryotoxic in rats at doses that are not toxic to the mother. It has also proven to be embryo-lethal when administered at higher doses in the first half of the gestation period. Women receiving mercaptopurine in the first trimester of pregnancy have an increased incidence of abortion; the risk of malformation in offspring surviving first trimester exposure is not accurately known. In a series of 28 women receiving mercaptopurine after the first trimester of pregnancy, 3 mothers died undelivered, 1 delivered a stillborn child, and 1 aborted; there were no cases of macroscopically abnormal fetuses.

Since such experience cannot exclude the possibility of fetal damage, mercaptopurine should be used during pregnancy only if the benefit clearly justifies the possible risk to the fetus, and particular caution should be given to the use of mercaptopurine in the first trimester of pregnancy.

Effects on Fertility
The effect of mercaptopurine on human fertility is unknown for either males or females, but there are reports of successful fatherhood/motherhood after receiving treatment during childhood or adolescence.

Special Populations

Pregnant Women
As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving MERCAPTOPURINE TABLETS USP (see Sexual Function/Reproduction).

Nursing Women
6-mercaptopurine has been detected in the breast milk of renal transplant patients receiving immunosuppressive therapy with azathioprine, a pro-drug of 6-mercaptopurine. Mothers receiving MERCAPTOPURINE TABLETS USP should not breast feed.

Pediatrics: See DOSAGE AND ADMINISTRATION.

Geriatrics: No specific studies have been carried out in the elderly. However, it is advisable to monitor renal and hepatic function in these patients, and if there is any impairment, consideration should be given to reducing the MERCAPTOPURINE TABLETS USP dosage.

Monitoring and Laboratory Tests
The most consistent dose-related toxicity is bone marrow suppression. This may be manifest by anemia, leukopenia, thrombocytopenia, or any combination of these. Since mercaptopurine may have a delayed effect, it is important to withdraw the medication temporarily at the first sign of an abnormally large fall in any of the formed elements of the blood. Full blood counts must be taken daily during remission induction and careful monitoring of haematological parameters should be conducted during maintenance therapy. If a patient has clinical or laboratory evidence of severe bone marrow toxicity, particularly myelosuppression, TPMT testing should be considered.

TPMT Testing
Although available, phenotypic or genetic screening tests for TPMT deficiency are not currently uniform for patient care in Canada. Genotypic testing can determine the allelic pattern of a patient. Currently, 3 alleles—TPMT*2, TPMT*3A and TPMT*3C— account for about 95% of individuals with reduced levels of TPMT activity. Individuals homozygous for these alleles are TPMT deficient and those heterozygous for these alleles have variable TPMT (low or intermediate) activity. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in erythrocytes and can also be informative. Caution must be used with phenotyping since some coadministered drugs can influence measurement of TPMT activity in blood, and recent blood transfusions will misrepresent a patient's actual TPMT activity.

Monitoring plasma levels of mercaptopurine during therapy is of questionable value. It is technically difficult to determine plasma concentrations which are seldom greater than 1 to 2 µg/mL after a therapeutic oral dose.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Hematologic
The most frequent adverse reaction to mercaptopurine is myelosuppression. Patients without TPMT enzyme activity (homozygous-deficient) are particularly susceptible to hematologic toxicity, and some patients with low or intermediate TPMT enzyme activity are more susceptible to hematologic toxicity than patients with normal TPMT activity, although the latter can also experience severe toxicity. Maintenance of remission generally involves multiple drug regimens whose component agents cause myelosuppression. Anemia, leukopenia, and thrombocytopenia are frequently observed. Dosages and schedules are adjusted to prevent life-threatening cytopenias (see WARNINGS AND PRECAUTIONS).

Neoplasms benign, malignant and unspecified (including cysts and polyps) (2-6%)
Very rare: Secondary Leukemia and myelodysplasia (see WARNINGS AND PRECAUTIONS)

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with mercaptopurine for inflammatory bowel disease (an unauthorized indication).

Gastrointestinal (3 %)
Intestinal ulceration has been reported very rarely. Nausea, vomiting and anorexia are uncommon during initial administration, but they may occur during toxicity. Mild diarrhea and sprue-like symptoms have been noted occasionally, but it is difficult at present to attribute these to the medication. Oral lesions are rarely seen, and when they occur they resemble thrush rather than antifolic ulcerations. Rare reports of Oral Ulceration.

Rare reports of pancreatitis (in the licensed indications). Common reports of pancreatitis in the Inflammatory bowl disease (IBD) population (an unauthorized indication).

Renal
Hyperuricemia frequently occurs in patients receiving mercaptopurine as a consequence of rapid cell lysis accompanying the antineoplastic effect. Adverse effects can be minimized by increased hydration, urine alkalinization, and the prophylactic administration of a xanthine oxidase inhibitor such as allopurinol. The dosage of mercaptopurine should be reduced to one-third to one-quarter of the usual dose if allopurinol is given concurrently.

Immune system disorders (2 – 2.7%)
Hypersensitivity reactions with the following manifestations have been reported

Rare: Arthralgia; skin rash, drug fever

Before attributing fever to mercaptopurine, every attempt should be made to exclude more common causes of pyrexia, such as sepsis, in patients with acute leukemia.

Very Rare: Facial oedema

Skin and subcutaneous tissue disorders (< 2%)
Rare: alopecia

Miscellaneous
Transient oligospermia has been reported.

DRUG INTERACTIONS

Overview

The dosage of mercaptopurine may need to be reduced when this agent is combined with other drugs whose primary toxicity is myelosuppression. The concomitant administration of mercaptopurine with other hepatotoxic agents requires especially careful clinical and biochemical monitoring of hepatic function. Combination therapy involving mercaptopurine with other drugs not felt to be hepatotoxic should nevertheless be approached with caution. The combination of mercaptopurine with doxorubicin was reported to be hepatotoxic in 19 of 20 patients undergoing remission-induction therapy for leukemia resistant to previous therapy.

Azathioprine: The active metabolite of azathioprine is 6-MP.

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

Warfarin: Inhibition of the anticoagulant effect of warfarin when given with mercaptopurine has been reported.

