

DATA SHEET

LANVIS™

Thioguanine Tablets 40mg

Qualitative and Quantitative Composition

Each pale yellow, round biconvex tablet containing 40mg thioguanine is scored and coded "Wellcome U3B" on one side and plain on the other side.

Pharmaceutical form

Tablets.

Clinical particulars

Therapeutic Indications

LANVIS is indicated primarily for the treatment of acute leukaemias especially:-

acute myelogenous leukaemia

acute lymphoblastic leukaemia

LANVIS is also used in the treatment of chronic granulocytic leukaemia.

Posology and Method of Administration

The exact dose and duration of administration will depend on the nature and dosage of other cytotoxic drugs given in conjunction with LANVIS.

LANVIS is variably absorbed following oral administration and plasma drug levels may be reduced following emesis or intake of food.

Thioguanine can be used at any stage prior to maintenance therapy in short term cycles e.g. induction, consolidation, intensification. 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 Special Warnings and Special Precautions for Use and Undesirable Effects).

Adults:-For adults, the usual dosage of LANVIS is between 60 and 200mg/m² body surface area per day.Children:-

For children, similar dosages to those used in adults, with appropriate correction for body surface area, have been used.

Elderly Patients:-

There are no specific dosage recommendations in elderly patients. (See Dosage in renal or hepatic impairment).

LANVIS has been used in various combination chemotherapy schedules in elderly patients with acute leukaemia at equivalent dosages to those used in younger patients.

Dosage in renal or hepatic impairment:-

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

Contraindications

Hypersensitivity to any component of the preparation.
In view of the seriousness of the indications there are no other absolute contra-indications.

Special Warnings and Special Precautions for Use

LANVIS IS AN ACTIVE CYTOTOXIC AGENT FOR USE ONLY UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

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 Posology and Method of Administration and Undesirable Effects). 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 hepatic 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.

Monitoring:-

DURING REMISSION INDUCTION, FULL BLOOD COUNTS MUST BE CARRIED OUT FREQUENTLY.

Bone marrow suppression (leading to leucopenia and thrombocytopenia) and liver toxicity have been reported. Patients must be carefully monitored during therapy including blood cell counts and weekly liver function 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.

The leucocyte and platelet counts continue to fall after treatment is stopped, so at the first sign of an abnormally large fall in these counts, treatment should be temporarily discontinued.

Bone marrow suppression is readily reversible if LANVIS is withdrawn early enough.

During remission induction in acute myelogenous leukaemia the patient may frequently have to survive a period of relative bone marrow aplasia and it is important that adequate supportive facilities are available.

Patients on myelosuppressive chemotherapy are particularly susceptible to a variety of infections.

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

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.

Lesch-Nyhan syndrome:-

Since the enzyme hypoxanthine guanine phosphoribosyl transferase is responsible for the conversion of LANVIS 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 the drug. Resistance to azathioprine, which has one of the same active metabolites as LANVIS, has been demonstrated in two children with Lesch-Nyhan syndrome.

Interaction with Other Medicinal Products and Other Forms of Interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see Special Warnings and Special Precautions For Use).

The concomitant use of allopurinol to inhibit uric acid formation does not necessitate reduction of dosage of LANVIS as is necessary with mercaptopurine and azathioprine.

As there is *in vitro* evidence that aminosalicylate derivatives (eg. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent LANVIS therapy (see Special Warnings and Special Precautions for Use).

Use During Pregnancy and Lactation

Teratogenicity and effects on fertility:-

LANVIS like other cytotoxic agents is potentially teratogenic.

There have been isolated cases where men who have received combinations of cytotoxic agents including LANVIS, have fathered children with congenital abnormalities.

Use in pregnancy:-

The use of LANVIS should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving LANVIS.

Lactation:-

There are no reports documenting the presence of LANVIS or its metabolites in maternal milk. It is suggested that mothers receiving LANVIS should not breast feed.

