

DATA SHEET

1. PRODUCT NAME (strength pharmaceutical form)

LANVIS™ (Tioguanine Tablets 40mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

White to off-white tablet, round, biconvex scored and debossed with 'T40' on one side and plain on the other side.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 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.

4.2 Dose 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.

Tioguanine 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.

Dosing for TPMT-deficient patients

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe thioguanine toxicity from conventional doses of thioguanine and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established (see Warnings).

Most patients with heterozygous TPMT deficiency can tolerate recommended thioguanine doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see Warnings). Consideration should be given to reducing the dosage in patients with impaired hepatic function.

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.

Patients with NUDT15 variant

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 generally 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 section 5.2).

4.3 Contraindications

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

4.4 Special warnings and 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.

Patients in remission should not receive live organism vaccines until at least 3 months after their chemotherapy treatment has been completed.

TIOGUANINE 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 tioguanine as part of maintenance therapy for acute lymphoblastic leukemia and in other conditions associated with continuous use of tioguanine. 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.

Tioguanine 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:

SINCE 6-TIOGUANINE IS STRONGLY MYELOSUPPRESSIVE FULL BLOOD COUNTS MUST BE CARRIED OUT FREQUENTLY DURING REMISSION INDUCTION. PATIENTS MUST BE CAREFULLY MONITORED DURING THERAPY.

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. (see undesirable effects)

TPMT Testing

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive

effect of LANVIS and prone to developing rapid bone marrow depression following the initiation of treatment with LANVIS. There have been fatal cases of myelosuppression in patients with low or absent TPMT activity treated with thiopurines. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine.

Patients should be tested for TPMT activity before starting LANVIS. TPMT testing cannot substitute for complete blood count monitoring in patients receiving LANVIS. TPMT genotyping can be used to identify patients with absent or reduced TPMT activity. Patients with low or absent TPMT activity (homozygous for non-functional alleles) are at an increased risk of developing severe, life-threatening myelotoxicity from LANVIS if conventional doses are given. Alternative therapies may be considered for patients who have low or absent TPMT activity. LANVIS should be administered with caution to patients having one non-functional allele (heterozygous) who are at risk for reduced TPMT activity that may lead to toxicity if conventional doses are given. Dosage reduction is recommended in patients with reduced TPMT activity.

TPMT testing is widely available through pathology laboratories and genetic testing services.

NUDT15 Mutation

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 generally 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 section 5.2).

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.

Patients treated with thioguanine in combination with other immunosuppressive or chemotherapeutic agents, have shown increased susceptibility to viral, fungal, and bacterial infections, including severe or atypical infection. The infectious disease and complications may be more severe in these patients than in non-treated patients.

If the patient is infected during treatment appropriate measures should be taken, which may include antiviral therapy and supportive care.

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 (see Adverse Reactions).

Monitoring

SINCE 6-THIOGUANINE IS STRONGLY MYELOSUPPRESSIVE FULL BLOOD COUNTS MUST BE CARRIED OUT FREQUENTLY DURING REMISSION INDUCTION. PATIENTS MUST BE CAREFULLY MONITORED DURING THERAPY.

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.

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.

UV exposure

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.

4.5 Safe handling of LANVIS: (Special precautions for disposal).

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.

4.6 Interaction with other medicines 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).

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During concomitant administration of other myelotoxic substances or radiation therapy, the risk of myelosuppression is increased.

4.7 Fertility, 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.

4.8 Effects on ability to drive and use machines

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

4.9 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. Tioguanine 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: Bone marrow failure (see monitoring)

Hepato-biliary disorders

Very Common: Liver toxicity associated with vascular endothelial damage when tioguanine 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 veno-occlusive liver disease (hyperbilirubinaemia, tender hepatomegaly, weight gain due to fluid retention and ascites) or signs and symptoms of portal hypertension (splenomegaly, varices thrombocytopenia and oesophageal). Elevation of liver transaminases, blood alkaline phosphatase and gamma glutamyl transferase and jaundice may also occur. Histopathological features associated with this toxicity include portal fibrosis, nodular regenerative hyperplasia, peliosis hepatis and periportal fibrosis.

Common: Liver toxicity during short term cyclical therapy presenting as veno-occlusive liver disease.

Reversal of signs and symptoms of this liver toxicity has been reported upon withdrawal of short term or long term continuous therapy.

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

Renal and urinary disorders

Common - Hyperuricaemia and/or hyperuricosuria and urate nephropathy (see Warnings and Precautions)

Post Marketing Data

Skin and subcutaneous tissue disorders

Frequency not known - Photosensitivity

4.10 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.

Further management should be as clinically indicated or as recommended by the national poisons centre.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mode of Action:-

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

Tioguanine metabolites inhibit de novo purine synthesis and purine nucleotide interconversions. Tioguanine 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 tioguanine and mercaptopurine, and it is not to be expected that patients resistant to one will respond to the other.

Pharmacokinetic Properties

Tioguanine 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 tioguanine 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-tioguanine 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-tioguanine/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).

Biotransformation

NUDT15 R139C (NUDT15 c.415C>T) Variant

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. Reduced thiopurine doses for patients who carry the NUDT15 variants may decrease their risk of toxicity. Therefore, genotypic analysis determining NUDT15 genotype

should be determined for all patients, including paediatric patients, prior to initiating thiopurine treatment (see section 4.2). 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. The precise mechanism of NUDT15-associated thiopurine-related toxicity is not understood.

5.3 Preclinical safety data

Mutagenicity and carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Potato starch

Acacia

Stearic acid

Magnesium stearate

6.2 Incompatibilities

None reported

6.3 Shelf-life

5 years/60 months

6.4 Special precautions for storage

Store at 25 C.

Protect from light.

Keep dry.

6.5 Nature and contents of container

LANVIS Tablets 40mg Bottle of 25 tablets.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Pharmacy Retailing Pty Ltd
Trading as **Healthcare Logistics**
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

9. DATE OF FIRST APPROVAL

27 September 2004

10. DATE OF REVISION OF THE TEXT

28 August 2023

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
Format of Data sheet	As per new European SmPC style format
1; 4.2; 4.4; 4.8; 4.9; 5.1; 5.2; 5.3	Change in API name from thioguanine to tioguanine
4.2 & 4.4	Dosing and safety related changes.
4.2, 4.4 & 5.2	Safety Related Changes
4.4	Susceptibility to viral, fungal, and bacterial infections