Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lanvis 40mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablet containing 40 mg tioguanine.

Excipients with known effects:

Also contains 150mg Lactose Monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Lanvis 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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the treatment of leukaemias, particularly acute myeloblastic leukaemia and acute lymphoblastic leukaemia.

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 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 the paediatric population, 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 Renal and 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.

Special populations:

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 Lanvis 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 Lanvis doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see sections 4.4 and 5.2). 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 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 other absolute contraindications.

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. 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

LANVIS 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 the paediatric population receiving tioguanine as part of maintenance therapy for acute lymphoblastic leukaemia 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.
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 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 Lanvis 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 tioguanine 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 tioguanine 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.

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 sections 4.2 and 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 section 4.8).

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.

Lesch-Nyhan syndrome

Since the enzyme hypoxanthine guanine phosphoribosyl transferase is responsible for the conversion of tioguanine 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 Lanvis, has been demonstrated in two children with Lesch-Nyhan syndrome.

UV exposure

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 (see section 5.3).

Lactose intolerance

Patients with lactose intolerance should be advised that Lanvis contains a small amount of lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Cross-resistance

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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 tioguanine as is necessary with mercaptopurine and azathioprine.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Lanvis like other cytotoxic agents is potentially teratogenic (see section 5.3).

The use of tioguanine should be avoided 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 tioguanine.

Breastfeeding
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.

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

4.7 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.

4.8 Undesirable effects

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 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, 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 (see section 4.4).
Renal and urinary disorders	Common	Hyperuricosuria and urate nephropathy (see section 4.4).

[a] see description of selected adverse reactions

Description of selected adverse reactions:

Hepatobiliary 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).

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.

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.

The following events have been reported rarely: photosensitivity, electrolyte disturbances, ataxia, rash, tinnitus, cardiovascular disturbances, deafness and oculogyric crisis.

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. Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance Website: www.hpra.ie

4.9 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 Lanvis.

Management

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic and immunomodulating agent/purine analogue, ATC code: L01BB03

Mechanism of action

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

Pharmacodynamic effects

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

5.2 Pharmacokinetic properties

Absorption

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 to 118 nanomol (nmol)/ml are obtainable following intravenous administration of 1 to 1.2 g of 6-tioguanine/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 2-4 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 tioguanine in humans are available in the scientific literature.
6- tioguanine penetrates into the cerebrospinal fluid (CSF) following constant IV infusion administration after doses of 20 mg/m^2/h over 24 hours in the paediatric population with acute lymphoblastic leukaemia.

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, tioguanine nucleotides (6-TGN); TPMT, which converts tioguanine to 6-methyltioguanine (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).

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

Reproductive toxicity
Administration of tioguanine to pregnant rats, at a dose of 0.3 times the Maximum Recommended Human Dose (MRHD) was found to be highly toxic to rat fetuses but not to dams. The nature of the effects on foetal viability and development was highly dependent on the stage of gestation at the time of tioguanine administration.

Administration of Tioguanine before implantation induced, 75% foetal resorption and complete destruction of 10% of the litters. When tioguanine was administered at the time of implantation, all of the foetuses died.

Tioguanine was teratogenic in rats at doses of 0.37 and 0.75 times the MRHD when administered on the 12th days of gestation (corresponding to the organogenesis period). It induced a decrease in placental weight and foetal malformations that included: i) skeletal defects, ii) ventral hernia, iii) hydrocephalous and, iv) situs inversus (see section 4.6).

Genotoxicity
Tioguanine at doses of 0.03 and 0.06 times the MRHD induced a highly significant dose-dependent increase in the frequency of micronucleated polychromatic erythrocytes in mice, indicating that it induces genotoxic damage in vivo. This in vivo data is supported by in vitro studies showing that cell culture treatment with tioguanine (at concentrations ranging from 0.01 to 4 uM) also induced DNA damage.

Biologically relevant doses of ultraviolet A (UVA) generate ROS in cultured cells with tioguanine-substituted DNA and tioguanine and UVA are synergistically mutagenic (see section 4.4).

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

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original bottle and in the carton in order to protect from light. Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Lanvis tablets are supplied in amber (Type III) glass bottles with a polypropylene/HDPE child-resistant closure, containing 25 tablets.

6.6 Special precautions for disposal and other handling

Safe handling of Lanvis

It is recommended that the handling of Lanvis tablets follows the "Guidelines for the Handling of Cytotoxic Drugs" issued by the Royal Pharmaceutical Society of Great Britain Working Party on 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.
Pregnant staff should not handle cytotoxic agents.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 1 April 2009

10 DATE OF REVISION OF THE TEXT

December 2022