Vaccinations: Vaccination with live organism vaccines are not recommended in immunocompromised individuals (see WARNINGS AND PRECAUTIONS).

Thioguanine: There is usually complete cross-resistance between mercaptopurine and thioguanine.
Trimethoprim-Sulfamethoxazole: The dosage of mercaptopurine may need to be reduced when mercaptopurine is combined with other drugs whose primary or secondary toxicity is myelosuppression. Enhanced marrow suppression has been noted in some patients also receiving trimethoprim-sulfamethoxazole.

Aminosalicylate derivatives: As there is *in vitro* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent mercaptopurine therapy (See WARNINGS AND PRECAUTIONS).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Once complete hematologic remission is obtained with induction and consolidation therapies, maintenance therapy with MERCAPTOPURINE TABLETS USP in combination with other agents can be considered. This is indicated in children with acute lymphatic leukemia. The use of mercaptopurine in maintenance schedules for adults with acute lymphatic leukemia has not been established to be effective. If remission is achieved, maintenance doses will vary from patient to patient. A usual daily maintenance dose of mercaptopurine is 1.5 to 2.5 mg/kg/day as a single dose. It is to be emphasized that in children with acute lymphatic leukemia in remission, superior results have been obtained when mercaptopurine has been combined with other agents (most frequently with methotrexate) for remission maintenance. Mercaptopurine should rarely be relied upon as a single agent for the maintenance of remissions induced in acute leukemia.

It is to be emphasized that in children with acute lymphatic leukemia in remission, superior results have been obtained when mercaptopurine has been combined with other agents (most frequently with methotrexate) for remission maintenance. Mercaptopurine should not relied upon as a single agent for the maintenance of remissions induced in acute leukemia.

Dosage in TPMT-deficient Patients
Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe MERCAPTOPURINE TABLETS USP toxicity from conventional doses of mercaptopurine and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established. (See ACTION AND CLINICAL PHARMACOLOGY.)

Most patients with heterozygous TPMT deficiency tolerated recommended MERCAPTOPURINE TABLETS USPdoses, but some require dose reduction. Genotypic and phenotypic testing of TPMT status are available. (See ACTION AND CLINICAL PHARMACOLOGY.)

Dosage in the Elderly
No specific studies have been carried out in the elderly. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. It is advisable to monitor renal and hepatic function in these patients, and if there is any impairment, consideration should be given to reducing the MERCAPTOPURINE TABLETS USP dosage.

Missed Dose
If a dose is missed, the patient should be instructed to take their next dose as scheduled. Doses should not be doubled.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs and symptoms of overdosage may be immediate such as anorexia, nausea, vomiting and diarrhea; or delayed such as myelosuppression, liver dysfunction, and gastroenteritis. There is no known pharmacologic antagonist of mercaptopurine. The drug should be discontinued immediately if unintended toxicity occurs during treatment. If a patient is seen immediately following an accidental overdosage of the drug, induced emesis may be useful. Active measures (such as the use of activated charcoal or gastric lavage) may not be effective in the event of overdose unless the procedure can be undertaken within 60 minutes of ingestion. Dialysis cannot be expected to clear mercaptopurine. Hemodialysis is thought to be of marginal use due to the rapid intracellular incorporation of mercaptopurine into active metabolites with long persistence.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

6-mercaptopurine is sulphydryl analogue of the purine base hypoxanthine and acts as a cytotoxic antimetabolite.

6-mercaptopurine is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular metabolism to thioguanine nucleotides for cytotoxicity. The 6-mercaptopurine metabolites inhibit de novo purine synthesis and purine nucleotide interconversions. The thioguanine nucleotides are also incorporatead into nucleic acids and this contributes to the cytotoxic effects of the drug.

6-mercaptopurine is converted into the active thioguanine nucleotides by the enzyme hypoxanthineguanine phosphoribosyltransferase. The conversion of 6-mercaptopurine into its active thioguanine nucleotides is a stepwise process, via thioinosinic acid. 6-mercaptopurine can also undergo methylation by the enzyme thiopurine methyltransferase to form S-methylated nucleotides, which are also cytotoxic.

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

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

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

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

Pharmacodynamics

The cytotoxic effect of 6-mercaptopurine can be related to the levels of red blood cell 6-mercaptopurine derived thioguanine nucleotides, but not to the plasma 6-mercaptopurine concentration.

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

Pharmacokinetics

Summary of mercaptopurine's Pharmacokinetic Parameters in the patient population

	C_{max}	$t_{½}$ (min)	$AUC_{0-\infty}$	Clearance ($mL/min/m^2$)	Volume of distribution (L/kg)
Single dose mean	-	90 ± 30	-	4832 ± 2562	0.9

Absorption: The bioavailability of oral 6-mercaptopurine shows considerable inter-individual variability. When administered at a dosage of $75mg/m^2$ to 7 patients, the bioavailability averaged 16% of the administered dose, with a range of 5 to 37%. The variable bioavailability probably results from the metabolism of a significant portion of 6-mercaptopurine during first-pass hepatic metabolism.

Distribution: The mean time to peak plasma concentration is 2.2 hours with a range of 0.5 to 4 hours.

There is a negligible entry of mercaptopurine into cerebrospinal fluid. Plasma protein binding averages 19% over the concentration range 10 to 50 μg/mL (a concentration only achieved by intravenous administration of mercaptopurine at doses exceeding 5 to 10mg/kg).

Metabolism: The catabolism of mercaptopurine and its metabolites is complex. The main method of elimination for 6-mercaptopurine is by metabolic alteration. The kidneys eliminate approximately 7% of 6-mercaptopurine unaltered within 12 hours of the drug being administered.