Effects on Ability to Drive and Use Machines

There are no data on the effect of thioguanine on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the drug.

Undesirable Effects

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.

The following convention has been utilised for the classification of frequency of undesirable effects:- Very common $\geq 1/10$ ($\geq 10\%$), Common $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$), Uncommon $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$), Rare $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$), Very rare $< 1/10,000$ ($< 0.01\%$).

Gastrointestinal Disorders

Common: stomatitis,
 gastrointestinal intolerance

Rare: intestinal necrosis and perforation

Hepato-biliary disorders

Very Common: Liver toxicity associated with vascular endothelial damage when thioguanine is used in maintenance or similar long term continuous therapy which is not recommended (see Dosage and Administration and Warnings and Precautions).

Usually presenting 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.

Common: Liver toxicity during short term cyclical therapy presenting 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.

Rare: Centrilobular hepatic necrosis has been reported in a few cases including patients receiving combination chemotherapy, oral contraceptives, high dose thioguanine and alcohol.

Overdose

Signs:-

The principal toxic effect is on the bone marrow and haematological toxicity is likely to be more profound with chronic overdosage than with a single ingestion of LANVIS.

Treatment:-

As there is no known antidote the blood picture should be closely monitored and general supportive measures, together with appropriate blood transfusion instituted if necessary.

Pharmacological properties

Pharmacodynamic Properties**Mode of Action:-**

Thioguanine is a sulphhydryl analogue of guanine and behaves as a purine antimetabolite. It is activated to its nucleotide, thioguanilic acid.

Thioguanine metabolites inhibit de novo purine synthesis and purine nucleotide interconversions. Thioguanine is also incorporated into nucleic acids and DNA (deoxyribonucleic acid) incorporation is claimed to contribute to the agent's cytotoxicity. Cross resistance usually exists between thioguanine and mercaptopurine, and it is not to be expected that patients resistant to one will respond to the other.

Pharmacokinetic Properties

Thioguanine is extensively metabolised *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.

Studies with radioactive thioguanine show that peak blood levels of total radioactivity are achieved about 8-10 hours after oral administration and decline slowly thereafter. Later studies using HPLC have shown 6-thioguanine to be the major thiopurine present for at least the first 8 hours after intravenous administration. Peak plasma concentrations of 61-118 nanomol (nmol)/mL are obtainable following intravenous administration of 1 to 1.2g of 6-thioguanine/m² body surface area.

Plasma levels decay biexponentially with initial and terminal half lives of 3 and 5-9 hours respectively. Following oral administration of 100mg/m², peak levels as measured by HPLC occur at 2-4 hours and lie in the range of 0.03-0.94 micromolar (0.03-0.94 nmol/mL). Levels are reduced by concurrent food intake (as well as vomiting).

Preclinical Safety Data

Mutagenicity and carcinogenicity:-

In view of its action on DNA, thioguanine is potentially mutagenic and carcinogenic.

Pharmaceutical particulars

List of Excipients

Lactose monohydrate
Potato starch
Acacia
Stearic acid
Magnesium stearate

Incompatibilities

None reported.

Shelf Life

5 years.

Pharmaceutical Precautions

Store at 25°C.
Protect from light.
Keep dry.

Nature and Contents of Container

LANVIS Tablets 40mg Bottle of 25 tablets

Instructions for Use/Handling

Safe handling of LANVIS:-

It is recommended that the handling of LANVIS Tablets follows the "Guidelines for the Handling of Cytotoxic Drugs" according to prevailing local recommendations and/or regulations. If halving of a tablet is required, care should be taken not to contaminate the hands or inhale the drug.

Disposal:-

LANVIS tablets surplus to requirements should be destroyed in a manner appropriate to the prevailing local regulations for the destruction of dangerous substances.

Medicine Classification

Prescription Only Medicine

Name and Address

Pharmacy Retailing Pty Ltd
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58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

Date of Preparation

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