

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrLANVIS®

Thioguanine

Tablets, 40 mg, Oral

USP

Antileukemic Agent

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RECENT MAJOR LABEL CHANGES

Warnings and Precautions (7), NUDT15 variant patients	09/2018
Dosage and Administration, NUDT15 variant patients	09/2018
Action and Clinical Pharmacology, NUDT15 variant patients	09/2018
Indications	09/2017

TABLE OF CONTENTS

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics	4
1.2 Geriatrics.....	4
2 CONTRAINDICATIONS	4
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	4
4 DOSAGE AND ADMINISTRATION	5
4.1 Dosing Considerations.....	5
4.2 Recommended Dose and Dosage Adjustment	5
4.3 Missed Dose	6
5 OVERDOSAGE	7
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	7
7 WARNINGS AND PRECAUTIONS	7
7.1 Special Populations	11
7.1.1 Pregnant Women	11
7.1.2 Breast-feeding.....	11
7.1.3 Pediatrics.....	11
7.1.4 Geriatrics	12
8 ADVERSE REACTIONS	12
8.1 Adverse Reaction Overview	12
8.2 Post-Market Adverse Reactions	12
9 DRUG INTERACTIONS	14
9.1 Serious Drug Interactions Box.....	14
9.2 Overview	14
9.3 Drug-Drug and Drug-Vaccine Interactions	14
10 ACTION AND CLINICAL PHARMACOLOGY	15
10.1 Mechanism of Action.....	15
10.2 Pharmacodynamics.....	16
10.3 Pharmacokinetics	16
11 STORAGE, STABILITY AND DISPOSAL	19
12 SPECIAL HANDLING INSTRUCTIONS	19
PART II: SCIENTIFIC INFORMATION	20

13	PHARMACEUTICAL INFORMATION	20
14	NON-CLINICAL TOXICOLOGY.....	20
	PATIENT MEDICATION INFORMATION.....	21

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

1.1 Pediatrics

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

1.2 Geriatrics

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.

2 CONTRAINDICATIONS

LANVIS® is contraindicated in;

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING. 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.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 WARNINGS AND PRECAUTIONS: Hematologic).
- Liver toxicity (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic).
- Potential severe infection after immunisation using a live organism vaccine (see WARNINGS AND PRECAUTIONS: Immune).

4 DOSAGE AND ADMINISTRATION

4.1 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).

4.2 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 1).

Table 1 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 (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

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 (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

4.3 Missed Dose

If a scheduled dose is missed, the dose should be taken as soon as the patient remembers, unless it is almost time for the patient's next dose. Two doses should not be taken together. If more than two doses are missed, the patient should consult with their doctor.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

Signs and symptoms of overdose 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 overdose of the drug, it may be useful to induce emesis.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet/40mg	gum acacia, lactose, magnesium stearate, potato starch, and stearic acid. <i>For a complete listing see Dosage Forms, Composition and Packaging section</i>

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.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

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.

Driving and Operating Machinery

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

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.

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.

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.

Sensitivity/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.

7.1 Special Populations

7.1.1 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.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

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).

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.1 Adverse 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.

8.2 Post-Market Adverse 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 hepatportal 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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

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).

9.2 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.

9.3 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 3.

Table 3 - 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 <i>in vitro</i> 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).

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

Thioguanine is incorporated into the DNA and the RNA of human bone marrow cells. Studies with intravenous ³⁵S-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 ³⁵S-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 thioguanilic 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).

10.3 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 ³⁵S-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 (³⁵S)-thioguanine in three patients showed that the apparent volume of distribution of (³⁵S)-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.

Elimination: 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 ³⁵S-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).

Special Populations and Conditions

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 (see DOSAGE AND ADMINISTRATION).

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 WARNINGS AND PRECAUTIONS)

Hepatic Insufficiency: 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 (see WARNINGS AND PRECAUTIONS).

Renal Insufficiency: 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 (see WARNINGS AND PRECAUTIONS).

11 STORAGE, STABILITY AND DISPOSAL

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

12 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.

PART II: SCIENTIFIC INFORMATION

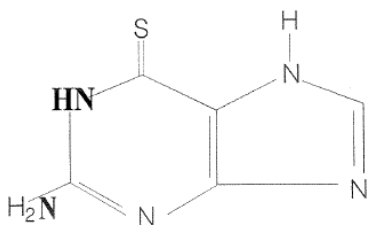
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: thioguanine

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

Molecular formula and molecular mass: C₅H₅N₅S, 167.20



Structural formula:

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

14 NON-CLINICAL TOXICOLOGY

Repetitive administration of thioguanine is much more toxic to animals than a single dose. Thus in the mouse, the LD₅₀ is about 100 mg/kg for a single intraperitoneal dose whereas when 5 successive daily doses are given intraperitoneally, the LD₅₀ is about 5 mg/kg/day. The drug is less toxic and less active by the oral route, the LD₅₀ 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.

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. LANVIS® must only be given to you by a healthcare professional experienced in the use of drugs to treat cancer.

Side effects of LANVIS® can include:

Bone marrow suppression (neutropenia, thrombocytopenia or anemia): Lanvis® can affect your bone marrow's ability to make blood cells. It can cause you to have low blood cell counts and platelets. This can cause life-threatening infections and bleeding and is especially dangerous if your body does not make enough of the enzyme, thiopurine methyltransferase (TPMT).

Neutropenia is a low white blood cell count.

Thrombocytopenia is low platelets in the blood.

Anemia is a low red blood cell count.

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. This is a cancer of the blood and bone marrow.

LANVIS® will not be given to you as treatment to help prevent your cancer from coming back after it had disappeared. It will also not be given as a long-term treatment.