Variability in mercaptopurine metabolism is one of the major causes of interindividual differences in systemic exposure to the drug and its active metabolites. Mercaptopurine activation occurs via hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and several

enzymes to form 6-thioguanine nucleotides (6-TGNs). The cytotoxicity of mercaptopurine is due, in part, to the incorporation of 6-TGN into DNA. Mercaptopurine is inactivated via two major pathways. One is thiol methylation, which is catalyzed by the polymorphic enzyme thiopurine Smethyltransferase (TPMT), to form the inactive metabolite methyl-6-MP. TPMT activity is highly variable in patients because of a genetic polymorphism in the TPMT gene. For Caucasians and African Americans, approximately 0.3% (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90% of individuals have normal TPMT activity with two functional alleles. Homozygous-deficient patients (two non-functional alleles), if given usual doses of mercaptopurine, accumulate excessive cellular concentrations of active thioguanine nucleotides predisposing them to mercaptopurine hydrochloride toxicity. Heterozygous patients with low or intermediate TPMT activity accumulate higher concentrations of active thioguanine nucleotides than people with normal TPMT activity and are more likely to experience mercaptopurine toxicity. TPMT genotyping or phenotyping (red blood cell TPMT activity) can identify patients who are homozygous deficient or have low or intermediate TPMT activity. Another inactivation pathway is oxidation, which is catalyzed by xanthine oxidase (XO) and forms 6-thiouric acid. This is excreted in the urine.

In man, after oral administration of ^{35}S-6-mercaptopurine, urine contains intact mercaptopurine, thiouric acid (formed by direct oxidation by xanthine oxidase, probably via 6-mercapto-8-hydroxypurine) and a number of 6-methylated thiopurines. The methylthiopurines yield appreciable amounts of inorganic sulfate. The importance of the metabolism by xanthine oxidase relates to the fact that allopurinol inhibits this enzyme and retards the catabolism of mercaptopurine and its active metabolites. A significant reduction in mercaptopurine dosage is mandatory if a potent xanthine oxidase inhibitor and mercaptopurine are used simultaneously in a patient (see WARNINGS AND PRECAUTIONS).

Excretion: The elimination half-life of 6-mercaptopurine is 90 ± 30 minutes, but the active metabolites have a longer half-life. The apparent body clearance is 4832 ± 2562 mL/min/m^2.

Special Populations and Conditions

Pediatrics: Pharmacokinetics in the pediatric population have not been specifically studied.

Geriatrics: Pharmacokinetics in the geriatric population have not been specifically studied.

Gender: Pharmacokinetics based on gender have not been studied.

Race: Pharmacokinetics based on race have not been studied.

Hepatic Insufficiency: Pharmacokinetics in individuals with hepatic insufficiency have not been studied (See WARNINGS AND PRECAUTIONS, Hepatotoxicity).

Renal Insufficiency: slower elimination of the drug and a greater cumulative effect (See WARNINGS AND PRECAUTIONS, Renal).

Genetic Polymorphism: Pharmacokinetics effects due to genetic polymorphism have not been studied.

STORAGE AND STABILITY

Mercaptopurine Tablets USP should be stored in a dry place between 15˚ and 30˚C.

SPECIAL HANDLING INSTRUCTIONS

Tablets should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

All materials which have come in contact with cytotoxic drugs should be segregated and incinerated at 1000˚C or more. Sealed containers may explode.

Personnel regularly involved in the preparation and handling of cytotoxic agents should have biannual blood examinations.

Care should be taken when handling or halving the tablets so as not to contaminate hands or to inhale the drug.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each scored tablet contains 50 mg mercaptopurine and the following non-medicinal ingredients: Corn starch, hypromellose, lactose monohydrate, lactose, sodium starch glycolate, magnesium stearate, potato starch and stearic acid.

MERCAPTOPURINE TABLETS USP 50 mg are pale yellow, scored, biconvex tablets, with product identification “54 420” on one side. Bottles of 25 and 250 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

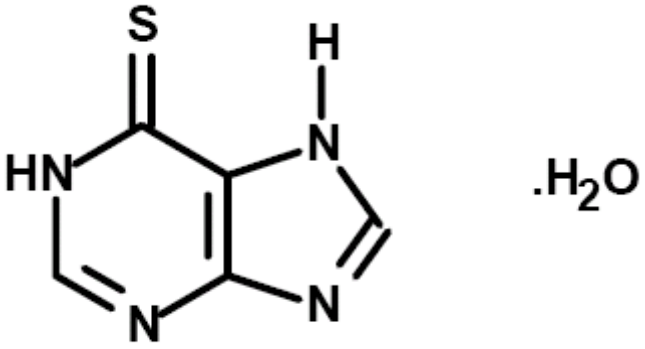
Proper name: Mercaptopurine

Chemical name: 1,7-dihydro-6H-purine-6-thione monohydrate

Molecular formula: C5H4N4S•H2O

Molecular mass: 170.20

Structural formula:



Physicochemical properties:

pKa: 7.8 and 11.2

Mercaptopurine is a yellow, odourless, crystalline powder.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single center, randomized, single-dose, double-blind, two-way crossover, bioequivalence study of Mercaptopurine Tablets USP, 50 mg versus the Canadian reference product, Purinethol® 50 mg tablets (Novopharm Limited) in 61 healthy, male subjects under fasting conditions. A summary of the bioavailability data is presented in the table below.

6-Mercaptopurine (1 x 50 mg) From measured data **uncorrected for potency** Least Square Mean Arithmetic Mean (CV %)				
Parameter	Mercaptopurine Tablets*	Purinethol® Tablets†	% Mean Ratio	90% Confidence Interval
AUC_{0-t} (h·ng/mL)	126.677 134.072 (35.28)	124.983 130.804 (31.25)	101.36	96.14; 106.85
$AUC_{0-\infty}$ (h·ng/mL)	127.340 134.171 (35.51)	126.297 132.115 (31.09)	100.83	95.52 ; 106.43
C_{max} (ng/mL)	61.499 67.36 (44.58)	62.748 69.918 (44.63)	98.01	88.49 ; 108.55
T_{max}§ (h)	1.500 (0.500- 3.000)	1.000 (0.500 -4.000)		
$T_{½}$€ (h)	2.143 (127.03)	2.235 (74.29)		

* Mercaptopurine Tablets 50mg, Roxane Laboratories on behalf of SteriMax Inc.
† Purinethol (Mercaptopurine Tablets 50 mg) Manufactured by Novopharm Limited, Canada
§ Expressed as median (range) only
€ Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Since mercaptopurine is an analogue of hypoxanthine it is initially activated to 6-thioinosinate via hypoxanthine-guanine phosphoribosyltransferase. Occasionally resistance may develop to this agent as well as 6-thioguanine and this has been associated with the loss of this enzyme in experimental tumors. 6-Thioinosinate is able to inhibit several enzymes involved in purine metabolism. These enzymes include phosphoribosylpyrophosphate amidotransferase, inosinate dehydrogenase and adenylossinate synthetase as well as other enzymes whose inhibition is of minor consequence.

