Lanvis Tablets 40mg

Thioguanine

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets containing 40mg thioguanine.

PHARMACEUTICAL FORM

Tablets. Thioguanine tablets are white to off-white tablet, round, biconvex scored and imprinting ‘T40' on upper side, without score and debossing on lower side.

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

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

Thioguanine is indicated primarily for the treatment of acute leukaemias especially, acute myelogenous leukaemia and acute lymphoblastic leukaemia.

POSOLOGY AND METHOD OF ADMINISTRATION

General

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 drug 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 *Special Warnings and Precautions for Use and Undesirable Effects*)

Posology

- **Adults**

For adults, the usual dosage of thioguanine 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.

- **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 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.

- **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 *Special Warnings and Precautions for Use and Pharmacokinetic Properties*).

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 *Special Warnings and Precautions for Use and Pharmacokinetic Properties*). 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 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 *Pharmacokinetic Properties*).

Method of administration

Oral.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in *List of Excipients*.
In view of the seriousness of the indications there are no other absolute contraindications.

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 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 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 leucopoenia and thrombocytopenia (see *Hepatic Effects*). Anaemia has been reported less frequently.
Bone marrow suppression is readily reversible if thioguanine is withdrawn early enough.

Thiopurine S-methyltransferase (TPMT) deficiency

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.

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 *Pharmacokinetic Properties)*.

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.

Infections in all populations
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 *Undesirable Effects*).

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.

Cholestasis of pregnancy has occasionally been reported in association with thioguanine therapy (see *Fertility, Pregnancy and Lactation*). If cholestasis of pregnancy occurs, case by

case assessment is necessary considering the risk-benefit profile of the product (potential withdrawal / dose reduction).

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, 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 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.

Excipient warnings

Patients with lactose intolerance should be advised that thioguanine 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

- **Vaccines**

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

- **Other myelotoxic substances or radiation therapy**

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

- **Allopurinol**

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

- **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 thioguanine therapy (see *Special Warnings and Precautions for Use*).

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 thioguanine 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.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine therapy. Early diagnosis and discontinuation of thioguanine may minimise impact on the foetus. However, a careful assessment of benefit to the mother and impact on the foetus should be performed, if cholestasis of pregnancy is confirmed (see *Special Warnings and Precautions for Use*).

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.

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 ≥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%).

Tabulated list of adverse reactions

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Very common	Bone marrow failure (see *Special Warnings and Precautions for Use*)

Gastrointestinal disorders	Common	Stomatitis, gastrointestinal disorder
	Rare	Necrotising colitis
Hepatobiliary disorders	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 glutamyl-transferase increased, jaundice, portal fibrosis, nodular regenerative hyperplasia, peliosis hepatitis,
	Common	Veno-occlusive liver disease in short-term cyclical therapy
	Uncommon	Cholestasis of pregnancy
	Rare	Hepatic necrosis
Renal and urinary disorders	Common	Hyperuricaemia and/or hyperuricosuria and urate nephropathy (see *Special Warnings and Precautions for Use*)
Skin and subcutaneous tissue disorders	Not known	Photosensitivity

Description of selected adverse reactions

Hepatobiliary disorders

The liver toxicity associated with vascular endothelial damage occurs at a frequency of very common when thioguanine is used in maintenance or similar long term continuous therapy which is not recommended (see *Posology and Method of Administration and Special Warnings and Precautions for Use*).

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

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

OVERDOSE

Symptoms

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 centre, where available.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-neoplastic and immunomodulating 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.

PHARMACOKINETIC PROPERTIES

ABSORPTION

Studies with radioactive thioguanine show that peak blood levels of total radioactivity are achieved about 8 to 10 h 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 h after intravenous administration. Peak plasma concentrations of 61 to 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 h, respectively. Following oral administration of 100 mg/m^2, peak levels as measured by HPLC occur at 2 to 4 h 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 in humans are available in the scientific literature. 6-thioguanine 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

Thioguanine is extensively metabolised *in vivo*. The four different enzymes responsible for 6-TG metabolism are as follows: hypoxanthine (guanine) phosphoribosyl transferase (H(G)PRT), which converts 6-thioguanine into thioguanosine monophosphate (6-TGMP), which is further metabolized by protein kinases to the active species, thioguanine nucleotides (6-TGN); TPMT, which converts 6-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 6-thioguanine into inactive metabolites. 6-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).

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

Recent studies indicate that a strong association exists between the NUDT15 variant NUDT15 c.415C>T [pArg139Cys] (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 c415C>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 of 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 *Posology and Method of Administration*). 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.

PRECLINICAL SAFETY DATA

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
Purified water

INCOMPATIBILITIES

None reported.

SHELF-LIFE

The expiry date is indicated on the packaging.

STORAGE CONDITIONS

Store below 30ºC.
Protect from light.
Keep dry.

NATURE AND CONTENTS OF CONTAINER

Amber glass bottle with child resistant closure containing 25 tablets.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Safe handling:

It is recommended that the handling of thioguanine 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:

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

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MANUFACTURER

Excella GmbH & Co. KG
Nurnberger Strasse 12
90537 Feucht
Germany

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