IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Lanvis 40mg Tablets
Tioguanine
PA1691/006/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Lanvis 40mg, in the treatment of leukaemias, particularly acute myeloblastic leukaemia and acute lymphoblastic leukaemia, is approvable. A national marketing authorisation was granted on 01 April 1979.

This application concerns a mutual recognition procedure with Ireland acting as Reference Member State (RMS) and Spain as the Concerned Member State (CMS). The application is submitted according to Article 10a of Directive 2001/83/EC, so called well-established use, based on an original marketing authorisation in the RMS and bibliographic application.

This medicinal product is available on prescription only, which may not be renewed.

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Lanvis 40mg Tablets
Name(s) of the active substance(s) (INN)	Tioguanine
Pharmacotherapeutic classification (ATC code)	L01BB L01BB03
Pharmaceutical form and strength(s)	40mg Tablets
Marketing Authorisation Number(s) in Ireland PA)	PA 1691/006/001
Marketing Authorisation Holder	Aspen Pharma Trading Limited
MRP/DCP No.	IE/H/0556/001/MR
Reference Member State	IE
Concerned Member State	ES

II. QUALITY ASPECTS

II.1. Introduction

This application is for Lanvis 40mg Tablets

II.2 Drug substance

The active substance is tioguanine, an established active substance, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current regulatory requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Lanvis 40 mg Tablets contain 40 mg of the active ingredient, Tioguanine.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the tablets dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Lanvis 40 mg tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The HPRA has been assured that GLP standards were followed in an appropriate manner in the studies conducted.

III.2 Pharmacology

Tioguanine is an antimetabolite of the purine analogue type. It is cell cycle-specific for the S phase of cell division. Activity occurs as the result of activation in the tissues and may include inhibition of DNA synthesis with a lesser effect on RNA synthesis.

The pharmacology of tioguanine is well known and the non-clinical literature data is adequately described. The non-clinical overview on pharmacology is acceptable.

III.3 Pharmacokinetics

The pharmacokinetics of tioguanine is well known and the available non-clinical literature data is adequately described. The non-clinical overview on pharmacokinetics is acceptable.

III.4 Toxicology

The toxicology of tioguanine is well known and the available non-clinical literature data is adequately described. The non-clinical overview on toxicology is acceptable. Non-clinical literature data indicating significant toxicities associated with

tioguanine, including genotoxicity, carcinogenicity, foetotoxicity and teratogenicity are adequately addressed by the information included in sections 4.4, 4.6 and 5.3 of the SmPC. There are no recent non-clinical studies raising safety concerns not previously identified.

III.5 Ecotoxicity/environmental risk assessment

There are 2 outstanding issues regarding the environmental risk assessment, the applicant commits to addressing these issues as a follow-up measure.

III.6 Discussion on the non-clinical aspects

Tioguanine is a widely used well-established active substance and the pharmacodynamic, pharmacokinetic and toxicological properties of tioguanine are well-known. The applicant has not provided additional non-clinical safety studies and further studies are not required. An overview based on literature review is appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Tioguanine is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the MR procedure is in accordance with that accepted for the currently authorised national product Lanvis (PA1691/006/001; Aspen Pharma Trading Ltd).

The applicant provided comprehensive clinical overviews of the development of the active substance and its efficacy and safety in use over the past 50 years in the treatment of leukaemias. These overviews adequately support the product's authorised indications and posology.

The main clinical overview submitted during the procedure (March 2015) provides a critical analysis of the clinical data published on tioguanine, based on a literature search with a publication cut-off date of February 2015. There was an addendum to the clinical overview (October 2016) to update the Company Core Datasheet (CCDS) to include a warning regarding patients with an inherited mutated nudix hydrolase 15 (NUDT15) gene who are at risk for severe thiopurine toxicity (e.g. severe leukopenia and alopecia) from conventional doses of thiopurines (including tiogaunine).

The evidence presented for demonstrating that the constituents of tioguanine have well established use, with an acceptable level of safety and efficacy, is acceptable. This document summarises the results of tioguanine clinical studies published since the original regulatory approval.

IV.2 Pharmacokinetics

Tioguanine is partially absorbed when administered orally and absorption is extremely variable.

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.

Following oral administration of 100 mg/m2, 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).

Subsequently, tioguanine is eliminated from the body largely by extensive metabolism in the liver and other tissues. It is eventually excreted in the urine almost exclusively as metabolites.

Recent studies indicate patients with an inherited mutated nudix hydrolase 15 (NUDT15) gene are at risk for severe thiopurine toxicity (e.g. severe leukopenia and alopecia) from conventional doses of thiopurines (including tioguanine). The precise mechanism of NUDT15-associated thiopurine-related toxicity is not understood.

IV.3 Pharmacodynamics

Tioguanine, a sulphydryl analogue of guanine, behaves as a purine antimetabolite. It is activated to its nucleotide, thioguanylic acid. As cytotoxic antimetabolites, 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 tiogaunine's cytotoxicity.

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

IV.4 Clinical Efficacy

Tioguanine is indicated for the treatment of leukaemias, particularly acute myeloblastic leukaemia (AML) and acute lymphoblastic leukaemia (ALL). The use of tioguanine in clinical practice has evolved since it was first licensed nationally in 1979. Tioguanine has been studied in several clinical trials, including clinical trials conducted by independent research and international collaboration groups. It has been tested in ALL clinical trials, particularly in children and adolescents, both in first and second line therapy protocols.

As a consequence of accumulated clinical efficacy data, currently tioguanine is used as a component of multi-agent chemotherapy in several therapeutic protocols for the treatment of leukaemias, particularly AML and ALL, for:

intensive induction chemotherapy in newly diagnosed patients,
consolidation, continuation and maintenance regimens for patients in complete remission,
re-induction or salvage therapy for those with relapsing or refractory disease.

IV.5 Clinical Safety

The safety profile of tioguanine is well known and well established; it has a toxicity profile that is clinically acceptable in light of its mechanism of action, indications and patient profile.
The most common adverse drug reactions are haematological and bone marrow suppression (expected from the pharmacological action of the drug) is the commonest dose limiting toxicity. The main non-haematological adverse drug reactions are infection (related to bone marrow suppression) hepatic (particularly veno-occulusive liver disease), renal and gastrointestinal.

Risk management plan (RMP)
The MAH has submitted a risk management plan in accordance with the requirements of Directive 2001/83/EC as amended. A summary of the safety concerns for the solution for infusion as approved in the RMP is provided below:

Summary of safety concerns	
Important identified risks	Bone marrow toxicity Necrotising colitis Hepatotoxicity (including veno-occlusive disease and portal hypertension (PH)
Important potential risks	Non-melanoma skin cancer Teratogenicity
Missing information	Exposure during breast feeding

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.
Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

With regard to PSUR submission, the MAH should take the following into account:

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines

web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

As the use of tioguanine is well established and supported by many publications over the years concerning both its safety and efficacy, no new clinical studies to evaluate the benefit/risk balance were submitted by the applicant. With reference to the scientific literature provided, the overall benefit risk for this product from a clinical perspective remains positive.

V. OVERALL CONCLUSIONS

Based on the review of the data on quality, safety and efficacy, the overall benefit risk for this product remains positive for the indications authorised and the HPRA considers the product approvable.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

VI. REVISION DATE

The marketing authorisation has been granted unlimited validity in the RMS.