DRUG NAME: Mercaptopurine

SYNONYM(S): 6-mercaptopurine, 6-MP

COMMON TRADE NAME(S): PURINETHOL®

CLASSIFICATION: antimetabolite, cytotoxic

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

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

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 (For more information, see Interactions table)
|                 | • preferably taken on an empty stomach; may be taken with food if needed
|                 | • children <20% exceeds total body water
| Distribution    | negligible
|                 | cross blood brain barrier?
|                 | volume of distribution 0.9 L/kg children: 22 L/m²
|                 | plasma protein binding 19%
| Metabolism      | hepatic: extensive activation by hypoxanthine-guanine phosphoribosyl transferase (HGPRT)
|                 | elimination by xanthine oxidase to 6-thiouric acid
|                 | thiopurine methyltransferase (TPMT) to 6-methylthiopurine
|                 | active metabolites thiopurine nucleotides
|                 | inactive metabolites 6-thiouric acid, 6-methylmercaptopurine
| Excretion       | renal excretion minimal at conventional doses; 20-40% at higher doses
|                 | urine 7-40% unchanged drug and metabolites
|                 | feces no information found
|                 | terminal half life 90 min children: <1 h
|                 | clearance 4,832 mL/min/m² children: 800 mL/min/m²

Adapted from standard reference unless specified otherwise.
USES:

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

*Other uses:*
- Lymphoma, non-Hodgkin’s

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 carcinogenic\(^{16}\)

**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 \(>5\%\) higher in the treatment group.

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinically important side effects are in <strong>bold, italics</strong></td>
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### ORGAN SITE

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>allergy/immunology</strong></td>
<td>hypersensitivity (2-3%)</td>
</tr>
</tbody>
</table>
| **blood/bone marrow/febrile neutropenia** | anemia (≥10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days⁷
leukopenia (≥10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days⁷
thrombocytopenia (≥10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days⁷ |
| **constitutional symptoms** | fever (1-10%)⁷ |
| **dermatology/skin** | alopecia (<1%)⁷
hyperpigmentation (1-10%)⁷
rash (1-10%)⁷ |
| **gastrointestinal** | emetogenic potential: rare¹⁰
abdominal cramps (1-10%)⁷
anorexia (1-10%)⁷
diarrhea (1-10%)⁷
intestinal ulceration (<1%)
nausea and vomiting (1-10%)⁷
stomatitis (1-10%)⁷ |
| **hepatobiliary/pancreas** | hepatotoxicity (30%)¹⁴ |
| **infection** | predisposition to bacterial and parasitic infections¹⁴ due to immunosuppression¹⁵ |
| **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 pregnancy⁴
oligospermia, transient¹⁵ (<1%) |
| **syndromes** | tumour lysis syndrome; in rare circumstances, certain patients may be at increased risk¹⁸ |

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.¹ 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:

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>allopurinol&lt;sup&gt;16,21&lt;/sup&gt;</td>
<td>delayed, major, established; increased mercaptopurine toxic effect</td>
<td>inhibition of xanthine oxidase by allopurinol reduces the rate of mercaptopurine elimination</td>
<td>mercaptopurine dose reduction to 25% of standard dose when given concomitantly&lt;sup&gt;5,6,14&lt;/sup&gt;</td>
</tr>
<tr>
<td>aminosalicylates&lt;sup&gt;21&lt;/sup&gt; (e.g., mesalamine,&lt;sup&gt;22&lt;/sup&gt; olsalazine, sulfasalazine)</td>
<td>delayed, moderate, possible; increased mercaptopurine toxic effect</td>
<td>inhibition of TPMT by aminosalicylates reduces the rate of mercaptopurine elimination</td>
<td>monitor for mercaptopurine toxicity</td>
</tr>
<tr>
<td>azathioprine&lt;sup&gt;16&lt;/sup&gt;</td>
<td>increased mercaptopurine toxic effect</td>
<td>therapeutic duplication as azathioprine is metabolized to mercaptopurine</td>
<td>do not administer concomitantly&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td>cotrimoxazole&lt;sup&gt;14,23&lt;/sup&gt;</td>
<td>decreased mercaptopurine therapeutic and toxic effect</td>
<td>cotrimoxazole may decrease absorption of mercaptopurine</td>
<td>significance not known; further investigation required&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>*cow’s milk&lt;sup&gt;8&lt;/sup&gt;</td>
<td>decreased bioavailability</td>
<td>inactivated by high concentration of xanthine oxidase in cow’s milk</td>
<td>avoid concurrent intake</td>
</tr>
<tr>
<td>methotrexate&lt;sup&gt;21&lt;/sup&gt;</td>
<td>delayed, moderate, possible; increased mercaptopurine toxic effect</td>
<td>moderate inhibition of xanthine oxidase by methotrexate reduces the rate of mercaptopurine elimination</td>
<td>primarily a concern with high-dose methotrexate; consider mercaptopurine dose reduction</td>
</tr>
<tr>
<td>muscle relaxants, nondepolarizing&lt;sup&gt;21&lt;/sup&gt; (e.g., atracurium, gallamine, metocurine, pancuronium, tubocurine, vecuronium)</td>
<td>rapid, moderate, suspected; decreased or reversed efficacy of muscle relaxants</td>
<td>inhibition of phosphodiesterase by mercaptopurine in the motor nerve terminal results in an anticurare action</td>
<td>closely monitor respiratory function</td>
</tr>
<tr>
<td>warfarin&lt;sup&gt;16,21,24&lt;/sup&gt;</td>
<td>delayed, moderate, suspected; inhibition of the anticoagulant effect of warfarin</td>
<td>unknown&lt;sup&gt;7&lt;/sup&gt;</td>
<td>monitor coagulation parameters; adjust warfarin dose as needed&lt;sup&gt;21&lt;/sup&gt;</td>
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</tbody>
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* 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.<sup>25-28</sup>

### SUPPLY AND STORAGE:

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

**Injection:** Not available in Canada.<sup>29</sup>
**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**: 2.5-5 mg/kg/day PO once daily
- **maintenance**: 1.5-2.5 mg/kg/day PO once daily

Round dose to the nearest 25 mg.

Preferably administer on an empty stomach; may be taken with food if needed. Avoid taking tablets with milk or milk based products.

For patients unable to swallow tablets, a dispersion can be prepared:

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.

**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 modification:

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/h)</th>
<th>Dosing interval (h)</th>
</tr>
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<tbody>
<tr>
<td>50-80</td>
<td>24-36</td>
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<tr>
<td>10-50</td>
<td>48</td>
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</tbody>
</table>

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

* For males \(N=1.23\); for females \(N=1.04\)

**Dosage in hepatic failure:**

Dosage adjustment recommended; specific guidelines not available

For more information, see paragraph following Side Effects table.

**Dosage in dialysis:**

Hemodialysis: not dialyzable

**Dosage in TPMT deficiency:**

Dose reduction to 5-25% of the standard dose

**Children:**

**Oral:**

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

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

**REFERENCES:**