How does LANVIS® work?

LANVIS® works by reducing the number of new blood cells your body makes.

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:

Tablets, 40 mg

Do not use LANVIS® if:

- your disease has previously stopped responding to LANVIS® or to treatment with another drug called PURINETHOL. The active ingredient in this drug is mercaptopurine.
- you are allergic to thioguanine or any of the other ingredients in this medicine, including any non-medicinal ingredient or component of the 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;
Females who are pregnant or plan to become pregnant:
 - LANVIS® may harm your unborn baby.
 - Avoid becoming pregnant while you are taking LANVIS®.
 - Use effective methods of birth control while you are taking LANVIS®.
Talk to your healthcare professional about methods of birth control that may be right for you.
 - If you do become pregnant while taking LANVIS®, stop using it and tell your healthcare professional right away.
- are breastfeeding or are planning to breastfeed. It is not known if LANVIS® passes into breast milk. You and your doctor should discuss whether you will take LANVIS® or breastfeed. You should not do both. Talk to your doctor about ways to feed your baby while you are taking LANVIS®.
- plan to father a child. Your partner should not become pregnant while you are using LANVIS®. You should use birth control to prevent pregnancy in your partner during your treatment. If your partner becomes pregnant while you are receiving LANVIS®, tell your healthcare professional right away.
- you have been vaccinated, or are planning to be vaccinated, with a live vaccine.
- Your body does not make enough of (you are deficient in) the enzyme called thiopurine methyltransferase (TPMT). If you do not have enough of this enzyme, you may get serious side effects if you use LANVIS®.
- you have kidney problems;
- you have liver problems;
- you have a mutation in your NUDT15 gene. If you have this mutation, you may be more likely to develop 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.
- You are going to be exposed to sunlight, sun lamps or tanning beds. Your treatment with LANVIS® may make you more sensitive to sun and ultraviolet (UV) light. Limit your exposure to the sun and to UV light while you are taking LANVIS®. Be sure to also wear protective clothing and use sunscreen with a high protection factor (spf).

Other warnings you should know about:

Intestinal necrosis and perforation can occur with LANVIS[®] use.

- Intestinal necrosis is a condition that occurs when there is low blood flow to the intestines.
- Intestinal perforation is when a hole forms in the wall of the intestine.
- These are serious and potentially life-threatening side effects of LANVIS[®] use. If you experience bloating or swelling in the abdomen, bloody stools, diarrhea severe abdominal pain and vomiting, call your healthcare professional right away. These may be signs that you are experiencing intestinal necrosis or a perforation.

Bone marrow suppression:

As LANVIS[®] use may cause low white blood cells, low red blood cells and low platelets, you may be at increased risk of infection, bleeding and bruising, be sure to:

- Wash your hands often.
- Keep your mouth and skin clean and healthy.
- Avoid people who are sick.
- 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.
- Rest if you need to.
- Call your doctor if you have a fever or other flu-like symptoms or if you have any bleeding, bruising, fatigue, tiny red spots on the skin or weakness.

Risk for cancer and damage to DNA:

Thioguanine, the medicinal ingredient in LANVIS[®], may cause cancer or damage to the genetic material in cells (DNA). Talk to your healthcare professional if you have questions about this.

Driving and operating machines:

Before you do tasks that require special attention, wait until you know how you respond to LANVIS[®] treatment.

Blood tests:

Your doctor will ask you to have blood tests done before you take LANVIS[®] for the first time. Some of these tests will be repeated every week and others will be repeated every month while you are taking LANVIS[®]. This is to check your blood cell counts and to monitor how well your liver is working.

Your doctor may also perform genetic testing before or during your treatment. These tests will determine if you have the NUDT15 gene mutation and if you are deficient in the enzyme, TPMT. The results of these tests will help your doctor to know if your response to LANVIS[®] 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.

Serious Drug Interactions

- Vaccines containing live viruses. There is a risk for serious infections if these are given with LANVIS®.
- Other cytotoxic drugs or radiation therapy. The risk for bone marrow suppression is increased when these are used with LANVIS®.
- Olsalazine, mesalazine or sulphasalazine. These are medicines that prevent inflammation and are used in the treatment of inflammatory bowel disease.

The following may also interact with LANVIS®:

- Busulfan. This is a medicine used to treat a type of cancer.

How to take LANVIS®:

- Take this medicine exactly as your healthcare professional has told you to.
- Take it once per day by mouth.
- Check with your healthcare professional if you are not sure how to take it.
- Your healthcare professional will tell you how much LANVIS® to take and when to take it.

Usual starting dose: 2 mg / kg of body weight

If, after one month of treatment, your condition has not improved, your dose may be increased to 3 mg / kg of body weight.

The amount of LANVIS® you will take will depend on your weight and how you respond to treatment.

Your healthcare professional may interrupt or stop your treatment, or reduce your dose of LANVIS®. This will depend on how you are feeling or if your disease has gotten worse.

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.
- If you miss two doses of LANVIS®, contact your doctor.

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. Your doctor will interpret the results.

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 breath.		X	
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	X		

eating, swelling, sores or ulcers in the mouth.			
Esophageal varices (swollen veins in the lower section of the esophagus that can bleed): vomiting blood, black or bloody stools, lightheadedness and loss of consciousness in severe cases.		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.

<p>Reporting Side Effects</p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> • 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. <p><i>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.</i></p>
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Storage:

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

LANVIS[®] is cytotoxic. Be careful not to contaminate your hands or inhale the drug when you are handling LANVIS[®].

Return unused tablets to your healthcare professional. Be cautious when you are packaging your leftover LANVIS[®] for transportation.

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.

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