

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tioguanine 40 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

40 mg tioguanine BP per tablet.

Excipients:

This product contains lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tioguanine 40 mg 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

Tioguanine is indicated primarily for the treatment of acute leukaemias especially acute myelogenous 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 tioguanine.

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

Tioguanine 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 tioguanine is between 100 and 200 mg/m² 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).

Tioguanine has been used in various combination chemotherapy schedules in elderly patients with acute leukaemia at equivalent doses to those used in younger patients.

Special populations:

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).

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe tioguanine toxicity (see 4.4). These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes (see 4.4). Genotypic testing of NUDT15 variants may be considered before initiating tioguanine therapy. In any case, close monitoring of blood counts is necessary.

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.

4.4 Special warnings and precautions for use

Tioguanine 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

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 sections 4.2 and 4.8). This liver toxicity has been observed in a high proportion of children 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.

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

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 tioguanine 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 tioguanine. 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 thioguanine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy. They generally require dose reduction, particularly those being NUDT15 variant homozygotes (see 4.2). The frequency of NUDT15 c.415C>T has an ethnic variability of approximately 10 % in East Asians, 4 % in Hispanics, 0.2 % in Europeans and 0 % in Africans. In any case, close monitoring of blood counts is 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. 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 which may be life-threatening or fatal. Appropriate treatment and supportive care should be instigated to manage the risk 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 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 section 4.6). If cholestasis of pregnancy occurs, case by case assessment is necessary considering the risk-benefit profile of the product (potential withdrawal/dose reduction).

Mutagenicity and carcinogenicity

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

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

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.

Aminosalicylate derivatives

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

4.6 Fertility, pregnancy and lactation

Tioguanine, like other cytotoxic agents is potentially teratogenic.

Fertility

There have been isolated cases where men, who have received combinations of cytotoxic agents including tioguanine, 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 tioguanine.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine therapy. Early diagnosis and discontinuation of tioguanine 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 section 4.4).

Breastfeeding

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

4.7 Effects 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. 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 $\geq 1/10$ ($\geq 10\%$), Common $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$), Uncommon $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$), Rare $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ 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.
	Uncommon	cholestasis of pregnancy
	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)
Infections and infestations	Not Known	Infections

^a see description of selected adverse reactions

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 tioguanine.

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 center, 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 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.

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 61-118 nanomol (nmol)/ml are obtainable following intravenous administration of 1 to 1.2 g 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 100 mg/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).

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/m²/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 monohydrate	NF
Starch, potato	HSE
Acacia	NF
Stearic acid	NF
Magnesium stearate	NF
Purified water	USP

6.2 Incompatibilities

None known.

6.3 Shelf life

60 months (unopened).

6.4 Special precautions for storage

Store below 25°C.

Keep dry.

Protect from light.

6.5 Nature and contents of container

Amber glass bottles with child-resistant polyethylene/polypropylene closures.

Pack size 25.

6.6 Special precautions for disposal

It is recommended that the handling of Tioguanine 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.

7. Marketing Authorisation Holder

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 39699/0045

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 October 1997/1 December 2008

10 DATE OF REVISION OF THE TEXT

20/11/2024