PRODUCT MONOGRAPH

PrLANVIS®

Thioguanine

Tablets, 40 mg

USP

Antileukemic Agent

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

Imported and Distributed in Canada by:
Aspri Pharma Canada Inc.
665 Millway Avenue,
Suite 31B,
Concord, Ontario
L4K 3T8

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PrLANVIS®

Thioguanine

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.

INDICATIONS AND CLINICAL USE

- LANVIS® (thioguanine) is indicated for treatment of acute leukemia.
- LANVIS® has also been used in chronic granulocytic (myelocytic, myeloid, myelogenous) leukemia.

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.

WARNINGS AND PRECAUTIONS

General

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 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, Mutagenesis and Impairment of Fertility

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 (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Hematologic

The most consistent, dose-related toxicity 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 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. Blood counts should be made at least once weekly. Life-threatening infections and bleeding have been observed as consequences of thioguanine-induced granulocytopenia and thrombocytopenia.

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.

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 bone marrow depression following the initiation of treatment with LANVIS®. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore, close monitoring of blood counts is still necessary.

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

Thioguanine therapy should be discontinued in patients with evidence of liver toxicity as reversal of signs and symptoms of liver toxicity have been reported upon withdrawal.

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. Elevations of liver enzymes have also been reported in association with liver toxicity but do not always occur.

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.

During remission induction particularly, when rapid cell lyis is occurring, adequate precautions should be taken to avoid hyperuricemia and/or hyperuricosuria and the risk of uric acid nephropathy.

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 infection in immunocompromised hosts. Therefore, immunisation with live organism vaccines (e.g. measles, mumps, etc.) are not recommended.

The effect of thioguanine on the immunocompetence of patients is unknown.

Renal
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.

Special Populations

Pregnant Women: Thioguanine has been shown to be teratogenic in rats when given in doses 5 times the human dose. 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 this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, 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.

Geriatric Use: 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).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Gastrointestinal: Less frequent adverse reactions include nausea, vomiting, anorexia, and stomatitis. 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).

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 consolidation and maintenance of remission are also affected by 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.

Hyperuricemia frequently occurs in patients receiving thioguanine as a consequence of rapid cell lysis accompanying the antineoplastic effect. Adverse effects can be minimized by increased hydration, urine alkalinization, and the prophylactic administration of a xanthine oxidase inhibitor such as ZYLOPRIM (allopurinol). Unlike PURINETHOL (mercaptopurine) and IMURAN (azathioprine), thioguanine may be continued in the usual dosage when allopurinol is used conjointly to inhibit uric acid formation.

Hepatic: 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.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1 : Established or Potential Drug-Drug Interactions

Thioguanine	Effect	Clinical comment
Mercaptopurine	Complete cross resistance	Between PURINETHOL (mercaptopurine) and LANVIS®.
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 infection in immunocompromised hosts.	Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see WARNINGS AND PRECAUTIONS).

DOSAGE AND ADMINISTRATION

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.

Dosing Considerations

Thioguanine can be used for remission induction and remission consolidation. 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). Unlike mercaptopurine and azathioprine, thioguanine may be continued in the usual dosage when allopurinol is used conjointly to inhibit uric acid formation.

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 as well as in certain adults with chronic granulocytic leukemia. For this reason it is important to observe such patients closely.

OVERDOSAGE

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. Unlike mercaptopurine and azathioprine, its metabolism is not inhibited by the xanthine oxidase inhibitor, allopurinol.

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

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.

The oral administration of radiolabeled thioguanine revealed only trace quantities of parent drug in the urine. However, 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.

Plasma levels decay biexponentially with initial and terminal half-lives of 3 and 5-9 hours respectively.

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of thioguanine. (see WARNINGS AND PRECAUTIONS, Hematologic).

