PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrLANVIS®

Thioguanine

Tablets, 40 mg

USP

Antileukemic Agent

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PrLANVIS®

Thioguanine tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet/40 mg	gum acacia, lactose, magnesium stearate, potato starch, and stearic acid. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

LANVIS® is indicated for the treatment of acute leukaemia.

LANVIS is not recommended for maintenance therapy or similar long-term continuous treatments due to the high risk of liver toxicity.

Geriatrics (≥ 65 years of age): Clinical studies of thioguanine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

Pediatrics (≤ 18 years of age): Liver toxicity has been observed in a high proportion of children receiving thioguanine as part of maintenance therapy.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the SUMMARY PRODUCT INFORMATION, or DOSAGE FORMS, COMPOSITION AND PACKAGING sections of the product monograph. LANVIS® (thioguanine) should not be given to patients who experienced a previous hypersensitivity reaction to the drug or any of its components.

- LANVIS® should not be used in patients whose disease has demonstrated prior resistance to this drug. In animals and man, there is usually complete cross-resistance between mercaptopurine and thioguanine. Therefore, LANVIS should not be used in patients with a disease resistant to mercaptopurine, or vice versa.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

LANVIS is a cytotoxic agent and should be used only under the direction of physicians experienced in the administration of such agents. The following are significant adverse drug reactions reported during the treatment with LANVIS.

- Myelosuppression including life-threatening infections and bleeding, especially in patients with thiopurine S-methyltransferase deficiency (see **Hematologic** below).
- Liver toxicity (see **Hepatic/Biliary/Pancreatic** below**)**.
- Potential severe infection after immunisation using a live organism vaccine (see **Immune** below).

General

LANVIS® (thioguanine or 6-thioguanine) is a potent drug and should be used only under the direction of physicians experienced with cancer chemotherapeutic drugs. Since 6-thioguanine is strongly myelosuppressive, full blood counts should be taken weekly. Discontinue or reduce the dosage immediately at the first sign of abnormal depression of the bone marrow. During concomitant administration of LANVIS with other myelotoxic substances or radiation therapy, the risk of myelosuppression is increased.

Thioguanine is not recommended for maintenance therapy or similar long term continuous treatments due to the high risk of liver toxicity associated with vascular endothelial damage (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Carcinogenesis and Mutagenesis

In view of its action on cellular DNA, thioguanine is potentially mutagenic and carcinogenic, and consideration should be given to the theoretical risk of carcinogenesis when thioguanine is administered.

Gastrointestinal

Intestinal necrosis and perforation with fatal outcomes have been reported in patients who received thioguanine in combination with other cytotoxic agents.

Hematologic

The most frequent dose-related toxicity of LANVIS is bone marrow suppression. This may be manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Any one of these findings may also reflect progression of the underlying disease. Since LANVIS is usually one component of combination chemotherapy that causes myelosuppression, pancytopenia is observed in nearly all patients. Life-threatening infections and bleeding have been observed as consequences of thioguanine-induced granulocytopenia and thrombocytopenia.

Dosages and schedules must be adjusted to prevent life-threatening cytopenias whenever these adverse reactions are observed. Since thioguanine may have a delayed effect, it is important to withdraw the medication temporarily at the first sign of an abnormally large decrease in any of the formed elements of the blood. Since 6-thioguanine is strongly myelosuppressive, full blood counts should be made at least once weekly (see Monitoring and laboratory Tests).

It is recommended that evaluation of the hemoglobin concentration or hematocrit, total white blood cell count and differential count, and quantitative platelet count be obtained frequently while the patient is on thioguanine therapy. In cases where the cause of fluctuations in the formed elements in the peripheral blood is obscure, bone marrow examination may be useful for the evaluation of marrow status. The decision to increase, decrease, continue, or discontinue a given dosage of thioguanine must be based not only on the absolute hematologic values, but also upon the rapidity with which changes are occurring. In many instances, particularly during the induction phase of acute leukemia, complete blood counts will need to be done more frequently in order to evaluate the effect of the therapy. The dosage of thioguanine may need to be reduced when this agent is combined with other drugs whose primary toxicity is myelosuppression.

Thiopurine methyltransferase deficient patients: There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of thioguanine and prone to developing rapid and severe bone marrow depression following the initiation of treatment with LANVIS®. This toxicity could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine.

Genotypic or phenotypic tests of TPMT are recommended prior to initiating LANVIS® as patients with TPMT deficiency may need significantly reduced starting dose (see Dosage and Administration). Close monitoring of blood counts is also necessary (see Monitoring and Laboratory Tests).

NUDT15 variant patients: Case series and several published studies indicate that patients with inherited mutated nudix hydrolase 15 (NUDT15) gene are at increased risk for severe thiopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy and require substantial dose reduction. Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population. The optimal starting dose for heterozygous or homozygous deficient patients has not been established.