6-Thioinosinate is further metabolized to 6-thioxanthylic acid which is then incorporated into DNA and RNA as the 6-thioguanylate derivative. So far, no 6-thioinosinate derivatives have been detected in cellular nucleic acids. It has been observed that similar levels of incorporation of thioguanylate occur in nucleic acids following exposure of cells to equitoxic concentrations of either 6-mercaptopurine or 6-thioguanine. Similarly mercaptopurine cytotoxicity has been blocked with inhibitors of DNA synthesis such as thymidine or arabinosylcytosine. The hypothesis that incorporation of mercaptopurine metabolites into DNA is the primary mechanism involved in the production of cellular cytotoxicity is based on these observations.

TOXICOLOGY

Acute Toxicity Studies LD_{50}	6-mercaptopurine	Azathioprine
	(mg/kg)	(mg/kg)
Mouse (oral)	480	2500
Rat (oral)	-	400
Mouse(I.P.)	-	650
Mouse (Germ Free) (I.P.)	-	750
Mouse (Germ Free) (oral)	-	2500
Rat (I.P.)	-	310
Rat (oral)	-	400
Guinea Pig (I.M.)	25-50	-

Published and unpublished acute toxicity studies on mercaptopurine are scarce indeed. However, since mercaptopurine is the major metabolite of azathioprine it is perhaps of some value to consider the toxicology of the much more extensively studied azathioprine under the assumption that most of the toxicity of azathioprine is due to its metabolites including mercaptopurine.

Toxic doses of the order of 25 mg/kg in dogs, cats, rats and mice produced anorexia (with associated weight loss), reticulopenia, leukopenia and diarrhea. Microscopic lesions included hypoplasia of bone marrow and degenerative changes in the intestinal epithelium and liver.

Single doses of azathioprine in animals were relatively non-toxic, but repeated doses showed greatly enhanced toxicity. The principle toxic effect is marrow depression. Lymphoid tissue has also shown depletion on chronic administration. Dogs were more sensitive to the toxic effects of azathioprine than rodents. At 10 mg/kg for 10 days, deaths were due to agranulocytosis of marrow; acute ulcers of the rectal region were also seen.

Subacute Toxicity Studies

Intravenous Administration in Monkeys: A toxicity study was carried out using repeated doses of mercaptopurine: 20, 40 or 80 mg/kg over a period of 7 or 15 days administered intravenously to 4 monkeys, 2 males and 2 females. Pharmacotoxic signs were noted during compound administration but generally abated within 1 week following the cessation of injections. These

signs included moderate anorexia, slightly decreased activity, and slight piloerection. Two monkeys given 6-mercaptopurine for 15 consecutive days at the lowest dosage levels (20 mg/kg) exhibited soft stools and occasional diarrhea during compound administration in addition to those cited above.

Biochemical and hematological results indicated slight increases in blood urea nitrogen and serum transaminase units; and slight to moderate decrease in cell volume, hemoglobin and red cell counts. In addition, a marked decrease in white blood cell counts was noted in those monkeys given the compound for 15 consecutive days and slight to moderate decreases noted in the white blood cell counts during the 7-day dosage schedule. These values generally had returned to normal during the observation periods following the dosage period. Gross autopsy findings revealed only some pathological changes in the lungs and kidneys, other findings were neither consistent nor remarkable.

Intravenous Administration in Rats and Dogs (Azathioprine): The sodium salt of azathioprine was injected intravenously for 5 consecutive days to 3 groups of 6 rats each and for 10 days to 6 mongrel dogs. At doses of 25, 50, 100 and 200 mg/kg, all the rats injected with azathioprine survived the week of treatment and the subsequent 2-week observation period. Except for piloerection and slight sedation noticed only at the highest dose, no reactions were observed. Gross examination of organs and tissues of the treated animals at necropsy failed to disclose pathological changes.

The dogs were given doses of 2.5, 5.0 and 7.5 mg/kg. One dog on the high dose died 2 weeks after the beginning of treatment. A relationship between drug treatment and death could not be established or rejected with certainty. Leukocyte and platelet counts were always normal during and after treatment, but low values found in the third or fourth week after the beginning of treatment suggest the possibility of a slight temporary depression of bone marrow function.

Chronic Toxicity Studies (Azathioprine)

Rats: Groups of 10 young male CFN rats received azathioprine in the diet for up to 6 months. At a dose level of 2000 mg/kg of diet all 10 animals died within 16 days, and at 700 mg/kg of diet 7 rats died at intervals of up to 5 months. At a level of 200 mg/kg, 3 animals died. Growth and food consumption were depressed in the 3 survivors of the 700 mg/kg level. At the levels of 2000 mg/kg and 700 mg/kg no pathological changes were found in liver, kidney, pancreas, myocardium, adrenals, CNS, or intestinal tract. However, a number of animals had undescended testes, and there was failure of maturation of spermatogenesis with atypical cells being present. Bone marrows showed depletion of granulocytes, and spleens had depletion of lymphoid elements. The lungs had areas of edema, hemorrhage, and pneumonia. Thyroids were depleted of colloid.

In the rats which had received only 70 and 200 mg/kg of diet sections of bone marrow, testes, thyroid, spleen, lungs and all other organs were normal.

Dogs: Young Beagle dogs received azathioprine by capsule 5 days per week for 18 weeks. Two males and 2 females each received daily 1, 2, or 4 mg/kg. The level of 4 mg/kg produced signs

indicative of respiratory infection, some anorexia, and depression of growth. There was considerable diarrhea and some vomiting at all dose levels. The only pathological changes were found in one of the females at the level of 4 mg/kg, which died after 16 weeks. This animal exhibited some bone marrow depletion and extensive pneumonia.

