COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Thiosix 10 mg and 20 mg, tablets (6-thioguanine)

NL License RVG: 114680 - 114681

Date: 26 April 2022

This module reflects the scientific discussion for the approval of Thiosix 10 mg and 20 mg. The conditional marketing approval was granted on 2 April 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

6-MP	6-mercaptopurine
6-MTG	6-methyl thioguanine
6-MTIMP	6-methylthiosine 5'-monophosphate
6-TG	6-thioguanine
6-TGN	6-thioguanine nucleotides
6-TGDP	6-thioguanine diphosphate
6-TGMP	6-thioguanine monophosphate
6-TGTP	6-thioguanine triphosphate
ADR	adverse drug reaction
AE	adverse event
ASMF	active substance master file
AZA	azathioprine
BP	British Pharmacopoeia
b.w.	bodyweight
CAI	colitis activity index
CD	Crohn's disease
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
DAI	Disease assessment index
DNA	deoxyribonucleic acid
DSS	dextran sulphate sodium
ECCO	European Crohn's and Colitis Organisation
EDMF	european drug master file
ERA	environmental risk assessment
EU	European Union
FDA	Food and Drug Administration of the United States
GCP	good clinical practice
GI	gastrointestinal
GLP	good laboratory practice
GPA	global physician assessment
HBI	Harvey Bradshaw Index
IBD	inflammatory bowel disease
ICC	initiative on Crohn's and colitis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
i.e.	*id est* (that is)
iv	intravenous(ly)
MAH	marketing authorization holder
MEB	Medicines Evaluation Board of the Netherlands
MTX	methotrexate
NRH	nodular regenerative hyperplasia
NVMDL	Nederlandse Vereniging van Maag-Darm-Leverartsen
PASS	post-authorisation safety study
Ph.Eur.	European Pharmacopoeia

PL	package leaflet
RBC	red blood cells
RH	relative humidity
RMP	risk management plan
SAE	serious adverse event
SmPC	summary of product characteristics
SOC	system organ class
SOS	sinusoidal obstructive syndrome
SCCAI	Simple Clinical Colitis Activity Index
TNF-α	tumor necrosis factor α
TPMT	thiopurine S-methyltransferase
TSE	transmissible spongiform encephalopathy
UC	ulcerative colitis
VOD	veno-occlusive disease
WBC	white blood cells

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a conditional marketing approval for Thiosix 10 mg and 20 mg tablets from Teva Nederland B.V. in 2015 pursuant to Article 10(3) of Directive 2001/83/EC.

6-Thioguanine (6-TG) medicinal product Thiosix is indicated for maintenance treatment in inflammatory bowel disease (Crohn's disease or ulcerative colitis) in patients not responding or intolerant to standard thiopurine therapy (azathioprine (AZA), mercaptopurine (6-MP)). A lack of response is defined by the inability to reach clinical remission as evaluated by global clinical assessment and the reduction of steroids to a dose of prednisolone or its equivalent of ≤10 mg/day between weeks 12 and 24 after start of treatment with a dosage of AZA≥ 2.0 mg/kg body weight or 6- MP ≥ 1.0 mg/kg body weight, and no signs of resistance to 6-TGN.

Thiosix is indicated for adult patients.

A comprehensive description of the indications and posology is given in the SmPC.

The national procedure that lead to the conditional marketing authorization of Thiosix concerned a hybrid application claiming essential similarity with the innovator product Lanvis 40 mg, tablets (NL RVG 07070) which has been registered in the Netherlands by Aspen Pharma Trading since 1975 (original product). A hybrid procedure was chosen as a new therapeutic indication was included in the application. This is considered acceptable.

The innovator 6-TG medicinal product Lanvis has been authorised for the treatment of acute leukaemia, especially acute myelogenous leukaemia and acute lymphoblastic leukaemia, as well as chronic granulocytic leukaemia. For adults the recommended dosing of Lanvis in the treatment of acute leukaemias is between 60 and 200 mg/m2 body mass surface. According to the MAH, 6-TG has been used off-label in the Netherlands since 2001 for the treatment of patients with inflammatory bowel disease (IBD) not responding to standard thiopurine treatment in a much lower dose of 0.3 mg/kg b.w. with a maximum of 25 mg per day.

In support of the application that lead to the conditional marketing authorization of 6-TG medicinal product Thiosix the MAH submitted literature data on the safety and efficacy of 6-TG in patients with inflammatory bowel disease. No new non-clinical studies were conducted. A non-clinical overview is sufficient for this product as it contains a well-known active substance. The results of a bioequivalence study with Thiosix 20 mg versus Lanvis 40 mg tablets study were also provided.

Scientific advice

Scientific advice was given in December 2010 with regard to the dossier requirements for this application.

Need for data on the long-term clinical effects of 6-TG

6-TG Medicinal product Thiosix was granted a conditional marketing approval on 2 April 2015 as the current MAH committed to provide long-term clinical data to confirm the posology and long-term efficacy and safety in the maintenance setting.

The submitted data that lead to the conditional marketing authorization of Thiosix are described and assessed below. The additional data on the long-term clinical effects of 6-thioguanine that lead to the full marketing authorization of Thiosix are described and assessed in Annex I below.

II. QUALITY ASPECTS

II.1 Introduction

Thiosix 10 mg tablets:
White to slightly yellow, round, flat, bevelled edge tablet without inscription. The tablet bears a score line and can be divided into equal halves.

Thiosix 20 mg tablets:
White to slightly yellow, round, flat, bevelled edge tablet without inscription.

The tablets contain active substance 10 mg or 20 mg of 6-thioguanine respectively.

The tablets are packed in PVC/PVDC-Aluminium blisters.

The excipients are microcrystalline cellulose, sodium starch glycolate, mannitol, magnesium stearate and silica colloidal anhydrous.

II.2 Drug Substance

The active substance is 6-thioguanine, an established active substance described in the British Pharmacopoeia (BP). It is a pale yellow crystalline powder, which is practically insoluble in water and in ethanol (96%). It dissolves in dilute solutions of alkali hydroxides. Thioguanine has a consistent polymorphic form. No chiral carbons are present. Two tautomeric forms are known.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Thioguanine is synthesised in one reaction step followed by purification. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance to the drug substance specification has been provided. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three pilot-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). The substance was very stable at both storage conditions. A retest period of two years in the proposed packaging material has been granted.

