1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LANVIS 40 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of LANVIS contains 40 mg thioguanine.

Contains sugar: Lactose monohydrate 150,0 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

LANVIS is a white to off-white tablet, round, biconvex scored and imprinted “T40” on upper side, without score and debossing on lower side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LANVIS is indicated for:

- Short-term induction treatment of acute myelogenous leukaemia, and chronic myelocytic leukaemia in combination with other therapy.
- Delayed intensification treatment of acute lymphoblastic leukaemia in combination with other therapy.

Cross-resistance exists between LANVIS and mercaptopurine, and generally it is not expected that patients who no longer respond to mercaptopurine will respond to LANVIS or vice versa.

4.2. Posology and method of administration

Posology

The dosage of LANVIS and duration of administration must be carefully adjusted for each patient to obtain optimum benefit without toxic effects.

Therapy should be initiated in a specialised unit with full facilities for supportive therapy.

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

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

LANVIS 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 section 4.4).

Adults

For adults, the usual dosage of LANVIS is between 60 and 200 mg/m^2 body surface area per day.

Paediatric population

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

Special populations

Elderly population

There are no specific dosage recommendations in elderly patients (see *Renal or hepatic impairment* below). LANVIS has been used in various combination chemotherapy schedules in elderly patients with acute leukaemia at equivalent doses to those used in younger patients.

Renal or hepatic impairment

Consideration should be given to reducing the dosage in patients with impaired hepatic or renal function, since these will result in slower elimination of the medicine and a greater cumulative effect.

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 LANVIS and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established (see section 4.4).

Most patients with heterozygous TPMT deficiency can tolerate recommended LANVIS doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see section 4.4). Consideration should be given to reducing the dosage in patients with impaired hepatic function.

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 LANVIS 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 LANVIS 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). Close monitoring of blood counts is necessary.

Method of administration

For oral administration.

If halving a tablet is required, care should be taken not to contaminate the hands or inhale the medicine (see section 6.6).

4.3. Contraindications

LANVIS is contraindicated in:

- Patients with hypersensitivity to thioguanine or to any of the excipients in LANVIS (see section 6.1).
- Live vaccines must not be used on patients receiving LANVIS (see section 4.4).

4.4. Special warnings and precautions for use

LANVIS IS AN ACTIVE CYTOTOXIC MEDICINE FOR USE ONLY UNDER THE DIRECTION OF MEDICAL PRACTITIONERS EXPERIENCED IN THE ADMINISTRATION OF SUCH MEDICINES.

Immunisation

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are contraindicated. In all cases, patients in remission should not receive live organism vaccines until at least 3 months after their chemotherapy treatment has been completed (see section 4.3).

Hepatic effects

LANVIS SHOULD NOT BE USED FOR MAINTENANCE THERAPY OR SIMILAR LONG TERM CONTINUOUS TREATMENTS DUE TO THE HIGH RISK OF LIVER TOXICITY ASSOCIATED WITH VASCULAR ENDOTHELIAL DAMAGE (see section 4.2 and section 4.8).

This liver toxicity has been observed in a high proportion of children receiving LANVIS as part of maintenance therapy for acute lymphoblastic leukaemia and in other conditions associated with continuous use of LANVIS. 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, thrombocytopaenia and oesophageal varices). Histopathological features associated with this toxicity include hepatoportal sclerosis, nodular regenerative hyperplasia, peliosis hepatis and periportal fibrosis.

LANVIS 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

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 thrombocytopaenia 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.

Haematological effects

Treatment with LANVIS causes bone marrow suppression leading to leukopaenia and thrombocytopaenia (see *Hepatic effects*). Anaemia has been reported less frequently. Bone marrow suppression is usually reversible if LANVIS is withdrawn early enough.

Thiopurine S-methyltransferase (TPMT) deficiency

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. This problem could be exacerbated by co-administration with medicines 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.

NUDT15 mutation

Patients with inherited mutated NUDT15 gene are at increased risk for severe thiopurine toxicity, such as early leukopaenia and alopecia, from conventional doses of LANVIS 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 LANVIS 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.

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 section 4.8).

Monitoring

SINCE LANVIS IS STRONGLY MYELOSUPPRESIVE 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 medicine. Resistance to azathioprine, which has one of the same active metabolites as LANVIS, has been demonstrated in children with Lesch-Nyhan syndrome.

Exposure to ultraviolet light

Patients treated with LANVIS 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.

Bone marrow depression

If bone marrow depression occurs, the following precautions should be exercised:

1) avoiding exposure of patient to persons with bacterial infections.
2) consult a medical practitioner immediately if there is unusual bleeding or bruising.
3) care must be taken to avoid accidental cuts with sharp objects.
4) avoiding contact sports or any other situations where bruising or injury may occur.

Risk benefit

Risk-benefit should be considered when the following pre-existing medical problems are present:

1) bone marrow depression
2) chickenpox
3) herpes zoster
4) gout
5) renal stones
6) hepatic function impairment
7) infection and
8) renal function impairment.

Caution must be exercised in patients who have had therapy with cytotoxic medicines and radiation during the last 4 to 6 weeks prior to treatment with LANVIS.

Mutagenicity and carcinogenicity

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

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take LANVIS.

4.5. Interaction with other medicines and other forms of interaction

Serious Medicine Interactions

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

Other myelotoxic substances or radiation therapy

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

Busulphan

The combination of busulphan and LANVIS has resulted in the development of nodular regenerative hyperplasia, portal hypertension and oesophageal varices.

Allopurinol

The concomitant use of allopurinol to inhibit uric acid formation does not necessitate reduction of dosage of LANVIS.