Monkeys: Twenty-four Patas monkeys were divided into 4 groups each containing 3 males and 3 females. Respective groups were dosed orally with 0, 1.5, 3.0, and 6.0 mg/kg/day of azathioprine for 90 days. Monkeys were observed daily. Blood samples were collected once predose, on test days 6, 13 and 20, and on various other days. The following parameters were evaluated: hemoglobin concentration, erythrocyte count, total and differential leukocyte counts, platelet count, packed cell volume, reticulocyte count, erythrocyte sedimentation rate, numbers of Heinz bodies, methemoglobin content, mean corpuscular hemoglobin concentration, urea nitrogen, blood glucose, sodium and potassium concentrations, alkaline phosphatase activity, bilirubin content, SGOT activity, colloidal gold, and thymol turbidity. All animals were necropsied and the following tissues were examined by light microscopy: brain, eye, pituitary, adrenals, thyroid, kidneys, liver, spleen, lung, heart, stomach, small intestine, colon, urinary bladder, pancreas, thymus, bone marrow, tongue, salivary gland, ovary or testes, uterus and gall bladder.

Only 1 treated monkey, a female in the low dose group (1.5 mg/kg/day) survived the experiment. Deaths were dose-related and females usually died first. No abnormal behaviour was seen but monkeys in all treated groups failed to gain weight. Monkeys given the largest dose lost a small amount of weight.

The decrease in red blood cell counts, hemoglobin concentration and packed cell volume was dose and time related: the longer an animal was on treatment the lower the values were. Total leukocyte, neutrophil, platelet and lymphocyte counts were also decreased. A small change in albumin/globulin ratios for treated monkeys was not of statistical significance. Other hematologic parameters and clinical chemistries were not significantly altered.

The following lesions were considered to be drug induced: marked bone marrow hypoplasia in all treated monkeys; lymphocyte hypoplasia in the spleen characterized by a reduction in size, number, and cellularity of germinal centers; thymic atrophy; and focal centrolobular coagulative hepatic necrosis. These foci of necrosis were not surrounded by inflammatory cells. Oil red o stain revealed centrolobular fatty change in the liver.

Carcinogenicity Studies (Azathioprine)

Rats: Azathioprine was administered orally in the diet at doses of 0, 3, or 10 mg/kg/day to groups of 70 male and 70 female Sprague-Dawley rats for 90 and 97 consecutive weeks, respectively. The purpose of this study was to determine the carcinogenic potential of azathioprine. The rats were examined daily for clinical signs of toxicity and weekly to determine the incidence, size and location of tumors. Body weight and food consumption were measured weekly.

No clinical signs were noted which could clearly be associated with azathioprine administration. A life table analysis indicated comparable cumulative survival of the control and 3 mg/kg/day female group. Survival of the male 3 mg/kg/day group began to diverge from the control group by day 600. Reduced cumulative survival of the male and female 10 mg/kg/day groups compared to the controls began by 450 and 350 days, respectively. There were no effects on food consumption while an effect on body weight was limited to the 10 mg/kg male group. The mean weight of this group was lower than the untreated control group mean.

A marked depletion of body fat in the 10 mg/kg/day rats was the only gross finding, other than suspected tumors, associated with azathioprine administration.

An increased incidence of neoplasms of the skin, ear canal (including the auditory sebaceous or Zymbal's gland) and preputial gland was associated with azathioprine administration. The presence of a few neoplasms of the nonglandular stomach in the treated males was considered potentially significant due to their rare spontaneous occurrence. However, due to the lack of a human counterpart to the nonglandular portion of the rat stomach and the absence of neoplasms in the glandular portion of the stomach, the significance to humans is doubtful. Two mucinous adenocarcinomas of the duodenum, which were noted in the male 3 mg/kg/day group, were considered possibly significant. However, it would be inappropriate to definitely associate these neoplasms with azathioprine administration.

Additional histologic changes noted for the skin, external ear canal, preputial gland and nonglandular stomach were considered to represent preneoplastic changes of tissues demonstrated to be likely oncogenic target tissues. A reduced incidence of pituitary and mammary tumors, uterine polyps and uterine cystic endometrial hyperplasia was noted in the female 10 mg/kg/day group compared to the control group.

Mice: The purpose of this study was to determine the carcinogenic effects of azathioprine when given orally in the diet to mice during an 18-month period. Six hundred (300 males and 300 females) clinically healthy 21-day-old Charles River mice were used in this study. After a 21-day acclimation period, mice were randomly assigned to individual cages and to 1 of the 3 following dose groups of 100 males and 100 females: 0, 3, or 10 mg/kg/day. Dose groups were equally divided and half of each group was housed in 1 of 2 environmentally controlled rooms. All mice received water and a drug-diet or cellulose-diet mixture *ad libitum*.

Azathioprine was blended with the diet on a weight to weight basis using a Patterson-Kelly twin shell blender. Weekly body weights and food consumptions were used to calculate the amount of drug blended with ground Wayne Lab Blox to obtain proposed daily doses. Calculated average daily doses for the respective groups were 0 mg/kg/day for male and female controls, 2.99 and 10.12 mg/kg/day for treated males, and 2.98 and 9.99 mg/kg/day for treated females.

Mice in the high-dose group (10 mg/kg/day) were fed a drug-free diet during dose weeks 21 through 38 because high mortality due to drug toxicity was observed. Otherwise the drug-diet mixture was fed until there was 10 to 20% survival of that sex in any treatment group. Surviving

females were sacrificed after 524 to 530 days on study and surviving males after 600 to 602 days on study.

Mice were observed daily and palpated weekly for tumors. Body weights and food consumption were determined pretest and weekly thereafter. Complete necropsies were performed on each mouse after death or sacrifice. Representative sections of all major organs and tumors were fixed, prepared and examined histologically from high dose (10 mg/kg/day) and control mice. Target organs and all tumors were examined from low dose (3 mg/kg/day) mice. Azathioprine in the diet significantly reduced the survival of 3 mg/kg/day females and 10 mg/kg/day males and females. Paleness of the mucous membranes, probably due to anemia, was the only clinical sign considered to be drug related. Significant differences in food consumption and body weights were periodically observed, but they were not consistently present throughout the study.

