Drug Monograph

A - Drug Name

thioguanine

COMMON TRADE NAME(S): Lanvis®

back to top

B - Mechanism of Action and Pharmacokinetics

It is a 6-thiopurine analogue of the naturally occurring purine bases hypoxanthine and guanine. Intracellular activation results in incorporation into DNA as a false purine base. An additional cytotoxic effect is related to its incorporation into RNA. Thioguanine is cross-resistant with mercaptopurine. Cytotoxicity is cell cycle phase-specific (S-phase).

Absorption	Oral: Variable and incomplete, 14 - 46% (mean 30%) bioavailability	
Distribution	Not completely elucidated, crosses the placenta	
	Cross blood brain barrier?	Trace
	PPB	No information found
Metabolism	Predominantly in liver and other tissues; extensively metabolised by methylation, oxidation and deamination. Metabolism is not inhibited by xanthine oxidase inhibitors.	
	Active metabolites	2-amino-6-methylmercaptopurine
	Inactive metabolites	yes
Elimination	Mainly in urine	
	Urine	24-46% within 24 hours (little unchanged)

Half-life	5 - 9 hours

back to top

C - Indications and Status

Health Canada Approvals:

- Acute leukemia

back to top

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse effects include those reported for use of thioguanine as a component of combination chemotherapy, so some of these effects may be due to other chemotherapy drugs.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Photosensitivity (rare)	E
	Rash (rare)	E
Gastrointestinal	Anorexia (less common)	E
	Colitis (rare)	E D
	Diarrhea (common)	E
	GI perforation (rare)	E
	Mucositis (common)	E
	Nausea, vomiting (less common)	I
Hematological	Myelosuppression ± infection, bleeding (common, includes pancytopenia; may be severe - nadir 7-14 days, recovery 21 days)	E
Hepatobiliary	↑ LFTs (may be severe)	E
	Portal hypertension (may be severe)	E
	Veno-occlusive disease (may be severe)	E
Metabolic / Endocrine	Hyperuricemia (during periods of active cell lysis - common)	I

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The primary toxicity of thioguanine is dose-related **myelosuppression**.

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g., some leukemias and lymphomas) can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalinized, by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

Unlike mercaptopurine, thioguanine's metabolism is not inhibited by the **xanthine oxidase inhibitor** allopurinol. However, toxicity is markedly increased in patients with **inherited deficiencies of TPMT and HGPRT**.

Prolonged maintenance use may be associated with veno-occlusive disease or portal hypertension, with thrombocytopenia and abnormal liver function tests and is common in children and males. In some cases, portal hypertension may persist for 5 to 9 years after treatment cessation. Liver toxicity may be reversible. Nodular regenerative hyperplasia and centrilobular hepatic necrosis has been reported rarely.

Photosensitivity may lead to an increased risk of skin cancer. Patients should limit sun exposure, wear protective clothing and use sunscreen with an SPF ≥ 30.

back to top

E - Dosing

Refer to the local protocol by which the patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

Thioguanine should not be used in patients with mercaptopurine-resistant disease and is not recommended for maintenance treatment due to the high risk of liver toxicity.

Genotypic or phenotypic tests of TPMT are recommended prior to starting treatment as patients with TPMT deficiency may need significant starting dose reductions.

Adults:

Calculate doses to nearest 20 mg. Take as a single dose, on an empty stomach.

Induction:
2 mg/kg/day p.o, may increase to 3 mg/kg/day if no response after 4 weeks

Suggested dose adjustments per TPMT geno/phenotype:

TPMT geno/phenotype	**thioguanine dose**
Homozygous wild type or high activity (2 functional *1 alleles)	No change in starting dose. Adjust doses per protocol for myelosuppression. Allow 2 weeks to reach steady state after each dose adjustment.
Heterozygous or intermediate activity (one functional *1 allele, plus one non-functional allele *2, *3A, *3B, *3C or *4)	Reduce starting dose by 30-50% and adjust doses per protocol for myelosuppression. Allow 2-4 weeks to reach steady state after each dose adjustment. Reduce thioguanine dose first vs. other drugs.
Homozygous, mutant or low activity (2 non-functional alleles *2, *3A, *3B, *3C or *4)	Reduce starting dose 10-fold and dose 3 times weekly. Adjust dose per protocol for myelosuppression. Allow 4-6 weeks to reach steady state after each dose adjustment. Reduce thioguanine dose first vs. other drugs.

Dosage with Toxicity:

Dosage in Myelosuppression: Modify according to protocol by which patient is being treated.

Dosage with Hepatic Impairment:

Hepatic impairment may increase thioguanine exposure; consider reducing the starting dose. Dose should be held with evidence of hepatotoxicity or biliary stasis.

Dosage with Renal Impairment:

No data are available in renal impairment; consider reducing the starting dose.

Dosage in the elderly:

There are limited safety data in patients aged 65 and older. Dose selection should be cautious, starting at the lower end of the protocol dosing range, reflecting the increased risk with reduced hepatic, renal or cardiac function, co-morbidities and co-administered drugs.

Children:

See specific protocols for doses and dose modifications. Liver toxicity has been observed in children receiving thioguanine as part of maintenance therapy.

back to top

F - Administration Guidelines

Oral self-administration; drug available by outpatient prescription.

back to top

G - Special Precautions

Contraindications:

- Patients with hypersensitivity to this drug or any of its components
- Patients those disease has demonstrated prior resistance to this drug or mercaptopurine; thioguanine is cross-resistant with mercaptopurine
- Thioguanine is not recommended as maintenance treatment due to the high incidence of liver toxicity and veno-occlusive disease
- Live vaccines

Other Warnings/Precautions:

- Patients with inherited deficiencies of thiopurine methyltransferase (TPMT) or hypoxanthine guanine phosphoribosyltransferase (Lesch Nyhan syndrome) are at risk for excessive toxicity, as are patients taking drugs that inhibit TPMT such as sulfasalazine.

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: Yes
- Teratogenicity: Yes
- Fetotoxicity: Yes
  Thioguanine should not be used in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Excretion into breast milk: Likely
  Breastfeeding is not recommended.
- Fertility effects: Likely

back to top

H - Interactions

Unlike mercaptopurine, thioguanine's metabolism is not inhibited by the xanthine oxidase inhibitor allopurinol. It is unclear whether thioguanine dose reduction is required when given in combination with allopurinol.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Busulfan	Hepatotoxicity, esophageal varices, portal hypertension	Unknown	Monitor if given together for long-term therapy
TPMT inhibitors (sulfasalazine, mesalazine, olsalazine	↑ toxicity	↓ TPMT	Caution with concomitant use

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
TPMT geno/phenotype testing	Before starting treatment
CBC	Baseline and at least weekly
Liver function tests	Baseline and at each visit
Renal function tests	Baseline and at each visit
Clinical toxicity assessment for infection, bleeding, GI, skin and liver toxicity	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- thioguanine

back to top

K - References

Lanvis® (thioguanine) product monograph. Concord, Ontario; Triton Pharma Inc.; Sept 21, 2017.

June 2019 Updated emetic risk category.

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top