II.3 Medicinal Product

Pharmaceutical development

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

The development of the product has been described, the choice of excipients is justified and their functions explained. The objective of the development pharmaceutics was to obtain immediate release tablets containing qualitatively the same active substance as the product already on the market, Lanvis 40 mg, marketed by Aspen Pharma Trading Limited. The choices of the packaging and manufacturing process are justified in relation to the innovator. Breakability of the 10 mg tablets has been demonstrated according to the Ph.Eur. tablet monograph. The dissolution profiles for comparison to the innovator were obtained using four different media. Similarity was sufficiently demonstrated. The manufacture and composition of the batches used in the studies is identical to the marketed product. The biowaiver for the 10 mg tablet is justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured by dry granulation. The manufacturing process of the tablets is considered a standard process and has been adequately validated according to relevant European guidelines. Process validation data on the products has been presented for two production-scale batches.

Control of excipients

All excipients used comply with the requirements of their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, degradation,

breakability, dissolution, disintegration, resistance to crushing, friability, microbial purity and uniformity of dosage mass. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data form two production-scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided two production-scale batches per strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. The products are very stable at both storage conditions. A photostability study showed that the products are not sensitive to light. The 30 months shelf-life for both tablet strengths and no special storage condition is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting spongiform encephalopathies can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Thiosix 10 mg and 20 mg, tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Thiosix contains 6-thioguanine as active substance, which is a known active substance in treatment of leukemias. However, the MAH applied for a second line indication for inflammatory bowel disease (IBD), and the maximum dose is much lower than generally used in oncology indications (25 mg/day vs. 200 mg/m2).

Thiopurines such as azathioprine (AZA) or [6-]mercaptopurine ([6-]MP) are widely used as first-line maintenance drugs in the treatment of IBD. However, in clinical practice AZA and 6-MP are not effective in one-third of patients and up to one-fifth of patients discontinue thiopurine therapy because of dose dependent adverse events (AEs) and hypersensitivity reactions.

AZA and 6-MP are pro-drugs that undergo extensive metabolism. 6-TG is also a prodrug. These three substances share a common active metabolite 6-TG nucleotides (6-TGN), however 6-TG is converted more directly to the active therapeutic metabolite 6-TGN than AZA and 6-MP. AZA and 6-MP have additional active metabolites that are unlikely to occur following administration of 6-TG.

For this application no dedicated non-clinical studies have been performed with 6-TG, except one pharmacological study published by Kverka et al. (2011). The information provided is based on the available information in literature publications and in the Tabloid FDA label and the Lanvis SmPC.

III.2 Pharmacology

Metabolites of thiopurines have structural similarity to the endogenous purine-base guanine and incorporation in the deoxyribonucleic acid (DNA) of leucocytes results in strand breakage and subsequent immunosuppression. Additional immunomodulating properties mentioned are interference with protein and nucleic acid synthesis, failure of the DNA mismatch repair system, removing inhibition of T-cell apoptosis, and down-regulation of the expression of pro-inflammatory cytokines. Inhibition of purine de novo synthesis is an additional immunomodulating property of the thiopurines AZA and 6-MP. However, as this process is mediated by the metabolite 6-methylthiosine 5'- monophosphate (6-MTIMP) which is not formed during 6-TG metabolism, this mechanism of action will likely not be part of the immunomodulatory response of 6-TG (Van Asseldonk et al., 2009).

One proof of concept study has been performed and data were provided as literature reference (Kverka 2011). In this study acute or chronic colitis was induced in BALB/c mice by administration of one (nine days) or four cycles (five days DDS, nine days water) with 3% dextran sulphate sodium (DSS) dissolved in drinking water. In the acute model, animals were treated daily with 6-TG (10, 20 or 40 µg, oral) or AZA (30 or 60 µg, oral) or PBS for a total of nine days. Attenuation of DDS-induced colitis was seen with the mid and high dose of 6-TG but not of AZA. In the chronic model treatment was started after the second cycle up to end of the fourth cycle (for a total of 22 days) with either 6-TG (20 or 40 µg) or AZA (60 µg) or PBS. All thiopurine derivatives improved colitis, the 20 µg/day of 6-TG per dose was superior, because the 40 µg/day dose of 6-TG led to significant weight loss at the end of the therapy. In this study no signs of liver toxicity was seen in the 6-TG treated groups, while AZA appeared to induce histologic liver abnormalities.

The immunosuppressive effect of thiopurines is well known. Because of the different metabolism of AZA/6-MP and 6-TG, various metabolites which may be involved in hepatotoxic effects observed after AZA/6-MP treatment, are not formed after treatment with 6-TG. Levels of the metabolising enzyme TMPT level (for which genetic polymorphism is known) are an important factor for the determination of the possible side effects that may occur after treatment with AZA/6-MP, but also for how many thioguanine nucleotides (TGN) will be formed. While abundant TPMT levels will pose a possible risk for hepatotoxic side effects from 6-MMP, such a risk is not seen after treatment with 6-TG since 6- MTGs are much less associated with side effects.

III.3 Pharmacokinetics

Two publications were cited on urinary excretion of 6-TG and distribution of 6-TG in plasma, RBCs, liver, intestine and bile of mice. These studies used the i.p. route of administration. Data indicate that 25-30% of the administered dose is excreted in urine, mainly as unchanged 6-TG, and that levels in liver and intestine are 4-6 fold higher than in plasma or red blood cells. According to the Lanvis US label, only trace levels of 6-TG were present in brain (mice). As indicated, the pathway towards a shared active metabolite (6-TGN) differs between 6-TG and AZA/6-MP. Formation of Me-TMP from 6-TG is unlikely.

III.4 Toxicology

Publically available data on acute toxicity (mice), subchronic toxicity (mice), mutagenicity (in vitro, in vivo), reproductive toxicity (rat) of 6-TG was provided. Target organs are liver, hematopopietic tissue (resulting in reduced WBC and RBC), and gastro-intestinal tract. 6-TG was found to be mutagenic and teratogenic, and is considered potentially carcinogenic.

In a mouse study, it was found that sinusoidal obstructive syndrome (SOS)/nodular regenerative hyperplasia (NRH) is dependent on the 6-TG dose, and not a thiopurine class effect, thioguanine nucleotides are required for the pathogenesis of 6TG-SOS, and that inflammation plays a critical role in the pathogenesis of 6TG-SOS (Oancea et al., 2013). Also, it appeared that toxicity from TGN metabolites in the liver is not cumulative, probably because TGNs do not accumulate in hepatocytes, which is in contrast to activated lymphocytes or erythrocytes. This indicates that the risk for clinical NRH in patients is reduced by keeping the dose level as low as 25 mg/day max.

The Board noted that, considering the mechanism of action and the potential toxicity profile of 6-TG (mutagenic, teratogenic and potentially carcinogenic), exposure of the unborn infant is undesirable. A statement is included in section 4.6 of the SmPC that the use of Thiosix should be avoided during pregnancy, particularly during the first trimester. The applicant justified that a contraindication is not required. It is generally recommended for women with IBD only to become pregnant if the active condition is under control and the IBD is into remission. If a woman is pregnant and the IBD becomes active during pregnancy it is important for woman and child to treat the active condition. A contraindication for 6-TG during pregnancy would therefore not be appropriate if a patient is stable on 6-TG and altering the therapy is not indicated. During such an active phase of the condition, 6-TG may be the best therapy in the case alternative treatments may not be an option given the medical history of the patient.