Genotypic and phenotypic testing of NUDT15 variants should be considered before initiating thiopurine therapy in all patients (including paediatric patients) to reduce the risk of thiopurine-related severe leukocytopenia and alopecia, especially in Asian populations (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Hepatic/Biliary/Pancreatic

Thioguanine is not recommended for maintenance therapy or similar long term continuous treatments due to the high risk of liver toxicity associated with vascular endothelial damage (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS). This liver toxicity has been observed in a high proportion of children receiving thioguanine as part of maintenance therapy for acute lymphoblastic leukemia and in other conditions associated with continuous use of thioguanine. This liver toxicity is particularly prevalent in males. Liver toxicity usually presents as the clinical syndrome of veno-occlusive disease (hyperbilirubinaemia, tender hepatomegaly, weight gain due to fluid retention and ascites) or with signs of portal hypertension (splenomegaly, thrombocytopenia and oesophageal varices). Elevation of liver transaminases, alkaline phosphatase and gamma glutamyl transferase and jaundice may also occur. Histopathological features associated with this toxicity include hepatoportal sclerosis, nodular regenerative hyperplasia, peliosis hepatis and periportal fibrosis. Centrilobular hepatic necrosis has been reported in a few cases.

Thioguanine therapy should be discontinued in patients with evidence of liver toxicity. Although reversal of signs and symptoms of liver toxicity have been reported upon withdrawal, significant portal hypertension persisted in some cases for five to nine years after cessation of thioguanine therapy.

Patients must be carefully monitored (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Early indications of liver toxicity are signs associated with portal hypertension such as thrombocytopenia out of proportion with neutropenia and splenomegaly.

A few cases of jaundice have been reported in patients with leukemia who received thioguanine. Among these were two adult male patients and four children with acute myelogenous leukemia, and an adult male with acute lymphocytic leukemia who developed hepatic veno-occlusive disease while receiving chemotherapy for their leukemia. Six patients had received cytarabine prior to treatment with thioguanine, and some were receiving other chemotherapy in addition to thioguanine when they became symptomatic. While hepatic veno-occlusive disease has not been reported in patients treated with thioguanine alone, it is recommended that thioguanine be withheld if there is evidence of toxic hepatitis or biliary stasis, and that appropriate clinical and laboratory investigations be initiated to establish the etiology of the hepatic dysfunction. Deterioration in liver function studies during thioguanine therapy should prompt discontinuation of treatment and a search for an explanation of the hepatotoxicity.

Consideration should be given to reducing the dosage in patients with impaired hepatic function.

Immune
Immunisation using a live organism vaccine has the potential to cause serious infections in immunocompromised hosts. Therefore, immunisation with live organism vaccines (e.g. measles, mumps, etc.) is not recommended in patients treated with LANVIS®. In all cases, patients in remission should not receive live organism vaccines until at least 3 months after their chemotherapy treatment has been completed.

Renal
During remission induction, hyperuricemia and/or hyperuricosuria and uric acid nephropathy frequently occurs in patients receiving thioguanine as a consequence of rapid cell lysis accompanying the antineoplastic effect. These adverse effects can be minimized by increased hydration, urine alkalinization, and prophylactic administration of allopurinol (see Drug Interactions).

Consideration should be given to reducing the dosage in patients with impaired renal function.

Resistance
Since the enzyme hypoxanthine guanine phosphoribosyltransferase is responsible for the conversion of thioguanine to its active metabolite, it is possible that patients deficient in this enzyme, such as those suffering from Lesch-Nyhan syndrome, may be resistant to thioguanine.

Skin
Patients treated with 6-thioguanine are more sensitive to sun exposure, which may lead to an increased risk of skin cancers. Exposure to sunlight and UV light should be limited when taking LANVIS. Patients should be recommended to wear protective clothing and to use a sunscreen with a high protection factor.

Special Populations

Pregnant Women: Thioguanine, like other cytotoxic agents, is potentially teratogenic. Thioguanine has been shown to be teratogenic in rats when given in doses from 10 to 12 mg/kg (equivalent to 1.6 to 2mg/kg in humans). When given to the rat on the 4th and 5th days of gestation, 13% of surviving placentas did not contain fetuses, and 19% of offspring were malformed or stunted. The malformations noted included generalized edema, cranial defects, and general skeletal hypoplasia, hydrocephalus, ventral hernia, situs inversus, and incomplete development of the limbs.

There are no adequate and well-controlled studies in pregnant women. Drugs of this type have potential teratogenic activity and the benefits and risks must be weighed before use during pregnancy. If LANVIS is used during pregnancy, or if the patient becomes pregnant while taking LANVIS, the patient should be apprised of the hazard to the fetus. Whenever possible, use of the drug should be deferred until after the first trimester of pregnancy.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving thioguanine. Women of childbearing potential should be advised to avoid becoming pregnant.

