DRUG NAME: Mercaptopurine

SYNONYM(S): 6-mercaptopurine,[1] 6-MP[2]

COMMON TRADE NAME(S): PURINETHOL®

CLASSIFICATION: antimetabolite[1]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Mercaptopurine is a purine antagonist.[3] It is a pro-drug that is converted intracellullarly.[4] Mercaptopurine is first converted to thioinosine monophosphate (TIMP) by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT).[4] TIMP inhibits purine synthesis.[5] TIMP is sequentially metabolized to thioguanine monophosphate (TGMP) and then to thioguanosine triphosphate (TGTP).[5] The cytotoxic effect of mercaptopurine is a result of the incorporation of these nucleotides into DNA. Mercaptopurine is an immunosuppressant.[3] Mercaptopurine is specific for the S phase of the cell-cycle.[6]

PHARMACOKINETICS:

Oral Absorption	• incomplete and highly variable (5-35%); largely due to first pass metabolism in the liver • reduced bioavailability by cow's milk, due to high concentration of xanthine oxidase[7] • preferably taken on an empty stomach[8-11]; may be taken with food if needed • children[12]: <20%	
Distribution	exceeds total body water[5]	
	cross blood brain barrier?	negligible
	volume of distribution	0.9 L/kg children[12]: 22 L/m^2
	plasma protein binding	19%
Metabolism	hepatic: extensive[5] by hypoxanthine-guanine phosphoribosyl transferase (HGPRT); *elimination*[5] by xanthine oxidase to 6-thiouric acid *AND* thiopurine methyltransferase (TPMT) to 6-methylthiopurine	
	active metabolites[5]	thiopurine nucleotides
	inactive metabolites[13]	6-thiouric acid, 6-methylmercaptopurine
Excretion	renal excretion minimal at conventional doses[13]; 20-40% at higher doses	
	urine[14]	7-40% unchanged drug and metabolites
	feces	no information found
	terminal half life	90 min children[12]: <1 h
	clearance	4,832 mL/min/m^2 children[12]: 800 mL/min/m^2

Adapted from standard reference[15] unless specified otherwise.

USES:

Primary uses:
*Leukemia, acute lymphoid
*Leukemia, acute myelogenous
*Leukemia, chronic myeloid

*Health Canada approved indication

Other uses:
Lymphoma, non-Hodgkin's[3]

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.[14]

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.[6]

Hepatotoxicity: Hepatic injury can occur with any dose, but occurs with greatest frequency when doses exceed 2.5 mg/kg/day.[15]

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.[15,16] 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.[13] An estimated 10% of patients may be at increased risk for toxicity due to a heterozygous deletion or mutation.[13] Standardized TPMT genotyping is not currently available in Canada.
- Adverse GI effects occur less frequently in ***pediatric patients*** than in adults.[3,5]

Carcinogenicity: potentially carcinogenic[15]

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.[15]

Fertility: The effect of mercaptopurine on human fertility is not known in either males or females.[15] 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.[14]

Pregnancy: FDA Pregnancy Category D.[6] 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.[15]

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.[17] 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***	
allergy/immunology	hypersensitivity (2-3%)
blood/bone marrow/ febrile neutropenia	***anemia*** (>10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days[6]
	leukopenia (>10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days[6]
	thrombocytopenia (>10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days[6]
constitutional symptoms	fever (1-10%)[6]
dermatology/skin	alopecia (<1%)[6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hyperpigmentation (1-10%)[6]
	rash (1-10%)[6]
gastrointestinal	*emetogenic potential: rare*[18]
	abdominal cramps (1-10%)[6]
	anorexia (1-10%)[6]
	diarrhea (1-10%)[6]
	intestinal ulceration (<1%)
	nausea and vomiting (1-10%)[6]
	stomatitis (1-10%)[6]
hepatobiliary/pancreas	***hepatotoxicity*** (30%)[13]
infection	predisposition to bacterial and parasitic infections[13] due to immunosuppression[14]
metabolic/laboratory	hyperuricemia (1-10%)[6]
renal/genitourinary	renal toxicity (1-10%)[6]
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[3]
	oligospermia, transient[14] (<1%)
syndromes	tumour lysis syndrome; in rare circumstances, certain patients may be at increased risk[17]

Adapted from standard reference[15] unless specified otherwise.

Mercaptopurine-induced ***hepatotoxicity*** is most common when doses exceed 2.5 mg/kg/day.[15] A rapid onset of jaundice, cholestasis, ascites, hepatic encephalopathy, and/or elevated liver enzymes, often associated with hepatic necrosis and severe fibrosis, can occur.[3] 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.[15,19] Weekly monitoring of liver function tests when beginning treatment, followed by monthly monitoring, may allow early detection of hepatotoxicity.[15] 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[15,20]	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[4,5,13]

AGENT	EFFECT	MECHANISM	MANAGEMENT
aminosalicylates[20] (e.g., mesalamine,[21] 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[15]	increased mercaptopurine toxic effect	therapeutic duplication as azathioprine is metabolized to mercaptopurine	do not administer concomitantly[14]
cotrimoxazole[13,22]	decreased mercaptopurine therapeutic and toxic effect	cotrimoxazole may decrease absorption of mercaptopurine	significance not known; further investigation required[22]
*cow's milk[7,23,24]	decreased mercaptopurine bioavailability	inactivation of mercaptopurine by high concentration of xanthine oxidase in cow's milk	clinical significance is unclear[25-28]; may consider separating administration from milk consumption by 6-8 h[24]
methotrexate[20]	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[20] (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 anticurare action	closely monitor respiratory function
warfarin[15,20,29]	delayed, moderate, suspected; inhibition of the anticoagulant effect of warfarin	Unknown[6]	monitor coagulation parameters; adjust warfarin dose as needed[20]

* Xanthine oxidase is present in various concentrations in other milk including human and goat's milk, therefore concurrent use may also decrease levels/effects of mercaptopurine.[30-33]

SUPPLY AND STORAGE:

Oral: Teva[34] and SteriMax[34] supply mercaptopurine as scored 50 mg tablets. Tablets contain lactose. Store at room temperature. Protect from light.

Injection: Not available in Canada.[35]

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:

- induction[6]: 2.5-5 mg/kg/day PO once daily
- maintenance[6]: 1.5-2.5 mg/kg/day PO once daily

Round dose to the nearest 25 mg.
Preferable to administer on an empty stomach[8,9]; mercaptopurine may be taken with food if needed.[10,11]
Preferable to avoid taking tablets with milk or milk based products [7,23] or consider separating mercaptopurine administration from milk/milk product consumption by 6-8 h[24]; however, mercaptopurine may be taken with milk/milk products if needed.[26-28]

For patients unable to swallow tablets, a dispersion can be prepared[36,37]:
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 mercaptopurine[17]

Dosage in myelosuppression:

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

Dosage in renal failure:

a suggested dose modification[38]:

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

$$\text{Calculated creatinine clearance} = \frac{\text{N* x (140 - Age) x weight (kg)}}{\text{Serum Creatinine in µmol/L}}$$

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

Dosage in hepatic failure[14]:

dosage adjustment recommended; specific guidelines not available

Dosage in dialysis[14]:

hemodialysis: not dialyzable

Dosage in TPMT deficiency[38]:

dose reduction to 5-25% of the standard dose

Children:

Oral[2]:

75-100 mg/m^2 PO once daily, preferably at bedtime[38-41]
decrease dose by 50% in children less than 3 months of age

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