MS SAVITHA RAGHAVENDRAN
ASPEN PHARMA TRADING LIMITED
3018 LAKE DRIVE
CITYWEST BUSINESS CAMPUS
DUBLIN 24
IE-D24 TY81
IRELAND

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Department of Health

CERTIFICATE OF A PHARMACEUTICAL PRODUCT (1)

This certificate conforms to the format recommended by the World Health Organisation
(explanatory notes are attached)

Exporting (certifying) country: **UNITED KINGDOM**

Importing (requesting) country: **CHILE**

1 Name and dosage form of the product:

A) In the United Kingdom - Tioguanine 40mg Tablets, TABLET

B) In CHILE - Lanvis, TABLET

1.1 Active ingredient(s) (2) and amount(s) (3) per unit dose:

Active Ingredient(s)	Amount per unit dose
TIOGUANINE	40.000 MG

For complete qualitative composition including excipients, see attached. (4)

1.2 Is this product licensed to be placed on the market for use in the exporting country? (5) Yes

1.3 Is this product actually on the market in the exporting country? Yes

1.4 The product is not on the market in the exporting country because

N/A

2A.1 Product Licence/Marketing Authorisation

Number [7]: **PL 39699/0045**
Date of Issue: 01 May 2012

2A.2 The name and address of the Product Licence/Marketing Authorisation holder are:

Name: ASPEN PHARMA TRADING LIMITED

Address: 3016 LAKE DRIVE, CITYWEST BUSINESS CAMPUS, DUBLIN 24, IRELAND

2A.3 Status of the Product Licence/Marketing Authorisation holder [8]:

c) is not involved in manufacturing, packaging or labelling the dosage form but is responsible for the quality and release of the product

2A.3.1 For categories b,c and d the names and address of the manufacturing site where the dosage form is produced are [9]:

See attached page for Manufacturers/Packagers

2A.4 Is Summary Basis of Approval appended? [10] No

2A.5 Is the attached, officially approved product information complete and consonant with the licence? [11] Yes

2A.6 Applicant for certificate, if different from licence holder (name and address) [12] :

Name:

Address:

Section 2B is not included because the product named in this certificate is licensed in the UK[6]

3	Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? (14)	N/A

IF NO OR NOT APPLICABLE PROCEED TO QUESTION 4

3.1	Periodicity of routine inspections (years)	
3.2	Has the manufacturer of this type of dosage form been inspected?	
3.3	Do the facilities and operations conform to GMP as recommended by the World Health Organisation ? (15)	
4	Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product including Good Manufacturing Practice (GMP)? (16)	Yes
	If No, explain	

Additional Information:

NONE

Address of certifying authority:

The Medicines and Healthcare products Regulatory Agency,
10 South Colonnade, Canary Wharf, London E14 4PU, United Kingdom

Telephone Number: +44 (0) 20 3080 6593

Name of authorised person: Colin Atkinson

Signature: PLEASE SEE COVER LETTER

Stamp and Date: 07 May 2021

Names and Addresses of Manufacturers/Packagers (9)

Manufacturers

Name:	EXCELLA GMBH & CO. KG
Address:	NUERNBERGER STRASSE 12, FEUCHT, D-90537, GERMANY

Excipient	Modifier	Amount per unit dose
LACTOSE		150.000 MG
POTATO STARCH		25.000 MG
MAGNESIUM STEARATE		0.500 MG
ACACIA		8.000 MG
STEARIC ACID		1.500 MG
WATER PURIFIED	ND	

Explanatory Notes

1. This certificate, which is in the form recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the UK. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

2. Whenever possible International Non-proprietary Names (Inns) or national non-proprietary names have been used.

3. The formula (complete composition) of the dosage form should be given on the certificate or be appended.

4. Details of the quantitative composition are preferred but their provision is subject to the agreement of the Marketing Authorisation holder.

5. When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the Marketing Authorisation.

6. Sections 2A and 2B are mutually exclusive.

7. Indicate when applicable if the licence is provisional or the product has not yet been approved.

8. Specify whether the person responsible for placing the product on the market:

   (a) manufactures the dosage form and is responsible for the quality assurance and release of the product.
   (b) packages and/or labels a dosage form manufactured by another company but is responsible for the quality assurance and release of the product.
   (c) is not involved in manufacturing, packaging or labelling the dosage form but is responsible for the quality and release of the product.
   (d) is involved in none of the above.

9. This information is optional and can be provided only with the permission of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

   It should be noted that:

   information concerning the site of manufacture is part of the Marketing Authorisation. If the manufacturing site is changed the licence must be updated or it will cease to be valid.

   in the UK manufacture of pharmaceutical products is only permitted on licensed manufacturing sites. When the product-licence holder or applicant conforms to status (b), (c) or (d) as described in note 8 above the Manufacturing Licence holder is responsible for the manufacture of the dosage form.

10. This refers to the document prepared by some national regulatory authorities that summarises the technical basis on which the product has been licensed. The UK Medicines and Healthcare products Regulatory Agency does not prepare such a document.

11. This refers to product information approved by the Medicines and Healthcare products Regulatory Agency such as a Summary of Product Characteristics (SPC).

12. In this circumstance permission for issuing the certificate is required from the Marketing Authorisation holder. This permission must be provided to the Medicines and Healthcare products Regulatory Agency by the applicant.

13. Please indicate the reason that the applicant has provided for not requesting registration:

    (a) the product has been developed exclusively for the treatment of conditions - particularly tropical diseases - not endemic in the UK.
    (b) the product has been reformulated with a view to improving its stability under tropical conditions.
    (c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the UK.
    (d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient.
    (e) this type of product does not require a Marketing Authorisation in the UK.
    (f) any other reason.

14. "Yes" means the Medicines and Healthcare products Regulatory Agency arranges periodic inspections of the manufacturing plant in which the dosage form is produced. "No" means that manufacture is taking place in a country other than the UK and inspections are not carried out by any Regulatory Authority. "Not applicable" means that manufacture is taking place in a country other than the UK and inspection is conducted under the aegis of the country of manufacture.

15. The requirements of good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardisation (WHO Technical Report Series No. 822, 1992, Annex 1).

16. This section is to be completed when the product-licence holder or applicant conforms to status (b), (c) or (d) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form and the extent and nature of any controls exercised over each of these parties.

Certificate Number: PP10171423

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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/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).

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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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.

SUMMARY OF PRODUCT CHARACTERISTICS

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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 sulphasalzine. 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 tioguanine 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 indication 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.

Lesch-Nyhan syndrome

SUMMARY OF PRODUCT CHARACTERISTICS

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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 tioguanine, 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 therapyDuring 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.

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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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 ≥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
Renal and urinary disorders	Common	Hyperuricosuria and urate nephropathy (see section 4.4).
Skin and subcutaneous tissue disorders	Not Known	Photosensitivity (see see section 4.4)

[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.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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.

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 immunomudulating 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 61-118 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 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/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 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
24 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.

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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
15/11/2017