Nursing Women: It is not known whether thioguanine is excreted in human milk. Because of the potential for tumorigenicity shown for thioguanine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age): Liver toxicity has been observed in a high proportion of children receiving thioguanine as part of maintenance therapy for acute lymphoblastic leukaemia and in other conditions associated with continuous use of thioguanine. LANVIS is not recommended for maintenance therapy or similar long-term continuous treatments due to the high risk of liver toxicity (see Dosage and Administration).

Geriatrics (> 65 years of age): Clinical studies of thioguanine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Monitoring and Laboratory Tests
It is advisable to monitor liver function tests (serum transaminases, alkaline phosphatase, bilirubin) at weekly intervals when first beginning therapy and at monthly intervals thereafter. It may be advisable to perform liver function tests more frequently in patients with known pre-existing liver disease or in patients who are receiving thioguanine with other hepatotoxic drugs. Patients should be instructed to discontinue thioguanine immediately if clinical jaundice is detected (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Genotypic and phenotypic tests of thiopurine methyltransferase (TPMT) and mutated nudix hydrolase 15 (NUDT15) gene are recommended prior to initiating LANVIS® to identify patients with higher risk of toxicity.

Full blood counts should be taken at baseline and weekly during LANVIS therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

For this product there is a lack of modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Thioguanine is usually one component of combination chemotherapy and consequently it is not possible to ascribe the side effects unequivocally to this drug alone.

Post-Market Adverse Drug Reactions

Gastrointestinal: Common adverse reactions include stomatitis and gastrointestinal disorder. Less frequent adverse reactions include nausea, vomiting, and anorexia. Intestinal necrosis and perforation have been reported in patients who received multiple drug chemotherapy including thioguanine. Esophageal varices have been reported in patients receiving continuous busulfan and thioguanine therapy for treatment of chronic myelogenous leukemia (see DRUG INTERACTIONS). Necrotising colitis has been rarely reported.

While on the whole no significant clinical difference between thioguanine and mercaptopurine has been noted with respect to action or side effects, it has been observed that occasionally patients may experience better gastrointestinal tolerance to one or another drug of this type.

Hematologic: The most frequent adverse reaction to thioguanine is myelosuppression. The induction of complete remission of acute myelogenous leukemia usually requires combination chemotherapy in dosages which produce marrow hypoplasia. Since LANVIS is usually used in combination with multiple drug regimens whose component agents cause myelosuppression, pancytopenia is observed in nearly all patients. Dosages and schedules must be adjusted to prevent life-threatening cytopenias whenever these adverse reactions are observed.

Hepatic/Biliary/Pancreatic: Liver toxicity associated with vascular endothelial damage has been reported when thioguanine is used in maintenance or similar long term continuous therapy which is not recommended (see DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS). This usually presents as the clinical syndrome of hepatic veno-occlusive disease (hyperbilirubinaemia, tender hepatomegaly, weight gain due to fluid retention and ascites) or signs and symptoms of portal hypertension (splenomegaly, thrombocytopenia and oesophageal varices). Elevation of liver transaminases, alkaline phosphatase and gamma glutamyl transferase and jaundice may also occur.

Histopathological features associated with this toxicity include hepatoportal sclerosis, nodular regenerative hyperplasia, peliosis hepatis and periportal fibrosis.

Liver toxicity during short term cyclical therapy presents as veno-occlusive disease. Reversal of signs and symptoms of this liver toxicity has been reported upon withdrawal of short term or long term continuous therapy.

Centrilobular hepatic necrosis has been reported in a few cases; however, the reports are confounded by the use of high doses of thioguanine, other chemotherapeutic agents, oral contraceptives and chronic alcohol abuse.

Renal: Hyperuricemia frequently occurs in patients receiving thioguanine as a consequence of rapid cell lysis accompanying the antineoplastic effect. During remission induction particularly, when rapid cell lysis is occurring, adequate precautions should be taken to avoid hyperuricemia and/or hyperuricosuria and the risk of uric acid nephropathy. Adverse effects can be minimized by increased hydration, urine alkalinization, and the prophylactic administration of allopurinol (a xanthine oxidase inhibitor, see Drug Interactions).

Skin: Patients treated with 6-thioguanine are more sensitive to the sun. Exposure to sunlight and UV light should be limited, and patients should be recommended to wear protective clothing and to use a sunscreen with a high protection factor.

DRUG INTERACTIONS

Serious Drug Interactions

- Potential of serious infection after vaccinations with live organism vaccines (see below).
- Increased risk of myelosuppression during concomitant administration with other cytotoxic drugs or radiation therapy (see below).
- Increased toxicities when LANVIS is concomitantly used with aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine, see below).

Overview

Thiopurine methyltransferase (TPMT) is a major enzyme to convert thioguanine into inactive metabolites (see Action and Clinical Pharmacology). Drugs inhibiting TPMT, such as aminosalicylate derivatives, may increase the exposure of thioguanine and its active metabolites.

Suppressed immune response is experienced in patients with ALL and/or treated with cytotoxic agents including LANVIS. Therefore, immunization using a live organism vaccine has the potential to cause serious infections in those patients.