Overall, the Board concluded that the safety profile of 6-TG is well known. There is substantial experience with 6-TG in humans using higher doses (in the oncology indication). Further animal studies are not needed.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The MAH argued that thioguanine containing products are being used off-label or prepared at the pharmacy for the IBD indications applied for. The products proposed for marketing will be

prescribed to replace these currently used products. The introduction of Thiosix 10 mg and 20 mg tablets into the market is unlikely to result in any significant increase in the combined volumes for all thioguanine containing products, and would thus not be expected to have an adverse effect upon the environment.

Besides, a product with a higher dose for another indication (Lanvis, treatment of leukaemia) is on the market. According to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447), there could be a rationale for the absence of an ERA, taking into consideration that a possible significant increase of environmental exposure to the drug substance is not very likely. Since this is applicable for Thiosix, a formal environmental risk assessment is not considered necessary.

III.6 Discussion on the non-clinical aspects

This product is a hybrid formulation of Lanvis 40 mg tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

From a non-clinical point of view 6-TG can be considered a safe and effective treatment option inpatients not sufficiently responding to or intolerant to other thiopurine treatment.

IV. CLINICAL ASPECTS

IV.1 Introduction

6-thioguanine (6-TG) is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

For this hybrid application, the MAH has submitted one bioequivalence study, which is discussed below.

Among others the following CHMP guidelines were taken into account in the assessment of the marketing authorisation application:

- Guideline on the development of new medicinal products for the treatment of Crohn's disease. July 2008 (CPMP/EWP/2284/99 Rev. 1)
- Guideline on the development of new medicinal products for the treatment of ulcerative colitis. January 2008 (CPMP/EWP/18463/2006 Rev. 1)

Medical guidelines:

- Dignass A, et al.; European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis. 2010 Feb;4(1):28-62

- Dignass A, et al.; European Crohn's and Colitis Organisation (ECCO). The second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management. J Crohns Colitis. 2012 6:991-1030
- Dutch Guideline Diagnostics and Treatment of IBD in Adults. In Dutch: Richtlijn Diagnostiek en Behandeling van Inflammatoire Darmziekten bij Volwassenen. Nederlandse Vereniging van Maag-Darm-Leverartsen. 2008

IV.2 Pharmacokinetics

The MAH conducted a pilot bioequivalence study in which the pharmacokinetic profile of the test product Thiosix 20 mg (Teva Nederland B.V., NL) is compared with the pharmacokinetic profile of the reference product Lanvis 40 mg tablets (Aspen Pharma Trading Limited, Ireland).

The choice of the reference product in the bioequivalence study is appropriate, as the formulation is registered in the Netherlands. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

In support of a biowaiver for the lower strength no data on linear pharmacokinetics is available. The bioavailability was evaluated at a 40 mg dose as this is the only available strength of the comparator. It may be possible that in case of less than proportional increase in pharmacokinetics, at this dose the sensitivity to detect differences between two formulations is less. However, the product is not developed as a generic and has a different indication than the comparator. Bioavailability is compared in the study. As such, and taken into account the comparable dissolution and dose proportionality between the 10 and 20 mg strength, the lack of information on linear pharmacokinetics is acceptable, and a biowaiver was granted. A separate bioequivalence study with the lower strength is not required.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 16 healthy subjects (eight males, eight females), aged 18-49 years. Each subject received a single dose of 40 mg (2 x 20 mg test or 1 x 40 mg reference) of one of the two thioguanine formulations. The tablet was orally administered with 200 ml water after an overnight fast. Fasting was continued for four hours after dosing. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10 and 12 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. Fasting conditions were applied, which is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 16 subjects completed the study and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of thioguanine (40 mg) under fasted conditions.

Treatment N=16	AUC_{0-t} <x>g.h/ml	$AUC_{0-\infty}$ <x>g.h/ml	C_{max} <x>g/ml	t_{max} h	$t_{1/2}$ h
Test	30.4 ± 16.5	34.8 ± 19.2*	7.3 ± 4.6	2.0 (1.0 – 4.5)	2.0 (1.0 – 5.0)
Reference	35.1 ± 34.3	34.1 ± 32.6#	11.1 ± 15.6	3.2 ± 0.9*	4.2 ± 3.8#
[+]Ratio (90% CI)	1.02 (0.73 – 1.41)	--	0.96 (0.64 – 1.43)	--	--
CV (%)	56.1	--	71.3	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

[+]*ln-transformed values*
**n=13; #n=15 due to inadequate estimation of the elimination phase*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are not within the bioequivalence acceptance range of 0.80-1.25. Therefore, based on the submitted bioequivalence study administration of two Thiosix 20 mg tablets does not show bioequivalence with one tablet of Lanvis 40 mg. Due to a high variability wide 90% CI are observed. However, the point estimates indicate comparable pharmacokinetics. Although bioequivalence using the confidence limits for a hybrid application was not strictly demonstrated, the data indicate comparable bioavailability and are considered sufficient to extrapolate efficacy and safety data obtained with the Lanvis formulation to the Thiosix formulation.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Pharmacodynamics

The applicant presented a brief description of the thiopurine pharmacodynamics based on the review by Asseldonk et al. (2009). This review extensively describes the current knowledge on the metabolism of thiopurines, the mechanism of action in IBD and the side effects related to various metabolites formed.

The scientific rationale for 6-TG in the treatment of patients with IBD resistant (lack of response and/or intolerant) to standard thiopurine therapy is based on a different metabolic pathway, resulting in the same active metabolites (6-thioguanine nucleotides - 6-TGN) but without the formation of potential toxic metabolites (6-MMPR). This justifies the use of 6-TG in patients intolerant to AZA/6-MP. Patients that do not respond to AZA/6-MP because they do not reach effective 6-TGN levels due to high TPMT activity and a preferential shunting to 6-MMPR, might also benefit from 6-TG. These patients would need to be identified before start of 6-TG.

The difference in metabolic pathway hampers a direct extrapolation of both efficacy and safety from classical thiopurines to 6-TG. For instance, additional active metabolites with immunosuppressive properties (such as 6-MTIMP) are formed after AZA/6-MP administration, however, their relative contribution to the overall efficacy in vivo is not known. In addition, the accumulation of 6-TGN after administration of AZA/-6-MP or 6-TG in the leucocytes (target cells) compared to erythrocytes might be different, which could potentially impact both efficacy and safety. On the one hand potential hepatotoxic metabolites are not formed after treatment with 6-TG. On the other hand updated nonclinical data indicate that 6-TGNs play a role in the vascular disorders of the liver such as SOS/VOD/NHR caused by thrombotic and/or endothelial injury of the microvasculature and this effect was dose-dependent for 6-TG.

