

DRUG NAME: Mercaptopurine**SYNONYM(S):** 6-mercaptopurine,¹ 6-MP²**COMMON TRADE NAME(S):** PURINETHOL®**CLASSIFICATION:** antimetabolite,¹ cytotoxic³*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Mercaptopurine is a purine antagonist.⁴ It is a pro-drug that is converted intracellularly.⁵ Mercaptopurine is first converted to thioinosine monophosphate (TIMP) by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT).⁵ TIMP inhibits purine synthesis.⁶ TIMP is sequentially metabolized to thioguanine monophosphate (TGMP) and then to thioguanosine triphosphate (TGTP).⁶ The cytotoxic effect of mercaptopurine is a result of the incorporation of these nucleotides into DNA. Mercaptopurine is an immunosuppressant.⁴ Mercaptopurine is specific for the S phase of the cell-cycle.⁷

PHARMACOKINETICS:

Oral Absorption	<ul style="list-style-type: none"> incomplete and highly variable (5-35%); largely due to first pass metabolism in the liver reduced bioavailability by cow's milk,⁸ due to high concentration of xanthine oxidase (For more information, see Interactions table) preferably taken on an empty stomach⁹⁻¹²; may be taken with food if needed children¹³: <20% 	
Distribution	exceeds total body water ⁶	
	cross blood brain barrier?	negligible
	volume of distribution	0.9 L/kg children ¹³ : 22 L/m ²
	plasma protein binding	19%
Metabolism	hepatic: extensive ¹⁴ <i>activation by</i> ⁶ : <ul style="list-style-type: none"> hypoxanthine-guanine phosphoribosyl transferase (HGPRT) <i>elimination</i> ⁶ : <ul style="list-style-type: none"> xanthine oxidase to 6-thiouric acid thiopurine methyltransferase (TPMT) to 6-methylthiopurine 	
	active metabolites ⁶	thiopurine nucleotides
	inactive metabolites ¹⁴	6-thiouric acid, 6-methylmercaptopurine
	Excretion	renal excretion minimal at conventional doses ¹⁴ ; 20-40% at higher doses
	urine ¹⁵	7-40% unchanged drug and metabolites
	feces	no information found
	terminal half life	90 min children ¹³ : <1 h
	clearance	4,832 mL/min/m ² children ¹³ : 800 mL/min/m ²

Adapted from standard reference¹⁶ unless specified otherwise.

USES:**Primary uses:**

- *Leukemia, acute lymphoid
- *Leukemia, acute myelogenous
- *Leukemia, chronic myeloid

*Health Canada approved indication

Other uses:

Lymphoma, non-Hodgkin's⁴

SPECIAL PRECAUTIONS:

Contraindicated: Patients with hypersensitivity to mercaptopurine; patients whose disease showed prior resistance to mercaptopurine or thioguanine as there is complete cross resistance between the two drugs.¹⁵

Potential error: The synonyms 6-mercaptopurine or 6-MP should be avoided because the use of these names has been associated with 6-fold overdose.⁷

Hepatotoxicity: Hepatic injury can occur with any dose, but occurs with greatest frequency when doses exceed 2.5 mg/kg/day.¹⁶ For more information, see paragraph following **Side Effects** table.

Special populations: Toxicity may vary among different groups:

- Patients with low or intermediate **TPMT activity** accumulate higher concentrations of mercaptopurine cytotoxic metabolites compared to patients with normal TPMT activity.^{16,17} This results in unexpectedly high myelosuppression and has also been associated with the occurrence of secondary malignancies. Approximately 3% of whites and blacks express either a homozygous deletion or mutation of the TPMT gene.¹⁴ An estimated 10% of patients may be at increased risk for toxicity due to a heterozygous deletion or mutation.¹⁴ Standardized TPMT genotyping is not currently available in Canada.
- Adverse GI effects occur less frequently in **pediatric patients** than in adults.^{4,6}

Carcinogenicity: potentially carcinogenic¹⁶

Mutagenicity: It is not known if mercaptopurine is mutagenic in Ames test and mammalian *in vitro* mutation test. Mercaptopurine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.¹⁶

Fertility: The effect of mercaptopurine on human fertility is not known in either males or females.¹⁶ There are reports of healthy infants born to patients who had previously been treated with mercaptopurine in their childhood or adolescence. Transient oligospermia can rarely occur.¹⁵

Pregnancy: FDA Pregnancy Category D.⁷ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is contraindicated as mercaptopurine is detected in human breast milk.¹⁶