During concomitant administration of LANVIS with other cytotoxic drugs or radiation therapy, the risk of myelosuppression is increased.

Drug-Drug and Drug-Vaccine Interactions

A drug-drug interaction study with concomitant use of allopurinol (an inhibitor of xanthine oxidase) and LANVIS has not been conducted. It is unclear whether LANVIS dose reduction is needed when used in combination with allopurinol. Potential drug-drug and drug-vaccine interactions are presented in Table 1

Table 1: Established or Potential Drug-Drug Interactions

Thioguanine	Effect	Clinical comment
Mercaptopurine	Complete cross resistance among thioguanine and mercaptopurine .	LANVIS should not be used in patients with a disease resistant to mercaptopurine, and vice versa (see CONTRAINDICATIONS).

Busulfan (MYLERAN®)	Esophageal varices Liver toxicity	In one study, 12 of approximately 330 patients receiving continuous busulfan and thioguanine therapy for treatment of chronic myelogenous leukemia were found to have esophageal varices associated with abnormal liver function tests. Subsequent liver biopsies were performed in four of these patients, all of which showed evidence of nodular regenerative hyperplasia. Duration of combination therapy prior to the appearance of esophageal varices ranged from 6 to 45 months. With the present analysis of the data, no cases of hepatotoxicity have appeared in the busulfan alone arm of the study.
Aminosalicylate derivatives [(e.g. olsalazine, mesalazine or sulphasalazine)]	Inhibit Thiopurine methyltransferase (TPMT)	Based on *in vitro* evidence aminosalicylate derivatives should be administered with caution to patients receiving concurrent thioguanine therapy (See WARNINGS AND PRECAUTIONS).
Live viral vaccines	Potential to cause serious infections in immunocompromised hosts.	Vaccinations with live organism vaccines are not recommended in immunocompromised individuals, *e.g.* patients treated with LANVIS® (see WARNINGS AND PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Dosing Considerations

LANVIS® (thioguanine) is a potent drug and should be used only by physicians experienced with cancer chemotherapeutic drugs. Blood counts should be taken weekly. Discontinue or reduce the dosage immediately at the first sign of abnormal depression of the bone marrow.

Thioguanine can be used for remission induction and remission consolidation of acute lymphoblastic leukaemia. However, it is not recommended for use during maintenance therapy or similar long term continuous treatments due to the high risk of liver toxicity (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Recommended Dose and Dosage Adjustment

The dosage of thioguanine must be carefully adjusted for each patient to obtain optimum benefit without toxic effects. The usual initial dose is approximately 2 mg/kg body weight/day, orally. If after four weeks on this dosage there is no clinical improvement and no leukocyte depression, the dosage may be cautiously increased to 3 mg/kg/day.

The total daily dose may be given at one time. It is usually calculated to the closest multiple of 20 mg. Although the effect usually occurs slowly over a period of two to four weeks, occasionally there may be a rapid fall in leukocyte count within one or two weeks. This may occur in some adults with acute leukemia and high total leukocyte counts. For this reason it is important to observe such patients closely.

Geriatrics (≥ 65 years)

There are insufficient data to recommend a specific dose in geriatric patients with leukemia. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatrics (≤ 18 years)
For children, similar dosages to those used in adults, with appropriate correction for body surface area, have been used.

Thiopurine S-methyltransferase-deficient patients
Genotypic or phenotypic tests of thiopurine S-methyltransferase (TPMT) are recommended prior to initiating LANVIS® to identify high risk patients (see WARNINGS AND PRECAUTIONS: Hematologic, Monitoring and Laboratory Tests). Patients with inherited little or no TPMT activity are at increased risk for severe thioguanine toxicity (*e.g.,* severe myelosuppression) from conventional doses of thioguanine and generally require substantial dose reduction (see Table 2).

Table 2 Recommended starting doses of LANVIS by TPMT genotype and phenotype

TPMT Genotype and Phenotype	Dosing recommendations for LANVIS
Homozygous wild-type or normal, high activity (two functional *1 alleles)	Start with normal starting dose. Adjust doses of LANVIS and of other myelosuppressive therapy without any special emphasis on LANVIS. Allow 2 weeks to reach steady state after each dose adjustment.
Heterozygote or intermediate activity (one functional allele - *1, plus one of the nonfunctional alleles - *2, *3A, *3B, *3C, or *4)	Reduce the starting dose by 30-50%) and adjust doses of LANVIS based on degree of myelosuppression. Allow 2-4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing LANVIS over other agents
Homozygous variant, mutant, or low/ deficient activity (two nonfunctional alleles - *2, *3A, *3B, *3C, or *4)	Reduce the starting dose of LANVIS by 10-fold and dose thrice weekly instead of daily and adjust doses of LANVIS based on degree of myelosuppression. Allow 4-6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing LANVIS over other agents.