Overall, despite the uncertainties on the impact of certain differences in metabolic pathway, 6-TGN metabolites are considered to contribute most to the immunosuppressive effect of thiopurines. Therefore, the shared active metabolites provide a scientific rationale for use of 6-TG in the treatment of IBD.

IV.4 Clinical efficacy

Clinical experience

The applicant refers to 20 literature references between 2001 and 2011 in support of efficacy and safety, including about 788 IBD patients treated with 6-TG in a dose range of 10-100 mg per day. Based on the mean/median duration 101 patients received 6-TG for <6 months, 206 patients for 6-12 months and 481 patients for > 12 months. Most of the patients were between 18-65 years of age (mean/median age 40 years) at the start of 6-TG treatment. Studies were primarily conducted in Western Europe (the Netherlands, Germany, France, UK), and therefore the vast majority of the subjects were very likely Caucasian. A median/mean daily 6-TG dose of <25 mg per day (proposed dose) was administered to a total of 309 patients, with 57 patients receiving this treatment for less than six months (Derijks et al. 2003; de Boer et al. 2005b), 70 patients between six months and one year (Dubinsky et al. 2003b; Bonaz et

al. 2003), and 182 patients received low dose 6-TG for over one year (Gilissen et al. 2007, de Boer et al. 2008, de Boer et al. 2005a, van Asseldonk et al., 2011).

There were no studies with a randomized controlled design using the proposed or other formulations of 6-TG. The studies performed are either prospective, uncontrolled studies in a clinical research setting or retrospective database studies. The drug is only used in a few specialized centres in the EU and not recommended for routine use. At the time of submission of the marketing authorization application, European treatment guidelines on IBD (European Crohn's and Colitis Organisation (ECCO)) did not recommend the use of 6-TG, due to the liver abnormalities that have been reported, mostly nodular regenerative hyperplasia (NRH).

Efficacy

The applicant presented 11 uncontrolled studies (prospective and retrospective) to support the efficacy of 6-TG in the target population. These included 307 patients, of which two thirds were intolerant to AZA/6-MP. Five studies had a median duration of six-nine months, two studies had a median follow-up up till 22 months. The dose of 6-TG varied between 20-80 mg/day, the median dose in the majority of studies was 40 mg/day. Patients received various concomitant induction treatments for IBD. Response and/or remission rates varied between 35% to 89% using different measures for efficacy outcomes and the highest rates are based on the proportion of patients remaining in the study (Qasim et al. 2007).

No dose-finding studies have been performed, but the proposed 6-TG dosage was based on the dosages that were used in the published studies. Of the four studies presented by the applicant into more detail, the study by Bonaz et al. 2003 is most relevant as this study was primarily aimed at efficacy and all patients except one were treated with the proposed dose of 20 mg/day. This study included 49 patients of which 39 were intolerant to AZA/6-MP. Forty of the 49 patients (82%) presented with an active disease and/or were still on corticosteroids at the initiation of 6-TG therapy. Remission was seen in 52% (21/40) of patients during the median follow-up of seven months (range 1-20 months). Relapse occurred in 21% (6/28) of patients with a median follow-up of five months (1-12 months).

Based on the submitted data, the reported efficacy rates for the higher doses (40 mg) of 6-TG in IBD (35% to 89%) were in the same line as that of the low dose (20-25 mg) of 6-TG (52%, median follow-up seven months) and reported for AZA/6-MP in literature (77% after one year). These results are also comparable to the reported placebo rate being 55% at one year based on what is known for AZA/6-MP (Prefontaine et al. 2009, 2010).

At the time of submission of the marketing authorization application, limited long-term efficacy data are available, whereas 20% of patients relapsed after a median time of five months (Bonaz et al. 2003), which may increase over time. Further long-term data will be gathered to support the indication for maintenance treatment for at least one year. The applicant states that a total number of 182 patients received low-dose 6-TG over one year within the safety studies performed in the Netherlands, the largest safety study included 95 patients (de Boer et al. 2008). In view of the fact that the study was not designed for evaluating efficacy, but only to gather safety data, the results are considered circumstantial evidence for efficacy.

Although the studies based on clinical practice using higher doses suggest a beneficial effect in IBD and potentially an earlier effect compared to classical thiopurines, a robust estimation of the effect size at the proposed low dose of 6-TG in IBD compared to placebo or established treatment is lacking. To this end additional data would need to be gathered in a substantial number of both resistant and intolerant patients. It was uncertain whether the efficacy data obtained with the higher 6-TG doses could also apply to the lower dose as no studies using two doses are available. The interpretation of the effect size is further hampered by the high known placebo response rate in IBD patients.

No bioavailability data are available to extrapolate efficacy of AZA/6-MP treatment at the established dose to that of the proposed dose of 6-TG based on levels of shared active metabolites in the target cells. In contrast, based on data from use of thiopurines in the treatment of leukaemia, estimated levels of 6-TGN in white blood cells are about 3-times lower after 6-TG compared to AZA/6-MP treatment at the established dose. However, the actual levels in IBD at the proposed dose and implications for efficacy in IBD are not known.

Use in clinical practice forms the basis for this application at the proposed low dose of 6-TG. Approximately 750-1000 IBD patients were estimated to be treated with 6-TG in the Netherlands, according to gastroenterologists of the VU Medical Centre in Amsterdam. Available literature data from clinical practice in the Netherlands constitute a minority of the total number of patients estimated to be treated, with a maximum of about 180 patients continuing treatment for > one year, but efficacy data are lacking.

There is a scientific rationale for use of 6-TG in patients intolerant to classical thiopurines based on the differences in metabolic pathway and shared active metabolites 6-TGNs. Use of 6-TG in patients resistant to AZA/6-MP is plausible provided resistance is related to too low TGN-levels. Measurement of 6-TGN levels is however not commonly performed in clinical practice.

Limited data were available in patients with UC. However, these do not raise a concern and AZA/6-MP is known to have an established efficacy profile in both Crohn's disease and UC. Thiosix is not indicated in the paediatric population since little is known about use in children and adolescents with IBD.

The majority of studies used the Lanvis formulation and no studies have been performed with the proposed formulation. Although bioequivalence using the confidence limits for a generic application was not strictly demonstrated, the data indicated comparable bioavailability and are considered sufficient to extrapolate efficacy and safety data obtained with the Lanvis formulation to the Thiosix formulation.

