

DRUG NAME: Thioguanine**SYNONYM(S):** 2-amino-6-mercaptopurine,¹ 6-TG, TG**COMMON TRADE NAME(S):** LANVIS®**CLASSIFICATION:** antimetabolite, cytotoxic²*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Thioguanine is a purine antagonist.¹ It is a pro-drug that is converted intracellularly directly to thioguanine monophosphate³ (also called 6-thioguanic acid)⁴ (TGMP) by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT). TGMP is further converted to the di- and triphosphates, thioguanosine diphosphate (TGDP) and thioguanosine triphosphate (TGTP).⁵ The cytotoxic effect of thioguanine is a result of the incorporation of these nucleotides into DNA. Thioguanine has some immunosuppressive activity.¹ Thioguanine is specific for the S phase of the cell cycle.⁶

PHARMACOKINETICS:

Oral Absorption	<ul style="list-style-type: none"> incomplete and variable (14-46%)⁷ preferably taken on an empty stomach⁸; may be taken with food if needed children⁹: <20% 	
Distribution	crosses the placenta ¹⁰	
	cross blood brain barrier?	negligible ¹¹
	volume of distribution ¹²	148 mL/kg
	plasma protein binding	no information found
Metabolism	hepatic ¹⁰ <i>activation by</i> ⁴ : <ul style="list-style-type: none"> hypoxanthine-guanine phosphoribosyl transferase (HGPRT) <i>elimination by</i> ⁴ : <ul style="list-style-type: none"> guanase to 6-thioxanthine thiopurine methyltransferase (TPMT) to 2-amino-6-methyl thiopurine 	
	active metabolites ^{3,4}	thiopurine nucleotides
	inactive metabolites ⁴	6-thioxanthine, 2-amino-6-methyl thiopurine
	Excretion	renal excretion ¹² ; initially intact drug, then metabolites
	urine ¹²	5 h, 54%; 24 h, 75%
	feces	no information found
	terminal half life	90 min ^{4,6} children ⁹ : 2 h
	clearance	600-1,000 mL/min ⁴ children ⁹ : 1,000-2,000 mL/min/m ²

Adapted from standard reference¹³ unless specified otherwise.

USES:**Primary uses:**

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

Other uses:

- Brain tumours⁶
- Breast cancer⁶
- Lymphoma, non-Hodgkin's⁶

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindicated⁶: Patients with hypersensitivity to thioguanine; patients whose disease showed prior resistance to thioguanine or mercaptopurine as there is complete cross-resistance between the two drugs.

Potential error: The synonym 6-TG should be avoided because it may result in a 6-fold overdose.¹⁴

Hematologic¹³: Thioguanine may have a delayed effect, so it is important to monitor blood counts; delay treatment as required.

Hepatotoxicity¹³: Thioguanine is not recommended for maintenance therapy or similar long term continuous treatments due to high risk of liver toxicity. For more information, see paragraph following **Side Effects** table.

Special populations: Toxicity may vary among different patient groups:

- Patients with low or intermediate **TPMT activity** accumulate higher concentrations of thioguanine cytotoxic metabolites compared to patients with normal TPMT activity.⁶ 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.¹⁵ An estimated 10% of patients may be at increased risk for toxicity because of a heterozygous deletion or mutation. Standardized TPMT genotyping is not currently available in Canada.
- **Children** receiving continuous therapy thioguanine have a higher rate of liver toxicity, including vascular endothelial damage.¹³
- Liver toxicity is more prevalent in **males**.¹¹

Carcinogenicity: potentially carcinogenic¹¹

Mutagenicity: potentially mutagenic¹¹

Fertility: No information found.