NUDT15 variant patients

Genotypic and phenotypic testing of NUDT15 variants should be considered before initiating thiopurine therapy in all patients (including paediatric patients) to reduce the risk of thiopurine-related severe leukocytopenia and alopecia, especially in Asian populations patients (see WARNINGS AND PRECAUTIONS: Hematologic, Monitoring and Laboratory Tests).

Patients with inherited mutated NUDT15 gene are at increased risk for severe thiopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy and require substantial dose reduction. Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population. The optimal starting dose for heterozygous or homozygous deficient patients has not been established. Therefore, hematological parameters should be monitored during treatment with LANVIS.

The prescribing physician is advised to establish whether dose reduction is required based on patient response to treatment as well as their genetic profile.

Patients with variants in both the NUDT15 and TPMT enzymes are significantly less tolerant of thiopurines than those with risk alleles in only one of these two genes (see ACTION AND CLINICAL

PHARMACOLOGY)

Hepatic Impairment

There are no data on the effects of hepatic impairment on thioguanine exposure. Hepatic impairment may increase exposure of thioguanine since it is primarily metabolized in the liver. Consideration should be given to reducing the starting dose of LANVIS in patients with impaired hepatic function.

Renal Impairment

No information is available about thioguanine in patients with renal impairment. Consideration should be given to reducing the starting dose of LANVIS in patients with impaired renal function.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs and symptoms of overdosage may be immediate, such as nausea, vomiting, malaise, hypertension, and diaphoresis; or delayed, such as myelosuppression and azotemia. It is not known whether thioguanine is dialyzable. Hemodialysis is thought to be of marginal use due to the rapid metabolism of thioguanine into active intracellular derivatives with longer persistence than the parent drug.

There is no known pharmacologic antagonist of thioguanine. The drug should be discontinued immediately if unintended toxicity occurs during treatment. Severe hematologic toxicity may require supportive therapy with platelet transfusions for bleeding, and granulocyte transfusions and antibiotics if sepsis is documented. If a patient is seen immediately following an accidental overdosage of the drug, it may be useful to induce emesis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Thioguanine is a close relative of mercaptopurine and like the latter is an antimetabolite which blocks purine metabolism. Studies by Philips et al. have shown that unlike certain other purine antagonists, thioguanine does not produce substantial pathological changes in the intestinal epithelium of rodents and dogs, in the thoracic organs of rats or in the liver of animals studied. Direct radiation-like damage to lymphoid tissues does not occur. Pathologic changes are virtually limited to bone marrow and consist of neutropenia, reticulopenia, anemia, thrombopenia and prolongation of clotting time. The protracted but reversible aplasia of bone marrow closely resembles the effects of ionizing radiations. In man, thioguanine is extensively converted to 2-amino-6-methyl-mercaptopurine which is much less toxic and less effective than the parent compound.

Thioguanine has multiple metabolic effects and at present it is not possible to designate one major site of action. Its tumor inhibitory properties may be due to one or more of its effects on (a) feedback inhibition of *de novo* purine synthesis; (b) inhibition of purine nucleotide interconversions; or (c) incorporation into the DNA and the RNA. The net consequence of its actions is a sequential blockade of the synthesis and utilization of the purine nucleotides.

Pharmacodynamics

Thioguanine is incorporated into the DNA and the RNA of human bone marrow cells. Studies with intravenous ^{35}S-6-thioguanine have shown that the amount of thioguanine incorporated into nucleic acids is more than 100 times higher after five daily doses than after a single dose. With the 5-dose schedule, from one-half to virtually all of the guanine in the residual DNA was replaced by thioguanine. Tissue distribution studies of ^{35}S-6-thioguanine in mice showed only traces of radioactivity in the brain after oral

administration. Thioguanine concentrations in human cerebrospinal fluid (CSF) have not been measured, but observations on tissue distribution in animals, together with the lack of CNS penetration by the closely related compound, mercaptopurine, suggest that thioguanine does not reach therapeutic concentrations in the CSF.

Thioguanine is extensively metabolized *in vivo*. There are two principal catabolic routes: methylation to 2-amino-6-methyl-thiopurine and deamination to 2-hydroxy-6-mercaptopurine, followed by oxidation to 6-thiouric acid. Deamination and subsequent oxidation to thiouric acid occurs only to a small extent. The product of deamination by guanase, 6-thioxanthine is inactive, having negligible antitumor activity. This pathway of thioguanine inactivation is not dependent on the action of xanthine oxidase, and an inhibitor of that enzyme (such as allopurinol) will not block the detoxification of thioguanine even though the inactive 6-thioxanthine is normally further oxidized by xanthine oxidase to thiouric acid before it is eliminated. The product of methylation, 2-amino-6-methylthiopurine, is also substantially less active and less toxic than thioguanine, and its formation is likewise unaffected by the presence of allopurinol. Appreciable amounts of inorganic sulfate are also found in the urine, presumably arising from further metabolism of the methylated derivatives.