Overall, based on the data presented, the efficacy of 6-TG in IBD has been sufficiently demonstrated for short term treatment. In support of the maintenance indication additional data would be provided regarding posology and long term efficacy.

IV.5 Clinical safety

Overall, based on mean/median duration 101 patients received treatment with 6-TG for < six months, 206 patients for 6 – 12 months and 481 patients for >12 months. A median/mean daily 6-TG dose of <25 mg per day was administered to a total of 309 patients, with 57 patients receiving this treatment for less than six months, 70 patients between six months and one year, and 182 patients received low dose 6-TG for over one year.

The most commonly reported adverse events (AEs) leading to discontinuation were gastrointestinal complaints (such as nausea and vomiting), general malaise, hepatotoxicity, and myelotoxicity. Pancreatitis was rare. The retrospective database study by De Boer et al. (2005a) can be considered the most relevant given that all patients received the proposed dose and included the largest number of patients (n=95). A total of 26 events were reported in 20/95 patients discontinuing 6-TG, frequency in between brackets: gastrointestinal (GI) complaints n=8 (31%), hepatotoxicity n=4 (15%), myelodepression n=1 (4%), pancreaticotoxicity n=1 (4%), general malaise n=4 (15%), allergic reaction n=1 (4%) and other n=7 (27%). When 6-TG was discontinued, the side effects leading to withdrawal resolved spontaneously.

Qualitatively, the safety profile resembles what is known for classical thiopurines, pancreatitis appears to occur less often. A retrospective database study from the Netherlands showed that after administration of AZA, AEs can be subdivided into hepatoxicity (32%), gastrointestinal complaints (19%), myelosuppresion (12%), pancreatitis (11%), fever (11%), general malaise (9%), arthralgia (8%) and others (12%) (Jharap et al. 2010). Discontinuation rates due to tolerability issues varied between 7-34% throughout the studies and was about 20% in two retrospective database studies performed in the Netherlands with the proposed dose (de Boer et al. 2005a and van Asseldonk et al. 2011). This indicates that about 80% of patients intolerant to AZA could tolerate 6-TG. No deaths related to 6-TG were reported in any study.

Of major concern, however, is the occurrence of nodular regenerative hyperplasia (NRH). NRH is a liver condition characterized by a benign transformation of the hepatic parenchyma spread throughout the liver to result in small regenerative nodules. As a consequence, NRH may result in a form of portal hypertension: it typically presents with an unexpected onset of signs related to portal hypertension (weakness, ascites, splenomegaly, oesophageal varices). This usually in a patient with overall little or no evidence of prior chronic liver disease. Frequencies of NRH varied between 18-62% in five studies using 6-TG doses between 20-80 mg/day; the median 6-TG dose was 40 mg/day in most studies. On the other hand, four studies did not report NRH, of which three studies were performed in the Netherlands including 53 patients (Gilissen et al. 2007, de Boer et al. 2008, van Asseldonk et al. 2011). There are no studies using both doses of 20 mg and 40 mg to support the assumed dose-relationship and NRH was reported (6/24, 25%) in a study by Ferlitsch et al (2007) where at least low doses (median 10 mg) were used at the time of liver biopsy. Within their response, the applicant submitted an article in preparation by Asseldonk et al (2014) including 115 patients with liver biopsies who all received low dose 6-TG. They reported a frequency of NRH of 6% with the proposed low dose of 6-TG. This study confirms that NRH can exist without clinical symptoms. Reference is also made to publications on NRH in IBD patients who were not treated with thiopurines and healthy persons who were not treated with thiopurines, showing frequencies of 6% (De Boer et al. 2008) and 2.6% (Wanless et al. 1990) respectively.

Uncertainties remain on the true incidence of adverse events related to 6-TG due to the uncontrolled nature of the studies and small size, which also prevents detection of less frequently occurring events. Further, the studies in IBD lack information on methods for AE collection or AE reporting. Adverse events and frequencies in section 4.8 of the SmPC are currently based on thioguanine use in the haematology setting. A statement is included that the frequencies of AE in IBD might be different and additional information will become available post marketing. This approach is acceptable.

The current data indicate that lowering the dose from 40 mg to 20 mg daily may reduce the frequency of NRH, although no human data are available on a direct comparison between the low and higher doses. Some support for a dose-effect relationship is derived from the presented murine model (Oancea et al. 2013) and an observational study in humans (Pavlidis 2014) using a split dose regimen (twice the currently proposed dose). The true incidence of NRH remains unknown. A major limitation of the study by Van Asseldonk (2014) is that data were not obtained in a protocolled manner (timing of liver biopsy differs widely) and the proportion of patients treated with 6-TG who had a liver biopsy done is not known. Further, frequencies reported may be dependent on the patient's willingness to perform a liver biopsy which might result in an over- or underestimation of the real incidence. Many uncertainties remain with regard to covariates that could impact the reported frequency, such as IBD itself, prior use of AZA, etc. The same limitations, however, apply to other publications reporting (higher) frequencies of NRH. Inflammatory diseases have been associated with the occurrence of NRH and compared to what is known from IBD patients not using thiopurines the frequency of NRH with low dose 6-TG might be in the same order of magnitude, although data should be interpreted cautiously. Further, low dose 6-TG has been used in an estimated population of 750-1,000 IBD patients and no deaths or serious clinical complications have been reported. Based on the totality of data, the safety profile could be acceptable provided additional data on the incidence of NRH would be obtained post marketing.

Given the lower frequency of NRH reported in the study by Van Asseldonk (2014) the applicant proposed to drop the routine liver biopsies which were based on a recommendation by a European expert group (de Boer et al. 2006). This could be considered acceptable given the guidance and warnings included in the SmPC on liver toxicity. Further, a recommendation to stop 6-TG in case of lack of response is included to minimize exposure. There is no need for a specific warning on use in patients with elevated liver enzymes or signs of liver pathology which occurs often in IBD patients independent of therapy.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Thiosix 10 mg and 20 mg, tablets.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• GI complaints • Myelosuppression • Hepatotoxicity – Nodular Regenerative

	Hyperplasia
Important potential risks	• Carcinogenicity • Teratogenicity
Missing information	• Use in paediatric population • Use during pregnancy and lactation

Following the concern of the MEB on long-term safety with regard to Nodular Regenerative Hyperplasia (NRH), a Post-Authorisation Safety Study (PASS) was proposed as additional pharmacovigilance activity. Recording of adverse events, liver toxicity and NRH incidence are part of the protocol for the studies with 6-TG naïve and ongoing patient groups, receiving treatment at the recommended dose level.

Annual progress reports would be submitted after conditional approval. The RMP as laid down by the applicant is approvable.