The number of clinically palpable nodules was similar in control and treated mice. At necropsy enlarged thymuses, lymph nodes, and spleens were observed, especially in the high-dose group. Cystic endometrial hyperplasia was present in the majority of control and treated females.

Histologically, both male and female mice had a dose-related increase ($p<.01$) in lymphosarcomas. This increased incidence of lymphosarcoma in azathioprine-dosed females was also responsible for a significant ($p<.01$) increase in total malignant and/or malignant plus benign tumors. In treated male mice, the incidence of malignant or malignant plus benign tumors was not significantly increased.

Spontaneous murine leukemia (lymphosarcoma) is caused by an oncornavirus (Friend leukemia virus) with susceptibility of mice being controlled by several genes, most notably the FU-1 gene. Most adult mice are carriers, and neonatal mice have either been exposed or are exposed to the virus early in life. Murine leukemia virus induces the proliferation of neoplastic "T" lymphocytes. Young mice are experimentally more susceptible than older mice and immunosuppressive therapy is a widely used experimental technique in viral and chemical oncogenesis. Immunosuppression of DBA/2 mice, carrying Friend leukemia virus with antilymphocyte globulin induced leukemia similar to that noted in this experiment with azathioprine, an immunosuppressant agent.

Antilymphocyte globulin immunosuppression also increased the incidence of reticulum cell sarcoma in SJL/J mice and the incidence of tumors in resistant mice neonatally infected with polyoma virus. Synergistic immunosuppression with N-nitrosobutylurea and azathioprine induced leukemia, mean latent period of 189 days, in 14 of 24 (58%) C57 BL mice. Immunosuppression with azathioprine of NZB X NZW mice that had lupus nephritis also increased the incidence of lymphosarcoma. In view of the above, lymphosarcoma as observed in this current study in treated mice may have been secondary to azathioprine immunosuppression.

An increased number of squamous cell carcinomas was observed in the preputial area of treated mice, and for purposes of statistical comparison were considered to be of preputial gland origin. Although the total number of these tumors in either treated group of male mice was not significantly greater than the number in controls, a positive dose response was detected

statistically. The incidence of spontaneous preputial gland carcinomas reported in the literature is low; therefore, these tumors may have been induced by azathioprine. This is reinforced by the fact that a similar response was noted in rats given azathioprine in a companion study.

Fertility Study (Azathioprine)
Male Mice: Ten male Swiss-Webster mice, 47 to 57 days old, were given 20 mg/kg/day of azathioprine intraperitoneally 5 days a week for a total of 19 injections. Five of these males bred 13- to 15-week old virgin females, and 5 bred previously proven fertile females. Males continued to receive azathioprine until a vaginal plug was found in the female. Four of the males were then treated with azathioprine for 30 to 40 additional days and each was allowed to breed 4 more females. Five pups from each dam were raised to maturity. Fetuses in 8 litters were sacrificed at birth and stained with Alizarin Red S for the evaluation of skeletal anomalies.

In the first mating, 9 of 10 males were fertile (the pregnancies were normal) and 1 male was sterile. The 4 males treated for an additional 30 to 40 days, were all fertile. No anomalies were found in mice raised to maturity or in fetuses sacrificed at birth and examined for skeletal anomalies.

Female Mice: Eighteen virgin 7- to 15-week old female Swiss-Webster mice were given 20 mg/kg of azathioprine intraperitoneally 5 days a week for a total of 19 injections. Each was housed with a fertile male, and treatment was continued until a vaginal plug was found in the female.

After delivery, 2 litters were raised to maturity, 1 litter was sacrificed and examined for skeletal anomalies (Alizarin Red S technique), and the other litters were not studied.

Fourteen of eighteen females (78%) had vaginal plugs during the first estrus as compared with 43 of 70 (63%) in a control group indicating azathioprine did not interfere with breeding. Nine of these fourteen matings (64%) resulted in pregnancies. Values for conception in previous mating experiences range between 62 and 83%. No anomalies were observed in the fetuses examined.

Teratology Studies (Azathioprine)
Mice: Two or three consecutive daily doses of azathioprine were given intraperitoneally to pregnant Swiss-Webster mice. Doses of 4, 10, 20, and 30 mg/kg of body weight were given on days 0-2, 3-5, 6-8, 9-11, 12-14 or 15-17 of gestation, controls either received no treatment or intraperitoneal injection of dilute NaOH on corresponding days of gestation.

Products of conception were delivered by hysterectomy at 17 or 18 days of gestation and evaluated for resorption, fetal death, and runting (fetuses weighing less than 2 standard deviations below mean weight of controls). For the purpose of further study, live fetuses were divided into 3 groups: (1) examined for skeletal anomalies - 988 fetuses from 108 litters; (2) preserved in 10% formalin and dissection to discover external and visceral anomalies - 722 fetuses from 73 litters; and (3) evaluated for hematologic alterations by aspiration of heart blood

for hematocrit and cellular morphology, and for histologic and touch smear alterations of the liver and bone marrow by light microscopy.

Resorption, Deaths and Runting: Many conceptuses died when azathioprine was given after the second day of gestation; embryonic resorption was a characteristic finding. Several live fetuses were runted. In dams treated between days 12 and 14 of gestation, hydrops fetalis occurred and prevented evaluation for runting.

Skeletal Anomalies: Anomalies in fetuses from dams treated on days 3 to 5 of gestation included encephalocele and meningocele. Abnormal tails, fused ribs, hemivertebrae and vertebral arch anomalies occurred in fetuses from dams injected on days 6 to 8 of gestation.

Anomalies in fetuses from dams treated on days 9 to 12 of gestation included oligodactyl, scapulohumeral anomalies, micrognathia, abnormalities of the frontal and the parietal bones, and constriction of the fibulas.

External and Visceral Anomalies: Cleft palates were frequently seen among live fetuses whose dams received the drug during days 9 and 10 of gestation. Decrease in thymic size was apparent among offspring of dams receiving 10 mg/kg or more of azathioprine on days 9 and 10 or days 9 to 11 of gestation. Marked generalized edema, pallor, lethargy, apnea and death after a few feeble breaths were observed in a large portion of fetuses (18 of 45) from dams given 30 mg/kg between days 12 and 14 of gestation.

