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Summary of Product Characteristics

1. Name of the Medicinal Product

LANVIS TABLETS 40 MG

2. Qualitative and Quantitative Composition

40 mg thioguanine BP per tablet.

Excipients:

This product contains lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Lanvis 40 mg tablets are white to off–white tablet, round, biconvex scored and imprinting 'T40' on one side, without score and debossing on the other side.

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

4. Clinical Particulars

4.1 Therapeutic Indications

Thioguanine is indicated for the treatment of acute nonlymphocytic leukemia.

4.2 Posology and Method of Administration

Posology

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

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

Thioguanine can be used at various stages of treatment in short term cycles. 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

The usual dosage of thioguanine is between 100 and 200 mg/m^2 body surface area, per day.

Paediatric population

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

Use in the elderly

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

Thioguanine has been used in various combination chemotherapy schedules in elderly patients with acute leukaemia at equivalent doses 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.

TPMT-deficient patients

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe tioguanine toxicity from conventional doses of tioguanine and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established (see sections 4.4 and 5.2).

Most patients with heterozygous TPMT deficiency can tolerate recommended tioguanine doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see sections 4.4 and 5.2).

Method of administration

Oral.

4.3 Contraindications

Hypersensitivity to tioguanine or to any of the excipients listed in section 6.1.
In view of the seriousness of the indications there are no absolute contra-indications.
If you are pregnant or breastfeeding.

4.4 Special Warnings and Precautions for Use

Thioguanine 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. In all cases, patients in remission should not receive live organism vaccines until at least 3 months after their chemotherapy treatment has been completed.

Hepatic Effects

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 sections 4.2 and 4.8).
This 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.
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

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.

Haematological Effects

Treatment with thioguanine causes bone marrow suppression leading to leucopenia and thrombocytopenia (see Hepatic effects). Anaemia has been reported less frequently.

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

There are individuals with an inherited deficiency of the enzyme 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 thioguanine. 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.

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.

Monitoring

Since tioguanine 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.

Mutagenicity and carcinogenicity

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

It is recommended that the handling of Tioguanine tablets follows the Guidelines for the handling of cytotoxic drugs.

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

Lesch-Nyhan syndrome

Since the enzyme hypoxanthine guanine phosphoribosyl transferase 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 the drug. Resistance to azathioprine (Imuran*), which has one of the same active metabolites as thioguanine, has been demonstrated in two children with Lesch-Nyhan syndrome.

UV exposure

Patients treated with tioguanine 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.

Patients with lactose intolerance should be advised that tioguanine contains a small amount of lactose. Patients with rare hereditary disorders such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of Interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4).

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

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

4.6 Fertility, pregnancy and Lactation

Thioguanine, like other cytotoxic agents is potentially teratogenic.

Fertility

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

Pregnancy

The use of tioguanine 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 thioguanine.

Breastfeeding

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

4.7 Effect on ability to drive and use machines

None known.

4.8 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 ≥1/10 (≥10%), Common ≥1/100 and < 1/10 (≥1% and <10%), Uncommon ≥ 1/1000 and <1/100 (≥0.1% and <1%), Rare ≥1/10,000 and <1/1000 (≥0.01% and <0.1%), Very rare <1/10,000 (<0.01%).

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Very common	Bone marrow failure (see section 4.4).
Gastrointestinal disorders	Common	Stomatitis, gastrointestinal disorder
	Rare	Necrotising colitis
Hepatobiliary disorders[a]	Very common	Venoocclusive liver disease: hyperbilirubinaemia, hepatomegaly, weight increased due to fluid retention and ascites. Portal hypertension: splenomegaly, varices oesophageal and

		thrombocytopenia. Hepatic enzyme increased, blood alkaline phosphatase increased and gamma glutamyltransferase increased, jaundice, hepatoportalsclerosis, portal fibrosis, nodular regenerative hyperplasia, peliosis hepatitis.
	Common	Venoocclusive liver disease in short-term cyclical therapy.
	Rare	Hepatic necrosis.
Metabolism and Nutrition disorders	Common	Hyperuricaemia
Renal and urinary disorders	Common	Hyperuricosuria and urate nephropathy (see section 4.4).
Skin and subcutaneous tissue disorders	Not Known	Photosensitivity (see section 4.4)

[a] see description of selected adverse reactions

Hepato-biliary disorders

The liver toxicity associated with vascular endothelial damage occurs at a frequency of very common when tioguanine is used in maintenance or similar long term continuous therapy which is not recommended (see sections 4.2 and 4.4).

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 tioguanine and alcohol.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).
Additionally, you can also report to www.perrigo-pharma.co.il.

4.9 Overdose

Symptoms and 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 thioguanine.

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 center, where available.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: anti-neoplastic and immunomudulating agent/purine analogue, 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 interconversions.
Thioguanine is also incorporated into nucleic acids and DNA (deoxyribonucleic acid) incorporation is claimed to contribute to the agent's cytotoxicity.

Pharmacodynamic Effects

There is usually a cross-resistance between thioguanine and mercaptopurine; it is therefore not to be expected that patients with a tumour resistant to one will respond to the other.

5.2 Pharmacokinetics Properties

Absorption

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 1.2 g of 6-thioguanine/m^2 body surface area.

Plasma levels decay biexponentially with initial and terminal half-lives of 3 and 5.9 hours, respectively. Following oral administration of 100 mg/m^2, 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).

Distribution

Limited data on the distribution of tioguanine in humans are available in the scientific literature.
Tioguanine penetrates into the CSF following constant IV infusion administration after doses of 20 mg/m^2/h over 24 hours in children with ALL.

Biotransformation

Tioguanine is extensively metabolised *in vivo*.The four different enzymes responsible for tioguanine metabolism are as follows: hypoxanthine (guanine) phosphoribosyl transferase (H(G)PRT), which

converts tioguanine into thioguanosine monophosphate (6-TGMP), which is further metabolized by protein kinases to the active species, thioguanine nucleotides (6-TGN); TPMT, which converts tioguanine 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 tioguanine into inactive metabolites. Tioguanine 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).

Elimination

No data.

5.3 Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose
Potato Startch
Acacia
Stearic Acid
Magnesium Stearate

6.2 Incompatibilities

None known.

6.3 Shelf Life

24 months (unopened).

6.4 Special Precautions for Storage

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

After first opening, use within 25 days.

6.5 Nature and Contents of Container

Amber glass bottles with child resistant polyethylene/polypropylene closures.
Pack size 25 tablets.

6.6 Special precautions for disposal and other Handling

It is recommended that the handling of Tioguanine tablets follows the “Guidelines for the handling of cytotoxic drugs”.

7. Manufacturer

Excella GmbH, Germany.
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8. License Number

058-23-20936-05

9. License Holder

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