IV.7 Discussion on the clinical aspects

6-Thioguanine is a well-known immunosuppressive agent and licensed for the treatment of leukemia. Classical thiopurines (AZA/6-MP) have a well-established efficacy and safety as first-line treatment in maintenance of remission in IBD. The use of 6-TG within the experimental clinical setting of IBD is driven by the need for additional therapies. Other strategies currently explored to optimize azathiopurine therapy in IBD patients with inadequate thiopurine metabolite concentrations is the addition of low-dose allopurinol to dose-decreased AZA, also by the VU Medical Centre (Hoentjen et al. 2013).

There is a scientific rationale for use of 6-TG in patients intolerant to classical thiopurines based on the differences in metabolic pathway and shared active metabolites 6-TGNs. Use of 6-TG in patients resistant to AZA/6-MP is plausible provided resistance is related to too low TGN-levels. Measurement of 6-TGN levels is not commonly performed in clinical practice and there is only few data available from clinical practice.

The majority of data were obtained from use of 6-TG in patients intolerant to classical thiopurines.
Available data indicate that a considerable part of patients intolerant to AZA/6-MP tolerate 6-TG in the short-term, most likely because certain toxic metabolites are not formed after 6-TG metabolism. The safety profile resembles that known for thiopurines. However, 6-TG appears to be associated with an increased risk of NRH in the long term which could potentially also lead to irreversible liver damage. The actual extent of NRH at the proposed dose was unclear as is the relationship to the background incidence of NRH in patients with IBD without thiopurines. The lower frequency of NRH reported with the low proposed dose of 6-TG is supported by nonclinical data indicating a possible dose-response relationship for 6-TG and liver toxicity. Adequate monitoring and timely complete abrogation of 6-TG may minimize the risks. A clear guidance statement when to stop treatment with 6- TG in case of lack of response was included in section 4.2 of the SmPC to avoid unnecessarily long treatment. Additional data

on the incidence of NRH need to be obtained post marketing. The follow-up and monitoring of the incidence of NRH has been laid down in the RMP.

Efficacy of 6-TG cannot be simply extrapolated from what is known from AZA/6-MP due to the differences in metabolic pathway. This pertains to additional active metabolites formed after AZA/6-MP and potential different accumulation in the target cells. Given the available knowledge from the pertinent patient variability in response to AZA and 6-MP in patients with IBD and the large (genetic) variance in purine metabolism in general, treatment responses to 6-TG in IBD will be highly variable in virtually all patient groups, irrespective of response to previous or concomitant therapy. On top of this, IBD is an illness with a highly variable disease course in terms of severity, onset-duration dynamics, concomitant diseases and placebo response to any therapy (up to 50%).

Essentially the evidence of short-term efficacy is based on pharmacological extrapolation from AZA/6- MP experience in IBD, supplemented with, not particularly very robust (most studies were retrospective and/or uncontrolled), but overall sufficiently supportive, data from 20 studies conducted between 2001 and 2011, including a total 788 IBD patients treated with 6-TG, 309 patients with the proposed dose of 6-TG of <25 mg per day. The majority of these patients were intolerant to AZA/6-MP. Concerns remain on the magnitude of the beneficial effect of the proposed 20 mg/day (maximum of 25 mg/day) dose. The MEB accepts that this dose was chosen merely for safety reasons, but the data to support the proposed posology remain rather limited. Moreover, the MEB is not convinced that the available long-term data are sufficiently robust to support of the maintenance indication. Whether lowering the daily dose is the optimal strategy taking into account efficacy as well is not known; another option currently explored is a split dosing regimen of the higher dose of 40 mg (Pavlidis 2014) which also might reduce the risk of NRH.

The relative efficacy of 6-TG as compared to TNF-α inhibitors is not known. Experts considered low dose 6-TG a rescue drug for maintenance of remission in IBD patients failing and/or intolerant to all evidence-based conventional therapies, including TNF-α inhibitors (de Boer et al. 2006). This is mainly driven by the concern on NRH. The available data at the time of marketing authorization application suggest that the incidence of NRH might be lower than initially reported. Based on the mechanism of action 6-TG can be considered to be used next in line to classical thiopurines. The decision whether to start 6-TG or TNF-α inhibitors might be decided upon by the treating physician and in that respect 6-TG would add to the therapeutic arsenal. Patients with a lack of response should stop within a defined period of time and these could be switched to TNF-α inhibitors.

Overall, taking into account the pharmacodynamic rationale and the available data from clinical practice, it has been sufficiently shown that patients with IBD may benefit from short-term 6-TG therapy.

For this marketing authorisation application, reference is made to the clinical studies and experience with the innovator product Lanvis 40 mg, tablets. Two new clinical studies were conducted that address the long-term efficacy and safety of Thiosix. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profiles of the proposed and

reference product are similar. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The test consisted two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Thiosix 10 mg and 20 mg, tablets have a proven chemical-pharmaceutical quality and are hybrid forms of Lanvis 40 mg, tablets. Lanvis is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. Furthermore, the MAH has provided two long-term register studies (can be found in Annex I) which adequately confirm Thiosix efficacy and safety.

In the Board meeting of 2 April 2015 , the Board decided to grant the **conditional marketing authorisation** for Thiosix 10 mg and 20 mg, tablets. The condition for this authorisation was that the MAH would create a registry based on:

- Study TS-001 on the effectiveness and safety of 6-thioguanine (6-TG) in the treatment of inflammatory bowel disease (IBD) in 6-TG naïve patients.
- Study TS-002 on the effectiveness and safety of 6-TG in the long-term treatment of IBD.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a conditional marketing approval. Thiosix 10 mg and 20 mg, tablets was authorised in the Netherlands on 2 April 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Code M	Addition additional monitoring status	SmPC	14-4-2015	Approval	--
Code P	Addition protocol and SAP	None	13-7-2015	Approval	--
Code M	Change in additional monitoring status	SmPC	19-6-2015	Approval	--
Type IA B.III.2.b	Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	None	13-1-2016	Approval	--
Type 1B B.I.d.1.a.4	Extension or introduction of a retest period/ storage period supported by real time data	SmPC, PL	13-1-2016	Approval	--
Type IA B.I.b.1c	Addition of a new specification parameter to the specification with its corresponding test method	None	10-12-2016	Approval	--
Type IA B.I.b.2a	Minor change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	None	10-12-2016	Approval	--