A significant decrease in hematocrits (anemia) and an increased number of nucleated red blood cells were found in the blood of fetuses. Fetal bone marrows were hypoplastic, and hepatic hematopoiesis was increased. The hematologic parameters of a control group of dams were not changed, indicating mice fetuses are more susceptible to azathioprine than pregnant females.

Rats: Azathioprine was given *per os* at 50 mg/kg to 12 female Wistar rats from days 8 through 16 of pregnancy. Dams were weighed daily during the test. They were sacrificed on day 20 after mating, and the abdomen and uterus were opened. The number of live fetuses, dead fetuses, and resorption sites were counted. The uterus, fetal membranes and placentas were fixed in formalin for detailed examination. Fetuses were weighed and examined for morphological abnormalities; some were stained with the Alizarin Red technique to facilitate skeletal examination.

Administration of 50 mg/kg of azathioprine from days 8 to 16 of pregnancy killed 3 of 12 female rats and markedly reduced weight gains in survivors. Fetal losses in the survivors were severe: 95% of the fetuses were killed and resorbed. Viable fetuses were grossly normal, although they weighed less than viable control fetuses.

Rabbits: New Zealand White rabbits were bred and insemination was confirmed by examining vaginal smears for the presence of sperm. After mating, does were weighed and assigned to an experimental group. Does were observed and weighed daily during the experiment. Azathioprine was administered by stomach tube daily from days 8 to 16 of pregnancy to 6 does at 10 mg/kg/day, to 6 does at 50 mg/kg/day, and to 2 does at 30 mg/kg/day. Another group of

pregnant does was given 20 mg/kg/day of azathioprine for 3 consecutive days of pregnancy: 5 does during days 8 to 10, 3 does during days 10 to 12, 3 does during days 12 to 14, and 4 doses during days 14 to 16. A third group of does was given a single dose of 50 mg/kg of azathioprine: 2 does on day 8, 2 does on day 9, 3 does on day 10, 3 does on day 11, 3 does on day 12, 2 does on day 13, 2 does on day 14, 2 does on day 15, and 3 does on day 16 of pregnancy. A fourth group of does was dosed once orally with various amounts of azathioprine on day 11 of pregnancy: 4 does received 6.25 mg/kg, 4 does received 10 mg/kg, 4 does received 12.5 mg/kg, 2 does received 25 mg/kg, and 3 does received 50 mg/kg.

Rabbits were sacrificed on day 28 of gestation, and the uterus and fetuses were examined as previously described.

Administration of 50 mg/kg/day from days 8 through 16 of pregnancy killed 2 of 6 does, and marked weight loss was observed in the 4 survivors. The majority of the fetuses were killed and resorbed. The only viable fetus had no paws or tail and had phocomelia, cleft palate, and bilateral hare lip.

A dose of 30 mg/kg/day administered from days 8 to 16 killed 1 of 5 females, and 44% of all fetuses had died and been resorbed. All surviving fetuses had either phocomelia or oligodactyly.

No maternal death occurred after 10 mg/kg/day of azathioprine was given from days 8 through 16 of pregnancy, and weight gain in treated does was similar to that in controls. Few fetal deaths or resorptions were seen, but 22 of 51 viable fetuses were malformed. One fetus had amelia, 10 had phocomelia, and 11 had oligodactyly.

After 20 mg/kg azathioprine was given on days 8 to 10, 15% of the fetuses were malformed: 4 had short tails, and 3 had polydactyly. When the same dose was given to does on days 10 to 12, 71% of the fetuses had amelia and/or phocomelia, and 7 had oligodactyly. Some of these fetuses had no tails and others had cleft palates, and/or hare lip. Eighty-five percent of the fetuses were malformed when the does were given 20 mg/kg/day on days 12 to 14 of pregnancy. Twelve fetuses had phocomelia and 10 oligodactyly. No malformed fetuses were observed when dams were dosed (20 mg/kg/day) on days 14 to 16 of gestation.

In another series of experiments single 50 mg/kg doses of azathioprine were given to pregnant does. When this dose was given on day 8 all fetuses were resorbed. Most of the fetuses survived after treatment on day 9, but 17 of 18 were malformed. Dosing on day 10 caused fetal death, resorption, and fewer abnormalities. However, those abnormalities observed were more severe than those in the previous group. All 13 fetuses had no tails, cleft palate, phocomelia or Amelia with various combinations of eye, skull and ear defects, scoliosis, hare lip, and oligodactyly. When does were treated on day 11 or 12 all fetuses were malformed; although fetal deformities were less severe in does on day 12. Dosing on day 13 caused malformations in 81% of the fetuses. The percent of deformities dropped to 48% in does dosed on day 14, and no abnormalities were present in dams dosed on days 15 or 16 of gestation. This series of experiments indicated that the most severe teratogenic effects were obtained when azathioprine was given to pregnant rabbits on day 11 of gestation.

The next trial was designed to determine the effects of different dose levels of azathioprine on day 11 of gestation. When 25 or 50 mg/kg was given, viable fetuses had phocomelia, amelia, digital and tail abnormalities, cleft palate and various combinations of eye and ear defects, and oligodactyly. The incidence of malformations dropped to 44% when 12.5 mg/kg was given, 42% when 10 mg/kg was given, and 19% when 6.25 mg/kg was given to pregnant rabbits on day 11 of gestation. In all of these trials the major deformities were phocomelia or amelia, and digital and tail abnormalities. Many fetuses also had various combinations of cleft palate, hare lips, scoliosis, and eye, ear and skull defects.

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PART III: CONSUMER INFORMATION

[Pr]MERCAPTOPURINE TABLETS USP
mercaptopurine

This leaflet is part III of a three-part "Product Monograph" published when MERCAPTOPURINE TABLETS USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MERCAPTOPURINE TABLETS USP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
MERCAPTOPURINE TABLETS USP is indicated for maintenance therapy of acute lymphatic (lymphocytic, lymphoblastic) leukemia in combination with other drugs. The response to this drug depends upon the particular type of acute lymphatic leukemia and the age of the patient (child or adult).