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.¹⁸ When placebo-controlled trials are available, adverse events are included if the incidence is \geq 5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	hypersensitivity (2-3%)
blood/bone marrow/ febrile neutropenia	<i>anemia (>10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days</i> ⁷
	<i>leukopenia (>10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days</i> ⁷
	<i>thrombocytopenia (>10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days</i> ⁷
constitutional symptoms	fever (1-10%) ⁷
dermatology/skin	alopecia (<1%) ⁷
	hyperpigmentation (1-10%) ⁷
	rash (1-10%) ⁷
gastrointestinal	<i>emetogenic potential: rare</i> ¹⁹
	abdominal cramps (1-10%) ⁷
	anorexia (1-10%) ⁷
	diarrhea (1-10%) ⁷
	intestinal ulceration (<1%)
	nausea and vomiting (1-10%) ⁷
	<i>stomatitis (1-10%)</i> ⁷
hepatobiliary/pancreas	<i>hepatotoxicity (30%)</i> ¹⁴
infection	predisposition to bacterial and parasitic infections ¹⁴ due to immunosuppression ¹⁵
metabolic/laboratory	hyperuricemia (1-10%) ⁷
renal/genitourinary	renal toxicity (1-10%) ⁷
secondary malignancy	leukemia and myelodysplasia (<1%)
	cysts and polyps (2-6%)
sexual/reproductive function	increased risk of abortion if taken in first trimester of pregnancy ⁴
	oligospermia, transient ¹⁵ (<1%)
syndromes	tumour lysis syndrome; in rare circumstances, certain patients may be at increased risk ¹⁸

Adapted from standard reference¹⁶ unless specified otherwise.

Hepatotoxicity: Mercaptopurine-induced hepatotoxicity is most common when doses exceed 2.5 mg/kg/day.¹⁶ A rapid onset of jaundice, cholestasis, ascites, hepatic encephalopathy, and/or elevated liver enzymes, often associated with hepatic necrosis and severe fibrosis, can occur.⁴ Hepatotoxicity can also include anorexia and diarrhea. Jaundice usually appears 1 or 2 months after initiation of dose, but can occur as early as 1 week or as late as eight years after the start of treatment with mercaptopurine. Hepatic damage may be due to direct toxicity from the drug or a result of a hypersensitivity reaction.^{16,20} Weekly monitoring of liver function tests when beginning treatment, followed by monthly monitoring, may allow early detection of hepatotoxicity.¹⁶ More frequent monitoring should be considered when other hepatotoxic drugs are being used, or when there is pre-existing liver disease. Mercaptopurine should be discontinued with the onset of clinical jaundice, hepatomegaly, anorexia with tenderness in the right hypochondrium, deterioration in liver function tests, toxic hepatitis, or biliary stasis, at least until further investigations can be made.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
allopurinol ^{16,21}	delayed, major, established; increased mercaptopurine toxic effect	inhibition of xanthine oxidase by allopurinol reduces the rate of mercaptopurine elimination	mercaptopurine dose reduction to 25% of standard dose when given concomitantly ^{5,6,14}
aminosalicylates ²¹ (e.g., mesalamine, ²² olsalazine, sulfasalazine)	delayed, moderate, possible; increased mercaptopurine toxic effect	inhibition of TPMT by aminosalicylates reduces the rate of mercaptopurine elimination	monitor for mercaptopurine toxicity
azathioprine ¹⁶	increased mercaptopurine toxic effect	therapeutic duplication as azathioprine is metabolized to mercaptopurine	do not administer concomitantly ¹⁵
cotrimoxazole ^{14,23}	decreased mercaptopurine therapeutic and toxic effect	cotrimoxazole may decrease absorption of mercaptopurine	significance not known; further investigation required ²³
*cow's milk ⁸	decreased bioavailability	inactivated by high concentration of xanthine oxidase in cow's milk	avoid concurrent intake
methotrexate ²¹	delayed, moderate, possible; increased mercaptopurine toxic effect	moderate inhibition of xanthine oxidase by methotrexate reduces the rate of mercaptopurine elimination	primarily a concern with high-dose methotrexate; consider mercaptopurine dose reduction
muscle relaxants, nondepolarizing ²¹ (e.g., atracurium, gallamine, metocurine, pancuronium, tubocurine, vecuronium)	rapid, moderate, suspected; decreased or reversed efficacy of muscle relaxants	inhibition of phosphodiesterase by mercaptopurine in the motor nerve terminal results in an anticholinergic action	closely monitor respiratory function
warfarin ^{16,21,24}	delayed, moderate, suspected; inhibition of the anticoagulant effect of warfarin	unknown ⁷	monitor coagulation parameters; adjust warfarin dose as needed ²¹