Aminosalicylate derivatives

As there is *in vitro* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent LANVIS therapy (see section 4.4).

Blood dyscrasia-causing medicines e.g. ACE-inhibitors, anticonvulsants, antidepressants, NSAIDs, chloramphenicol: leukopenic and/or thrombocytopenic effects of LANVIS may be increased by concurrent or recent use of such medicines.

Killed virus vaccines

Normal defence mechanisms may be suppressed by LANVIS therapy; the patient's antibody response to the vaccine may be decreased.

Live virus vaccines

Normal defence mechanisms may be suppressed by LANVIS therapy; concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus; may increase the adverse effects of the vaccine virus and/or may decrease the patient's antibody response to the vaccine (see section 4.3).

4.6. Fertility, pregnancy and lactation

LANVIS, like other cytotoxic medicines, is potentially teratogenic.

Pregnancy

LANVIS should be avoided whenever possible during pregnancy, particularly during the first trimester.

Contraception in males and females

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

Fertility

There have been reports of men who have received combinations of cytotoxic medicines, including thioguanine, as in LANVIS, and have fathered children with congenital abnormalities.

Breastfeeding

Mothers receiving LANVIS should not breastfeed (see section 4.3).

4.7. Effects on ability to drive and use machines

LANVIS has no or negligible influence on the ability to drive and operate machinery.

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that LANVIS does not adversely affect their ability to do so safely (see section 4.8).

4.8. Undesirable effects

a) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Blood and the lymphatic system disorders	Bone marrow suppression, bone marrow failure		
Metabolism and nutrition disorders	Hyperuricaemia, loss of appetite		
Gastrointestinal disorders	Stomatitis, gastrointestinal intolerance, diarrhoea,	Intestinal necrosis, perforation, necrotizing colitis	

	nausea, vomiting, gastrointestinal disorder		
Hepato-biliary disorders	Veno-occlusive liver disease	Centrilobular hepatic necrosis	
Skin and subcutaneous tissue disorders		Skin rash or itching	Photosensitivity
Renal and urinary disorders	Hyperuricosuria, urate nephropathy		

b) Description of selected adverse reactions

Hepato-biliary disorders

Liver toxicity associated with vascular endothelial damage when LANVIS is used in maintenance or similar long-term continuous therapy, which is not recommended (see section 4.2 and section 4.4).

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, thrombocytopaenia 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 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, but reversal may not be seen and patients may still develop portal hypertension.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Signs and symptoms of overdosage may be immediate, such as nausea, vomiting, anorexia, malaise, stomatitis, hypotension and diaphoresis; or delayed, sucha s myelosuppression and azotaemia.

It is not known whether thioguanine is dialysable.

Treatment

There is no known antagonist to LANVIS and therefore prompt discontinuation of LANVIS is essential when toxicity develops, so as to avoid irreversible depression of the bone marrow. Haematology should be closely monitored and blood and transfusion (platelets, granylocytes), instituted if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 26. Cytostatic agents

Pharmacotherapeutic group: Antimetabolites, purine analogues

ATC code: L01BB03

Mechanism of action

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

Thioguanine metabolites inhibit *de novo* purine synthesis and purine nucleotide interconversion. It is cell cycle-specific for the S-phase of cell division.

Thioguanine is also incorporated into nucleic acids and DNA (deoxyribonucleic acid) incorporation is claimed to contribute to the medicine's cytotoxicity, but it has a lesser effect on RNA synthesis. In man, thioguanine is extensively converted to 2-amino-6-methylmercaptopurine which is much less toxic and less effective than the parent compound.

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. Its action is not prolonged by the xanthine oxidase inhibitor allopurinol. Thioguanine penetration across the blood-brain barrier is poor.

5.2. Pharmacokinetic properties

Absorption

Studies with radioactive thioguanine show that peak blood levels of total radioactivity are achieved about 8 to 10 hours after oral administration and decline slowly thereafter.

Following oral administration of 100 mg/ m^2, peak levels as measured by HPLC occur at 2 to 4 hours and lie in the range of 0,03 to 0,94 micromolar (0,03 to 0,94 nmol/ ml).

Levels are reduced by concurrent food intake (as well as vomiting).

Distribution

Limited data on the distribution of thioguanine (TG) in humans are available in the scientific literature. The plasma protein binding of 6-TG in humans has not been measured.

Biotransformation

Thioguanine is extensively metabolized. The four different enzymes responsible for thioguanine metabolism are as follows: hypoxanthine (guanine) phosphoribosyl transferase (H(G)PRT), which converts thioguanine into thioguanosine monophosphate (6-TGMP), which is further metabolised by protein kinases to the active species, thioguanine nucleotides (6-TGN); TPMT, which converts thioguanine to 6-methylthioguanine (6-MTG, inactive metabolite) as well as 6-TGMP to 6-methyl-TGMP (an inactive metabolite) and xanthine oxidase (XDH or XO) and 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 6-thiouric acid (6-TUA).

Special populations

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 healthcare provider 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Acacia, lactose monohydrate, magnesium stearate, potato starch, stearic acid.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25° C.

Protect from light.

Keep dry.

Keep in the original packaging until required for use.

6.5. Nature and contents of container

Amber glass bottles of 25 tablets, sealed with plastic caps. Each bottle is packed into a preprinted carton together with a leaflet.

6.6. Special precautions for disposal and other handling

Safe handling

If halving a tablet is required, care should be taken not to contaminate the hands or inhale the medicine.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

C/26/119

9. DATE OF FIRST AUTHORISATION

16 April 1973

10. DATE OF REVISION OF TEXT

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