MERCAPTOPURINE TABLETS USP belongs to a group of medicines called Antileukemics, which are used to treat leukemia, a cancer of blood cells. MERCAPTOPURINE TABLETS USP is used to treat leukemia of specific types of blood cells.

What it does:
MERCAPTOPURINE TABLETS USP is converted in the body to the active form which is then incorporated into cancer cells and interferes with their growth. Since the growth of normal body cells may also be affected by mercaptopurine, other side effects also occur.

When it should not be used:
If you have previously experienced an allergic or bad reaction to mercaptopurine or any of the other ingredients in MERCAPTOPURINE TABLETS USP listed below.

You should not be immunized with a live vaccine if you are taking MERCAPTOPURINE TABLETS USP.

What the medicinal ingredient is:
Mercaptopurine is also known as 6-mercaptopurine or 6-MP.

What the important nonmedicinal ingredients are:
Corn starch, hypromellose, lactose monohydrate, lactose, sodium starch glycolate, magnesium stearate, potato starch and stearic acid.

What dosage forms it comes in:
Tablet 50 mg

WARNINGS AND PRECAUTIONS

BEFORE you use MERCAPTOPURINE TABLETS USP **talk to your doctor or pharmacist if:**

- you have previously experienced an allergic or bad reaction to mercaptopurine or any of the other ingredients in MERCAPTOPURINE TABLETS USP listed above.
- you are planning to have a baby (this question applies to both men and women).
- you are taking any other medicines (see Interaction with this Medication).
- you suffer from liver or kidney disease.
- you have a rare hereditary condition, where you have too little of the natural body chemical thiopurine methyltransferase (TPMT) enzyme in your body. If you are not sure, ask your doctor.
- you are planning to be immunized with a live vaccine.

The use of MERCAPTOPURINE TABLETS USP during pregnancy should be avoided if possible, especially in the first three months of pregnancy. If you are pregnant or are thinking of becoming pregnant, you should discuss with your doctor, whether the benefit of taking MERCAPTOPURINE TABLETS USP outweighs the possible risk of problems with your pregnancy, before starting your tablets.

Mothers receiving MERCAPTOPURINE TABLETS USP should not breast-feed. Talk to your doctor, pharmacist or nurse if you need to know of alternative methods to breast-feeding.

As with all cytotoxic chemotherapy, contraceptive precautions should be taken if either partner is taking MERCAPTOPURINE TABLETS USP.
MERCAPTOPURINE TABLETS USP may increase your risk of developing cancer, especially certain types of leukemia or lymphoma.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all other medication that you are taking, including the following which may interact with MERCAPTOPURINE TABLETS USP, such as allopurinol, azothioprine, mesalazine, olsalazine, sulphasalazine and warfarin.

If you are taking certain other medicines such as allopurinol, your doctor should decrease your dose of MERCAPTOPURINE TABLETS USP.

PROPER USE OF THIS MEDICATION

Usual dose:

- It is important to take your medicine at the right times. You must take it in the way your doctor has told you to. The label on your pack will tell you how many tablets to take and how often to take them. If the label doesn't say or if you are not sure, ask your doctor or pharmacist.
- The dosage is very variable and it may be changed from time to time by your doctor. If you are not sure or the dosage on the label has changed for no apparent reason, ask your doctor.
- The usual starting dose for adults and children is worked out by your doctor based on your body weight - 2.5 mg per kg of body weight per day, or on your body surface area - 50 to 75 mg per meter squared of body surface area per day. Elderly patients will have their kidney and liver function tested and if necessary the dose may need to be reduced.
- Your doctor may reduce your dose of MERCAPTOPURINE TABLETS USP if you have kidney or liver disease or you are taking any other medicines that can cause a decrease in the body's ability to produce white blood cells and platelets, such as other cytotoxic medicines.
- Swallow your tablets with a little water

From time to time while you are taking MERCAPTOPURINE TABLETS USP, your doctor will want you to have a blood test. This is to check your blood cell count and to change your dose if necessary.

MERCAPTOPURINE TABLETS USP belongs to a group of medicines called cytotoxics, which are an irritant to the eyes and skin. To prevent irritation it is important to wash your hands immediately after handling or halving the tablets, to avoid contact with the eyes and be careful not to inhale any particles of the tablet.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, go back to your regular dosing schedule and tell your doctor. Do not double your next dose.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Blood or liver problems: nausea, vomiting, loss of appetite, severe or prolonged diarrhea, abdominal pain, mouth ulcers, jaundice (yellowing of the skin and eyes)		✓	✓
	Hypersensitivity reactions such as swelling, rash, fever		✓	✓
	Unexpected bruising or bleeding (ie. Bleeding in urine, stool, gums)		✓	✓

MERCAPTOPURINE TABLETS USP may cause side effects in some people, mainly reduced cell production in the bone marrow.

During your treatment your doctor will take blood tests to check your liver function. Your doctor may take other blood and urine tests to monitor your uric acid levels, a natural body chemical of which levels may rise while being treated with MERCAPTOPURINE TABLETS USP. As with all cytotoxic medicines, there is an increased risk of damage to the genes in some cells. Cases of certain types of leukemia and of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with mercaptopurine.

This is not a complete list of side effects. For any unexpected effects while taking MERCAPTOPURINE TABLETS USP, contact your doctor or pharmacist.

HOW TO STORE IT

Keep your MERCAPTOPURINE TABLETS USP in a dry, safe place where children cannot see or reach them.

- MERCAPTOPURINE TABLETS USP should be stored in a dry place between 15˚ and 30˚C.
- Do not take any tablets after the expiry date shown on the pack
- If your doctor tells you to stop taking the tablets, please return any which are left over to your pharmacist for safe disposal. Only keep them if your doctor tells you to.

This medicine is for you. Only a doctor can prescribe it. Never give it to anyone else. It may harm them even if their symptoms are the same as yours

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.sterimaxinc.com or by contacting the sponsor, SteriMax Inc, at:
1-800-881-3550

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