Monitoring of plasma levels of thioguanine during therapy is of questionable value. There is technical difficulty in determining plasma concentrations, which are seldom greater than 1 to 2 µg/mL after a therapeutic oral dose. More significantly, thioguanine enters rapidly into the anabolic and catabolic pathways for purines, and the active intracellular metabolites have appreciably longer half-lives than the parent drug. The biochemical effects of a single dose of thioguanine are evident long after the parent drug has disappeared from the plasma. Because of this rapid metabolism of thioguanine to active intracellular derivatives, hemodialysis would not be expected to appreciably reduce toxicity of the drug.

In some animal tumors, resistance to the effect of thioguanine correlates with the loss of HGPRTase activity and the resulting inability to convert thioguanine to thioguanylic acid. However, other resistance mechanisms, such as increased catabolism of TGMP by a nonspecific phosphatase, may be operative. Although not invariable, it is usual to find cross-resistance between thioguanine and its close analogue, PURINETHOL (mercaptopurine).

Pharmacokinetics

Absorption
Clinical studies have shown that the absorption of an oral dose of thioguanine in man is incomplete and variable, averaging approximately 30% of the administered dose (range: 14% to 46%). Following oral administration of ^{35}S-6-thioguanine, total plasma radioactivity reached a maximum at eight hours and declined slowly thereafter. The parent drug represented only a very small fraction of the total plasma radioactivity at any time, being virtually undetectable throughout the period of measurements.

Distribution
There are limited data on the distribution of thioguanine in humans. A distribution study conducted using IV administration of (^{35}S)-thioguanine in three patients showed that the apparent volume of distribution of (^{35}S)-thioguanine was 148 mL/kg.

The plasma protein binding of thioguanine in humans has not been measured. Plasma protein binding of other thiopurines (azathioprine and mercaptopurine) was in the range of 20 - 30% respectively and therefore, the plasma protein binding of thioguanine is probably in a similar range.

In addition, it has been shown that RBCs act as a reservoir for the active metabolites, thioguanine nucleotides (6-TGN) after administration of mercaptopurine, which suggests that RBCs may also act as a reservoir for 6-TGN generated after administration of thioguanine.

Thioguanine penetrates into the cerebrospinal fluid (CSF) following constant IV infusion over 24 hours in children with acute lymphoblastic leukemia (ALL). The nature of penetration of thioguanine into the CSF after oral administration of LANVIS is unknown.

Metabolism

Thioguanine is extensively metabolised *in vivo*. The four enzymes responsible for thioguanine metabolism are as follows: 1) hypoxanthine (guanine) phosphoribosyl transferase (H(G)PRT), which converts thioguanine into thioguanosine monophosphate (6-TGMP), which is further metabolized by protein kinases to the active species, thioguanine nucleotides (6-TGN); 2) thiopurine methyltransferase (TPMT), which converts thioguanine to 2-amino-6-methylthioguanine (6-MTG, inactive metabolite) as well as 6-TGMP to 6-methyl-TGMP (an inactive metabolite); 3) xanthine oxidase (XDH or XO); and 4) aldehyde oxidase (AO), which also convert thioguanine into inactive metabolites. Thioguanine is initially deaminated by guanine deaminase (GDA) to form 6-thioxanthine (6-TX) and this becomes a substrate for the XDH catalysed formation of an inactive metabolite, 6-thiouric acid (6-TUA).

Individuals with an inherited deficiency of TPMT activity (*i.e.,* with homozygous or heterozygous deficient alleles of TPMT) may experience higher exposures of thioguanine and the active thioguanine nucleotides (6-TGN). This could lead to higher sensitivity to standard dose of thioguanine and severe myelosuppression (see WARNINGS AND PRECAUTIONS; Hematologic; Monitoring and Laboratory Tests).Recent studies indicate that a strong association exists between the NUDT15 variant NUDT15 c.415C>T [p.Arg139Cys] (also known as NUDT15 R139C [rs116855232]), which is thought to lead to a loss of function of the NUDT15 enzyme, and thiopurine-mediated toxicity such as leukopenia and alopecia. The frequency of NUDT15 c.415C>T has an ethnic variability of 9.8 % in East Asians, 3.9 % in Hispanics, 0.2 % in Europeans and 0.0 % in Africans, indicating an increased risk for the Asian population. Patients who are NUDT15 variant homozygotes (NUDT15 T risk alleles) are at an excessive risk of thiopurine toxicity compared with the C homozygotes (See WARNINGS AND PRECAUTIONS; Hematologic)

Reduced thiopurine doses for patients who carry the NUDT15 variants may decrease their risk of toxicity (See DOSAGE and ADMINISTRATION).

The precise mechanism of NUDT15-associated thiopurine-related toxicity is not fully established.