* Xanthine oxidase is present in various concentrations in other milk including human and goat's milk, therefore concurrent use may decrease levels/effects of mercaptopurine.²⁵⁻²⁸

SUPPLY AND STORAGE:

Tablets: Novopharm supplies mercaptopurine as a scored 50 mg tablet.¹⁶ Selected non-medicinal ingredients: lactose. Store in a dry place between 15-25° C and protect from light.

Injection: Not available in Canada.²⁹

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:**Oral:**

- induction⁷: 2.5-5 mg/kg/day PO once daily
- maintenance⁷: 1.5-2.5 mg/kg/day PO once daily

Round dose to the nearest 25 mg.

Preferably administer on an empty stomach^{9,10}; may be taken with food if needed.^{11,12} Avoid taking tablets with milk or milk based products.^{8,30}

For patients unable to swallow tablets, a dispersion can be prepared^{31,32}. Remove plunger from oral syringe, place dose in syringe barrel, replace syringe plunger against the dose, cap syringe. When dose is to be given, draw approximately 2 mL of water into syringe. Allow tablets to disintegrate over 1-3 min. The dose can be given directly or added to juice.

Note: a container other than an oral syringe can be used; e.g., a "med cup".

Concurrent radiation:

prophylactic cranial irradiation may be given to patients with ALL in phase II induction with mercaptopurine¹⁸

Dosage in myelosuppression:

modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure:

a suggested dose modification³³:

Creatinine clearance (mL/h)	Dosing interval (h)
50-80	24-36
10-50	48

Calculated creatinine clearance = $\frac{N \times (140 - \text{Age}) \times \text{weight (kg)}}{\text{Serum Creatinine in } \mu\text{mol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure¹⁵:

dosage adjustment recommended; specific guidelines not available
For more information, see paragraph following **Side Effects** table.

Dosage in dialysis¹⁵:

hemodialysis: not dialyzable

Dosage in TPMT deficiency³³:

dose reduction to 5-25% of the standard dose

Children:**Oral²:**

75-100 mg/m² PO once daily, preferably at bedtime³³⁻³⁶
decrease dose by 50% in children less than 3 months of age

For more information on oral administration, see **Dosage Guidelines: Adults.**

REFERENCES:

1. Repchinsky C, BSP. Compendium of Pharmaceuticals and Specialties. Ottawa, Ontario: Canadian Pharmacists Association; 2006. p. 1808-9.
2. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 4th ed. Philadelphia: Lippincott - Raven; 2002. p. 246.