Pregnancy: FDA Pregnancy Category D.¹⁰ 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 not recommended due to the potential secretion into breast milk.¹¹

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^{3,16} 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	
blood/bone marrow/ febrile neutropenia	<i>anemia</i>
	<i>leukopenia (> 10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days¹⁰</i>
	<i>thrombocytopenia (> 10%); onset 7-10 days, nadir 14-16 days, recovery 21-28 days¹⁰</i>
dermatology/skin	skin rash (1-10%) ¹⁰
gastrointestinal	<i>emetogenic potential: rare¹⁷</i>
	anorexia (1-10%) ¹⁰
	diarrhea (1-10%) ¹⁰
	esophageal varices (< 1%) ¹⁰
	nausea (1-10%) ¹⁰
	stomatitis (1-10%) ¹⁰
	vomiting (1-10%) ¹⁰
hepatobiliary/pancreas	<i>hepatotoxicity (< 1%)¹⁰</i>
infection	predisposition to bacterial and parasitic infections ¹⁵ due to immunosuppression
metabolic/laboratory	hyperuricemia (1-10%) ¹⁰
musculoskeletal	unsteady gait (1-10%) ¹⁰
syndromes	tumour lysis syndrome; in rare circumstances certain patients may be at increased risk ¹⁶

Adapted from standard reference¹³ unless specified otherwise.

Hepatotoxicity: Thioguanine is not recommended for chronic administration due to the high risk of liver toxicity associated with endothelial damage.¹³ Liver toxicity often presents as veno-occlusive disease (VOD), including hyperbilirubinaemia, tender hepatomegaly, weight gain due to fluid retention, and ascites. Liver toxicity can also present as portal hypertension including splenomegaly, thrombocytopenia and esophageal varices. Elevation in liver transaminases, alkaline phosphatase, and gamma glutamyl transferase and jaundice may also occur. Like mercaptopurine, hepatic damage may be due to direct toxicity from the drug or a result of a hypersensitivity reaction.¹⁸ Thioguanine should be discontinued in patients with evidence of liver toxicity. Thioguanine-induced liver toxicity may be reversible.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
allopurinol ⁴	no effect	thioguanine is not a direct substrate for xanthine oxidase, therefore an inhibitor of xanthine oxidase such as allopurinol does not block the elimination of thioguanine	no thioguanine dose reduction required when given concomitantly

AGENT	EFFECT	MECHANISM	MANAGEMENT
busulfan ⁶	moderate, delayed, established; increased risk of nodular regenerative hyperplasia of the liver	unknown	concurrent long-term continuous therapy with busulfan and thioguanine should be used with caution; monitor liver function tests closely

Thioguanine is catabolized by TPMT, therefore drugs that are inhibitors of TPMT (e.g., mesalamine, olsalazine, sulfasalazine) may increase the levels/effects of thioguanine.⁶

SUPPLY AND STORAGE:

Tablets¹³: GlaxoSmithKline supplies thioguanine as a scored 40 mg tablet. Selected non-medicinal ingredients: lactose. Store in a dry place between 15-25°C and protect from light.

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:

<i>Oral</i> ¹⁰ :	2-3 mg/kg/day or 75-200 mg/m ² /day PO once daily in 1-2 divided doses for 5-7 days or until remission is attained. Round dose to the nearest 20 mg. Preferably administer on an empty stomach ⁸ ; may be administered with food if needed. For patients unable to swallow tablets, a 40 mg/mL suspension can be prepared ¹⁹ : Crush tablets, mix with a suspending agent (e.g., COLOGEL®) equal to one-third the final volume, and then q.s. to the final volume with a 2:1 mixture of simple syrup and wild cherry syrup. The resulting suspension is stable for at least 84 days when stored in an amber glass bottle at room temperature. ^{1,19}	BCCA usual dose noted in <i>bold, italics</i>
<i>Concurrent radiation:</i>	no information found	
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
<i>Dosage in renal failure</i> ^{10,11} :	dosage adjustment recommended; specific guidelines not available	
<i>Dosage in hepatic failure</i> ^{10,11} :	dosage adjustment recommended; specific guidelines not available	
<i>Dosage in dialysis:</i>	hemodialysis ¹⁰ : not dialyzable	
<i>Dosage in TPMT deficiency</i> ¹⁵ :	dose reduction to 5-25% of the standard dose	

Children:

*Oral*²⁰: 80-100 mg PO once daily for 5-7 days

40-60 mg PO once daily

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

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