Type T	Addition readability test	PAR	18-1-2017	Approval	--
Type IB C.I.z	QRD update	SmPC	28-6-2017	Approval	--
Type IB C.I.2 a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/ biosimilar medicinal products following assessment of the same change for the reference product	SmPC	28-6-2017	Approval	--
Type IAin B.II.b.2.c.1	Replacement or addition of a manufacturer responsible for importation and/or batch release not including batch control/testing	None	1-2-2019	Approval	--
Type IB B.I.a.z	Addition of an alternative manufacturer for the starting material of active substance	None	1-4-2019	Approval	--
Type PSUR	Addition of PSUR	None	25-9-2019	Approval	--
Type IAIN C.I.3.a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a	SmPC, PL	19-12-2019	Approval	--

	procedure concerning PSUR or PASS				
Type IA A.7	Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient	None	31-3-2020	Approval	--
Type IB B.I.a.z	Addition of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient	None	31-3-2020	Approval	--
Type IB C.I.z	Update of SmPC and PIL according to Excipient-Guideline EMA/CHMP/302620/2017	SmPC, PL	23-9-2020	Approval	--
Type IA B.I.b.2.a	Minor change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing	None	25-4-2021	Approval	--

	process of the active substance				
Type PSUR	Addition of PSUR	None	30-11-2021	Approval	--
Type IA B.II.b.4.a	Change in the batch size (up to 10 fold) (including batch size ranges) of the finished product	None	17-1-2022	Approval	--
Type IAin C.I.12	Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	None	11-4-2022	Approval	--

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ANNEX I – SUBMISSION OF TWO LONG TERM EFFICACY STUDIES FOR THE APPROVAL OF THE MARKETING AUTHORISATION (RVG 114680 & 114681)

Recommendation

Based on the review of the data on safety and efficacy, the member state considers that the marketing authorisation application for Thiosix for the change of the conditional marketing approval to a regular marketing authorisation is approvable. Long-term efficacy and safety data have been provided and these were considered adequate.

Scope of the variation

The MAH applied for a marketing authorisation for Thiosix 6-TG tablets via the national application procedure. 6-TG Medicinal product Thiosix was authorized for marketing in 2015 on the condition that the long-term clinical effects of 6-TG would be evaluated in two registry studies. The design and results of these studies are discussed below.

Long term efficacy studies

TS-001: A 6-TG registry that explores the effectiveness and safety of 6-TG in the treatment of IBD in 6-TG naïve patients

Introduction
Study TS-001 is a prospective registry study on treatment with 6-TG medicinal product Thiosix in patients with IBD. The investigators' intention was to collect data reflecting the real-life use of Thiosix in patients with Crohn's disease (CD) and UC who responded inadequately (lack of response and/or intolerance) to standard thiopurine therapy (AZA and/or 6-MP). This information is used to compare the effectiveness of 6-TG in the subgroup of CD patients, to that of a historical control group of CD patients using methotrexate (MTX) (Seinen et al. 2013).

Study objectives
The objectives of this study were:

- Examine the effectiveness of 6-TG medicinal product Thiosix for maintenance treatment in 6-TG naïve UC and CD patients
- Examine the effectiveness of the current dosing scheme for 6-TG medicinal product Thiosix in 6-TG naïve IBD patients
- Compare the effectiveness of 6-TG medicinal product Thiosix with effectiveness of MTX in an external cohort of CD patients (historical matched control group)
- Characterize the IBD patient population for which 6-TG maintenance therapy is beneficial
- Monitoring of adverse drug reactions (ADRs), serious adverse events (SAEs), and signs of liver toxicity and NRH during maintenance treatment with 6-TG medicinal product Thiosix in 6-TG naïve IBD patients.
- Evaluation of the duration in which 6-TG medicinal product Thiosix was used (drug survival) and reasons for discontinuation of Thiosix therapy

Study population and treatment
In total 108 6-TG treatment naïve IBD patients are included. The patients received treatment (6-TG) corresponding to their bodyweight, which is acceptable. Furthermore, corticosteroid use at timepoint zero was not permitted. The following analysis sets were defined:

- **Efficacy analysis set 1:** this data set contained all patients who had a confirmed CD or UC diagnosis, reached complete steroid-free remission within 6 months after starting TG treatment with a dose ≤ 25 mg and had a non-missing value for the reason to start TG treatment. Steroid-free remission was defined as HBI < 5 or SCCAI ≤ 2 in absence of use of corticosteroids. Patients with IBD-undetermined, with a missing HBI/SCCAI score at T0, or patients who used corticosteroids and/or biological medications at T0 were excluded from this set. Patients who received Thiosix treatment up to 60 days before study entry were included in this analysis set.
- **Efficacy analysis set 2:** this data set contained all patients from Efficacy analysis set 1 who had a confirmed CD diagnosis plus all CD patients from the historical MTX cohort. This group will be used to compare the efficacy of TG treatment in the subgroup of CD patients.
- ***Modified* efficacy analysis set 1:** this data set consisted of all patients from the Efficacy analysis set 1 excluding patients with TG treatment up to 60 days before study entry (baseline visit).
- ***Modified* efficacy analysis set 2:** this data set consisted of all patients from the Efficacy analysis set 1 excluding patients with TG treatment up to 60 days before study entry (baseline visit), as well as patients with biological use up to 1 year before baseline.

Study parameters
Several parameters will be used to assess both efficacy and safety:

- Disease activity index (DAI):
    - For CD patients: Harvey Bradshaw Index (HBI, Harvey and Bradshaw 1980). The score for each item (see Table 3) and the type of complication were included in the database. A score of < 5 indicates that the patient is in remission (Vermeire et al., 2010).

Table 3. Harvey Bradshaw index

Clinical parameters	Score
General well-being	0 = very well, 1 = slightly below average, 2 = poor, 3 = very poor, 4 = terrible
Abdominal pain	0 = none, 1 = mild, 2 = moderate, 3 = severe
number of liquid stools per day	Number
Abdominal mass	0 = none, 1 = dubious, 2 = definite, 3 = tender
Complications	One point for each complication

    - For UC patients: Simple clinical colitis activity index (SCCAI, Walmsley et al., 1998). The score for each item (Table 4) were included in the database. A score of < 2 indicates that the patient is in remission (Walsh et al. 2014, Jowett, 2003).

Table 4. Simple Clinical Colitis Activity Index

Clinical parameters	Score
Bowel frequency during the day	0 = 1-3, 1 = 4-6, 2 =7-9, 3 = >9
Bowel frequency at night	1 = 1-3, 2 = 4-6
Urgency of defecation	1 = hurry, 2 = immediately, 3 = incontinence
Blood in stool	1 = trace, 2 = occasionally frank, 3 = usually frank
General well being	0 = very well, 1 = slightly below average, 2 = poor, 3 = very poor, 4 = terrible
Extracolonic features	1 per manifestation

  - IBD-undetermined: scores as appropriate.
- Concomitant corticosteroids use
- Concomitant other IBD medication
- C-reactive protein levels (normal level CRP < 10 mg/l)
- Faecal calprotectin levels (normal level FCP: < 100 microg/g faeces or < upper normal limit related to the test used)
- Endoscopic findings
- Patient being in remission according to physician's judgement

To avoid inter-observer variability, every effort should be made to ensure that all assessments are made or discussed with the same investigator, who is the primary responsible physician for the patient's treatment.