Excretion

Plasma levels of thioguanine decay biexponentially with initial and terminal half-lives of 3 and 5.9 hours respectively. Only trace amount of the parent drug was recovered in the urine following an oral administration of ^{35}S-thioguanine. The methylated metabolite, 2-amino-6-methylthiopurine (MTG), appeared very early, rose to a maximum six to eight hours after drug administration, and was still being excreted after 12 to 22 hours. Radiolabeled sulfate appeared somewhat later than MTG but was the principal metabolite after eight hours. Thiouric acid and some unidentified products were found in the urine in small amounts. It has been demonstrated in three adults after a single oral dose of thioguanine 40 mg that the mean (range) oral clearance (CL/F) was 588 (296 - 880) (mL/min/kg).

STORAGE AND STABILITY

LANVIS® (thioguanine) tablets should be stored between 15° and 25°C, in a dry place, protected from light.

SPECIAL HANDLING INSTRUCTIONS

Care should be taken when handling or halving the tablets so as not to contaminate hands or to inhale the drug.

Tablets should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport. All materials which have come in contact with cytotoxic drugs should be segregated and incinerated at 1000°C or more.

Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

LANVIS® (thioguanine) 40 mg tablets are pale, greenish-yellow, biconvex tablets, plain on one side and scored on the other side, with Wellcome on the upper half and U3B on the lower half.

Composition

LANVIS® tablets contains 40 mg of thioguanine. The non-medicinal ingredients are: gum acacia, lactose, magnesium stearate, potato starch, and stearic acid.

Packaging

LANVIS® tablets are available in bottles of 25 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

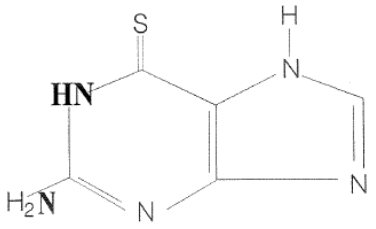
Drug Substance

Proper name: thioguanine

Chemical name: 6*H*-Purine-6-thione, 2-amino-1,7-dihydro-

Molecular formula and molecular mass: $C_5H_5N_5S$, 167.20

Structural formula:



Physicochemical properties:

Description: Pale yellow, crystalline powder; odorless or practically odorless. Insoluble in water, alcohol, chloroform; freely soluble in dilute solutions of alkali hydroxides.

TOXICOLOGY

Repetitive administration of thioguanine is much more toxic to animals than a single dose. Thus in the mouse, the LD_{50} is about 100 mg/kg for a single intraperitoneal dose whereas when 5 successive daily doses are given intraperitoneally, the LD_{50} is about
5 mg/kg/day. The drug is less toxic and less active by the oral route, the LD_{50} for mice given the drug on five successive days being about 12 mg/kg/day.

Although thioguanine has several times the potency of mercaptopurine in experimental animals, it is only slightly more potent in man. Clinical doses of 2.0 mg/kg/day are used with thioguanine as compared to 2.5 mg/kg/day for mercaptopurine.

In man, thioguanine is extensively converted to 2-amino-6-methyl- mercaptopurine which is much less toxic and less effective than the parent compound. This methylation occurs only to a minor degree in other species studied. This accounts for the difference in ratio of activity of mercaptopurine and thioguanine in different species.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrLANVIS®
Thioguanine tablets, USP

Read this carefully before you start taking LANVIS® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about LANVIS®.

Serious Warnings and Precautions

- LANVIS is a cytotoxic agent. This means it kills cells in your body including cancer cells. It must be given to you by a doctor with experience in the use of cytotoxic agents.

  LANVIS can cause serious side effects which include:

- A large decrease in the production of blood cells and platelets by the bone marrow (neutropenia, anemia and thrombocytopenia). This can cause life-threatening infections and bleeding. This is especially dangerous if you have a deficiency in an enzyme called thiopurine methyltransferase (TPMT).

- Liver damage.

- Severe infection following immunization with a live vaccine. You should not receive a live vaccine when you are taking LANVIS.

What is LANVIS® used for?
LANVIS is used to treat acute leukemia which is a cancer of the blood and bone marrow.

How does LANVIS® work?
LANVIS® belongs to a group of medicines called cytotoxic agents and is used to treat some types of cancer of the blood and bone marrow.

What are the ingredients in LANVIS®?
Medicinal ingredients: thioguanine
Non-medicinal ingredients: gum acacia, lactose, magnesium stearate, potato starch and stearic acid

LANVIS® comes in the following dosage forms:
40 mg tablets

Do not use LANVIS® if:
- your disease has demonstrated prior resistance to LANVIS® or PURINETHOL (mercaptopurine)
- you are allergic to thioguanine or any of the other ingredients in LANVIS
- you are allergic to any component of the LANVIS container

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LANVIS®. Talk about any health conditions or problems you may have, including if you:

- are pregnant, or you are planning a pregnancy
- are breastfeeding or are planning to breastfeed
- you have been vaccinated, or are planning to be vaccinated with a live vaccine
- have received a blood test and been told that you have a deficiency in an enzyme called thiopurine methyltransferase (TPMT) which may make you more likely to get serious side effects
- you have kidney problems
- you have liver problems
- you have a mutation in your NUDT15 gene, you may have a higher risk of developing low levels of white cells in your blood. This may cause you to get infections. The mutation may also put you at a higher risk of losing your hair. Patients of Asian descent may be particularly at risk