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

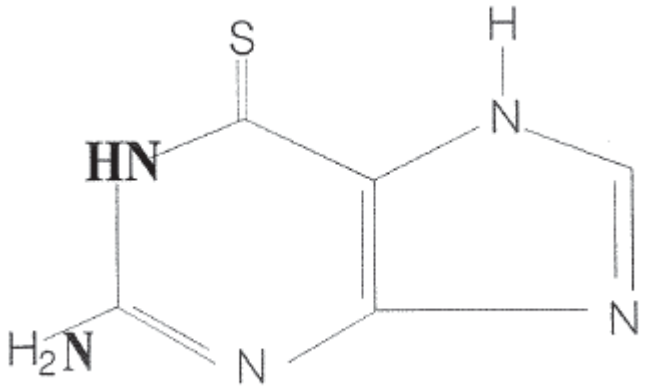
Drug Substance

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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PART III: CONSUMER INFORMATION

PrLANVIS®
Thioguanine

This leaflet is part III of a three-part "Product Monograph" published for LANVIS®, approved for sale in Canada, and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LANVIS®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- LANVIS® is used for treatment of acute leukemia (a cancer of the blood and bone marrow).
- LANVIS® has also been used in chronic granulocytic (myelocytic, myeloid, myelogenous) leukemia (a slowly progressing disease in which too many white blood cells are made in the bone marrow).

What it does:

LANVIS® belongs to a group of medicines called cytotoxics, it is used to treat some types of cancer.

When it should not be used:

Do not take LANVIS® if :

- your disease has demonstrated prior resistance to LANVIS®.
- you have a history of a hypersensitivity reaction (a severe allergic reaction) to any ingredient in LANVIS®.

What the medicinal ingredient is:

The medicinal ingredient in LANVIS® is thioguanine.

What the important nonmedicinal ingredients are:

The nonmedicinal ingredients in LANVIS® are: gum acacia, lactose, magnesium stearate, potato starch, and stearic acid.

What dosage forms it comes in:

LANVIS® is available as 40 mg tablets.

WARNINGS AND PRECAUTIONS

LANVIS® is a potent drug and should be used only by physicians experienced with cancer chemotherapeutic drugs.

LANVIS® is not recommended for maintenance therapy or similar long term continuous treatments.

BEFORE you use LANVIS® talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient in LANVIS®.
- you are pregnant or likely to become pregnant.
- you are breastfeeding a baby.
- you have been vaccinated, or are planning to be vaccinated with a live vaccine.
- the results of your blood test show that you are not able to receive LANVIS®, your doctor will tell you.
- you have kidney disease.
- you have liver problems.

LANVIS® is not recommended for maintenance therapy or long term continous treatment.

INTERACTIONS WITH THIS MEDICATION

It is important that your doctor know about all your medication so that you get the best possible treatment. Tell your doctor about all the medications you are taking including those you have bought yourself.

There is usually complete cross-resistance between PURINETHOL (mercaptopurine) and LANVIS®.

Use aminosalicylate derivatives (antibacterial drugs), e.g. olsalazine, mesalazine or sulphasalazine with caution if you are receiving these concurrently with LANVIS®.

If you have a weak immune system, vaccination with live viral vaccines is not recommended.

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor will tell you the amount of LANVIS® you need to take and how frequently. The usual initial dose is approximately 2 mg/kg body weight/day, orally. The dosage may be cautiously increased to 3 mg/kg/day after 4 weeks.

Overdose:

In the event you accidentally take more doses than prescribes immediately contact your doctor or hospital emergency department or the nearest poison control centre.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience the following while taking LANVIS®.

- Low white blood cells. 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 or nurse if you have a fever or other flu-like symptoms.

- Low red blood cells. This means that you may feel tired or look pale. Rest if you need to. Talk to your doctor or nurse if it gets worse.
- Low platelets. These are tiny pieces of cells that help your blood to clot after you have an injury. When the platelets count is low 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 blood in your urine, black tarry stools, lots of bruising, or tiny red dots on your skin.
- Increase in liver enzymes and/or bilirubin. This may cause your skin to look yellow. Call your doctor if you notice this.
- Increase in uric acid. This may cause symptoms like gout, including joint pain.
- Loss of appetite. Try to eat small meals frequently through the day.
- Nausea and vomiting. Talk to your doctor, nurse or pharmacist. Eat small meals. Drink fluids.
- Swelling of mouth and throat. Call your doctor.

If you feel unwell or have any symptoms that you do not understand, contact your doctor immediately.

This is not a complete list of side effects. For any unexpected effects while taking LANVIS®*, contact your doctor or pharmacist.*

HOW TO STORE IT

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

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.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet does not contain the complete information about your medicine. If any questions remain unanswered or you are not sure about something, you should ask your doctor or pharmacist.

You may want to read this leaflet again. **Please Do Not Throw It Away** until you have finished your medicine.

This document plus the full product monograph prepared for health professionals can be found by contacting Aspri Pharma Canada Inc. at 1-855-868-8440 or www.aspripharma.com.

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