3. National Institute for Occupational Safety and Health (NIOSH). Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. Cincinnati, Ohio: NIOSH - Publications Dissemination; September 2004. p. 31-40.
4. McEvoy GK. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2006. p. 1135-7.
5. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 4th ed. Philadelphia: Lippincott - Raven; 2002. p. 264-7.
6. Chabner BA, Longo DL. Cancer chemotherapy and biotherapy. 3rd ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 295-314.
7. Anonymous. Mercaptopurine: Drug Information. In: Rose BD, editor. UpToDate Wellesley, Massachusetts: UpToDate 14.2; 2006.
8. Rivard GE, Lin KT, Leclerc JM, et al. Milk could decrease the bioavailability of 6-mercaptopurine. *Am J Pediatr Hematol Oncol* 1989;11(4).
9. Riccardi R, Balis FM, Ferrara P, et al. Influence of food intake on bioavailability of oral 6-mercaptopurine in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 1986;3(4):319-24.
10. Burton NK, Barnett MJ, Aherne GW, et al. The effect of food on the oral administration of 6-mercaptopurine. *Cancer Chemother Pharmacol* 1986;18(1):90-1.
11. Lafolie P, Bjork O, Hayder S, et al. Variability of 6-mercaptopurine pharmacokinetics during oral maintenance therapy of children with acute leukemia. *Med Oncol Tumor Pharmacother* 1989;6(4):259-65.
12. Lonnerholm G, Kreuger A, Lindstrom B, et al. Oral mercaptopurine in childhood leukemia: influence of food intake on bioavailability. *Pediatr Hematol Oncol* 1989;6(2):105-12.
13. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Oncology. 4th ed. Philadelphia: Lippincott - Raven; 2002. p. 248.
14. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 404-11.
15. DRUGDEX Evaluations [database on the Internet]. Mercaptopurine. Thompson MICROMEDEX®, 2006. Available from <http://www.micromedex.com>. Accessed 18 October, 2006.
16. Novopharm Limited. Mercaptopurine Tablet Product Monograph. Toronto, Ontario; 2005.
17. Xin HW, Fischer C, Schwab M, et al. Thiopurine S-methyltransferase as a target for drug interactions. *European Journal of Clinical Pharmacology* 2005;61(5-6):395-8.
18. Stephen Nantel, MD. Personal communication. Hematologist, BMT/Leukemia Group Vancouver General Hospital, BC;7 February 2007.
19. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 November 2005.
20. Perry CP, MD. Hepatotoxicity of chemotherapy. In: Rose BD, editor. UpToDate. Wellesley, Massachusetts: UpToDate 14.3; 2006.
21. Drug Interaction Facts [database on the Internet]. Mercaptopurine. Facts and Comparisons 4.0, 2006. Available from <http://www.micromedex.com>. Accessed 17 October, 2006.
22. Gilissen LP, Bierau J, Derijks LJ, et al. The pharmacokinetic effect of discontinuation of mesalazine on mercaptopurine metabolite levels in inflammatory bowel disease patients. *Alimentary Pharmacology & Therapeutics* 2005;22(7):605-11.
23. Rees CA, Lennard L, Lilleyman JS, et al. Disturbance of 6-mercaptopurine metabolism by cotrimoxazole in childhood lymphoblastic leukaemia. *Cancer Chemotherapy & Pharmacology* 1984;12(2):87-9.
24. Martin LA, Mehta SD. Diminished Anticoagulant Effects of Warfarin with Concomitant Mercaptopurine Therapy. *Pharmacotherapy* 2003;23(2):260-4.
25. Atmani D, Benboubetra M, Harrison R, et al. Goats' milk xanthine oxidoreductase is grossly deficient in molybdenum. *J Dairy Res* 2004;71(1):7-13.
26. Baghiani A, Harrison R, Benboubetra M, et al. Purification and partial characterisation of camel milk xanthine oxidoreductase. *Arch Physiol Biochem* 2003;111(5):407-14.
27. Benboubetra M, Baghiani A, Atmani D, et al. Physicochemical and kinetic properties of purified sheep's milk xanthine oxidoreductase. *J Dairy Sci* 2004;87(6):1580-4.
28. Abadeh S, Killackey J, Benboubetra M, et al. Purification and partial characterization of xanthine oxidase from human milk. *Biochim Biophys Acta* 1992;1117(1):25-32.
29. Bradlee Zrudlo. Personal communication. Scientific Regulatory Officer Special Access Programme; October 2006.
30. Sofianou-Katsoulis A, Khakoo G, Kaczmarek R, et al. Reduction in bioavailability of 6-mercaptopurine on simultaneous administration with cow's milk. *Pediatric Hematology & Oncology* 2006;23(6):485-7.
31. Woods DJ, Simonsen K. Administration of liquid dose forms of 6-mercaptopurine to paediatric patients. *Journal of Paediatrics and Child Health* 1995;31(1):62.
32. Trissel LA. Stability of Compounded Formulations. 3rd ed. Washington, District of Columbia: American Pharmacists Association; 2005. p. 268-9.
33. Dorr RT, Von-Hoff DD. Cancer chemotherapy handbook. 2nd ed. Norwalk, Connecticut: Appleton & Lange; 1994. p. 680-5.
34. Rivard GE, Infante-Rivard C, Dresse MF, et al. Circadian Time-Dependent Response of Childhood Lymphoblastic Leukemia to Chemotherapy: A Long-Term Follow-up Study of Survival. *Chronobiology International* 1992;10(3).
35. Schmiegelow K, Glomstein A, Kristinsson J, et al. Impact of morning versus evening schedule for oral methotrexate and 6-mercaptopurine on relapse risk for children with acute lymphoblastic leukemia. *Nordic Society for Pediatric Hematology and Oncology (NOPHO). Journal of pediatric hematology/oncology* 1997;19(2):102-9.
36. Koren G, Langevin AM, Olivieri N, et al. Diurnal Variation in the Pharmacokinetics and Myelotoxicity of Mercaptopurine in Children With Acute Lymphocytic Leukemia. *AJDC* 1990;144:1135-7.