Other warnings you should know about:

- LANVIS® is not recommended for maintenance therapy or long-term continuous treatment because it may cause liver damage.
- LANVIS may make you more sensitive to sun exposure. Limit your exposure to the sun and to UV light when you are taking LANVIS. Wear protective clothing and use sunscreen with a high protection factor.
- You should avoid getting pregnant while taking LANVIS.
- You should avoid getting a woman pregnant while taking LANVIS.
- LANVIS may cause a decrease in your white blood cells (leukopenia). This means that you are at greater risk of having an infection. Wash your hands often. Keep your mouth and skin clean and healthy. Avoid people who are sick. Call your doctor if you have a fever or other flu-like symptoms.
- LANVIS may cause a decrease in your red blood cells (**anemia**). This means that you may feel tired or look pale. Rest if you need to. Talk to your doctor.
- LANVIS may cause a decrease in your platelets (**thrombocytopenia**). Platelets are tiny pieces of cells that help your blood to clot after you have an injury. When the platelets count is decreased you may be more likely to bleed or bruise abnormally. Try not to bump into things or cut yourself. Blow your nose gently. Avoid getting constipated. Brush your teeth gently with a soft toothbrush. Avoid products containing aspirin or ibuprofen. Call your doctor immediately if you notice any of the following: bleeding, bruising, fatigue, tiny red dots on the skin, weakness.

Blood tests

Your doctor may ask you to have a blood test while you are taking Lanvis. This is to check your blood cell count. Your doctor may also perform genetic testing (i.e. looking at your TPMT and/or NUDT15 genes) before or during your treatment to determine if your response to this medication may be affected by your genetics. Your doctor may change your dose of Lanvis after these tests.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LANVIS®:

- Anti-inflammatory medicines like olsalazine, mesalazine or sulfasalazine used to treat inflammatory bowel disease
- Live viral vaccines
- Busulfan, an anticancer medicine.

How to take LANVIS®:

Take this medicine exactly as your doctor has told you to. Check with your doctor if you are not sure how to take it.

Usual dose:
Your doctor will tell you how much LANVIS to take and when to take it.

Overdose:

If you think you have taken too much LANVIS®, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of LANVIS, take it as soon as possible.
- If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule as prescribed by your doctor.
- Never take two doses at the same time to make up for a missed dose.

What are possible side effects from using LANVIS®?

These are not all the possible side effects you may feel when taking LANVIS®. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- loss of appetite
- increased sensitivity to sun exposure

LANVIS may cause abnormal blood test results. Your doctor may perform blood tests before you take LANVIS and while you are taking it.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Neutropenia (decreased white blood cells): aches, feeling tired, fever, flu-like symptoms, any signs of infections (sore throat, sore mouth or urinary problems)		X	
Thrombocytopenia (decreased platelets in the blood): bruising, fatigue, tiny red dots on the skin, weakness.		X	
Anemia (decreased red blood cells): dizziness, feeling tired and weak, loss of energy, shortness of		X	

breath.			
Liver damage: abdominal pain, dark urine, fatigue, itching, loss of appetite, nausea, rash, swelling in the abdomen, vomiting, weight loss, yellowing of the skin or eyes (jaundice).		X	
COMMON			
Veno-occlusive disease (a condition where liver veins are blocked): enlargement of liver which causes abdomen to swell and fluid to accumulate there, yellowing of the skin or eyes (jaundice), vomiting of blood.		X	
Nausea	X		
Vomiting	X		
Diarrhea (loose or watery and frequent stools)	X		
Stomatitis (mouth sores and swelling): burning sensation and pain in the mouth, difficulty eating, swelling, sores or ulcers in the mouth.	X		
Esophageal varices (swollen veins in the lower section of the esophagus that can bleed)		X	
Hyperuricemia (high level of uric acid in the blood): fever, pain in a joint, swelling of a joint, or kidney problems.		X	
RARE			
Intestinal necrosis or perforation (potentially life threatening conditions where intestines are damaged): bloating or swelling in the abdomen, bloody stools, diarrhea (loose or watery and frequent stools), severe abdominal pain, vomiting.			X
Severe liver damage: confusion, disorientation, coma, pain in upper right side of the abdomen, sleepiness, yellowing of the skin or eyes (jaundice).			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store LANVIS in a dry place between 15° and 25°C. Protect it from light.

LANVIS is cytotoxic. Care should be taken when handling or halving the tablets so as not to contaminate hands or to inhale the drug.

Return unused tablets to the manufacturer for destruction. Take precautions when packaging LANVIS for transport.

Keep out of reach and sight of children.

If you want more information about LANVIS®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html) or the Aspen Pharmacare Canada Inc. website (www.aspenpharma.ca), or by calling 1-844-330-1213.

This leaflet was prepared by:
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