Safety Parameters
The following safety assessments will be recorded in the study database:
- AEs, including severity and relation to 6-TG
- Reason for 6-TG discontinuation
- Complete blood count
- Safety laboratory data/ signs of liver toxicity :

1. Clinical signs of NRH or non-cirrhotic portal hypertension
2. Histologically confirmation of NRH

Efficacy analysis set 1

Maintenance of remission, allowing 1 steroid course < 3 months
Thus far, about 45% (95% C.I. 0.363 – 0.548) of study patients remained in steroid-free remission for more than 1 year. The subgroup analyses indicate that maintenance of remission may be obtained in CD and UC patients who experienced adverse effects upon treatment with conventional thiopurines, in those with an insufficient response to other thiopurines, as well in patients who experienced adverse events and an insufficient response to other thiopurines. The lowest remission rate is observed for the subgroup of patients who experienced adverse effects, but not an insufficient response, on conventional thiopurines of which approximately 40% are still in steroid-free remission at 12 months with a lower limit of the confidence

interval of approximately 30%. Observed remission rates vary to some extent across the different subgroups. However, the variation is limited and observed remission rates in all subgroups can be considered clinically relevant considering these rates and also potential safety risks of biological treatment (e.g. increased risk of infections). Because of this, 6-TG may be considered for all subgroups. CD And UC patients who had an insufficient response to other thiopurines appear to have the highest probability of maintaining remission for at least 12 months.

The overall target efficacy of 55% was not reached. Therefore, the MAH submitted publications from medical literature and expert opinions to substantiate its position that a remission rate of 45% is clinically relevant. It is remarked that the study settings and endpoints of studies in literature differ to some extent from those in the registry studies.

In a publication by Almer et al. (2008) on the clinical effects of 6-TG in CD patients, a remission rate of 35% based on HBI and global physician assessment (GPA) scores was observed at 12 months in patients refractory to azathioprine and 6-mercaptopurine. In other publications on 6-TG treatment, in which patients were not necessarily treatment-refractory to azathioprine and/or 6-mercaptopurine and remission rates were not necessarily evaluated by HBI and/or SCCAI, observed corticosteroid-free remission rates at 12 months ranged from 43% (Ward et al. 2017) up to 65% (Bayoumi et al. 2020).

Taking into account the aforementioned limitation with respect to the interpretation of the study results, the remission rates for active substances of medicinal products which are authorized for marketing for CD and UC patients appear to be comparable or lower. For CD patients, remission rates after a treatment period of about 12 months were reported for infliximab (18-38%), adalimumab (36-41%), vedolizumab (25-45%), and ustekinumab (37-47%). More specifically, corticosteroid-free remission rates after a treatment period of about 12 months were reported for infliximab (18-38%), vedolizumab (29-45%), and ustekinumab (37-47%). For UC patients, remission rates after a treatment period of about 12 months were reported for infliximab (20.2-37.9%), golimumab (25-41%), vedolizumab (31-46%), and ustekinumab (38-53%). More specifically, corticosteroid-free remission rates after a treatment period of about 12 months were reported for golimumab (33-41%), vedolizumab (31-46%), and ustekinumab (38-53%).

Taking into account aforementioned study results with respect to 6-TG and other active substances, a corticosteroid-free remission rate of 45% after 12 months of maintenance treatment may also be obtained in CD and UC patients who were intolerant to, or who had an insufficient response to azathioprine and/or 6-mercaptopurine. The submitted opinions of gastroenterological and patient associations support that a corticosteroid-free remission rate of 45% after 12 months of maintenance treatment is also clinically relevant for CD and UC patients in remission who were intolerant to, or who had an insufficient response to azathioprine and/or 6-mercaptopurine. From these results it can be concluded that the observed 45% corticosteroid-free remission rate can be considered clinically relevant.

Maintenance of complete steroid-free remission at 12 months

There are only few numerical and proportional differences between the analysis including <3 months steroid treatment and this analysis (44% effectiveness vs. 45% effectiveness in Efficacy

Set 1), where the difference is created by 2 CD patients who discontinued 6-TG within 3 months of T0. It is therefore reasonable to assume that steroid treatment of <3 months was no major factor in maintaining remission in > 12 months of treatment. This was considered acceptable.

Concomitant treatments during 12 months after T0

The MAH gathered data on concomitant medication during 6-TG treatment as much as possible and recorded in the study database per visit. However, data on the exact start and stop dates were not actively recorded. Therefore, these data on use and duration of concomitant medication were based on the reported medications at every visit. Concomitant use of corticosteroids, biological medications and surgery were investigated in this way.

The use of corticosteroids will hamper the comparison with general literature as in literature a remission is considered a steroid-free remission. Therefore the MAH submitted analysis of a complete corticosteroid-free remission. Additionally, the MAH provided data on biological treatments initiated during the treatment with 6-TG. The MAH defined these patients as failure to 6-TG treatment, which is considered acceptable as well. Finally, surgery was found not to influence the effectiveness parameters.

Analysis of disease scores (HBI and SCCAI)

All patients were in remission at T0. The mean HBI score at T0 was 1.94 (SD 1.56). The mean score increased slightly over time to a mean score of 2.51 (SD 2.70) at month 12. All means remained under the score of 3 over the entire study.

The mean SCCAI score at T0 was 0.95 (SD 0.909). This score increased in month 3 to 2.04 (SD 3.156). The mean scores decreased to 1.41 (SD 2.52) in month 12.

Of patients 13.9% (13.6% for CD patients and 14.3% for UC patients) retained steroid-free remission at 12 months with HBI scores of ≤ 4 or SCCAI scores ≤2 throughout the study as well as CRP and FCP levels under the ULN of 10 mg/l and 100 µg/g respectively. These results are efficacy indicating and are therefore considered acceptable.

Effectiveness analysis of GPA

Based on the physician's assessment, 61% of the patients was in remission at T0. Hence, some patients were in steroid-free clinical remission at T0, but were not considered in remission according to the GPA. However, a steady increase of patients in remission according to (available) GPA scores is seen over time (61% at baseline to 82% at month 12).The steady increase of GPA is considered meaningful in this context as is supports the information derived from the primary endpoints and the other secondary endpoints.

Efficacy analysis Modified efficacy dataset 1 and 2

Modified efficacy analysis set 1 is a modification of the Efficacy analysis set 1 where 8 patients have been removed due to Thiosix 6-TG use up to 60 days before study entry (baseline). It was found that there are few numerical and proportional differences between the analysis including <3 months steroid treatment and this analysis, where the impact is only seen in the group of CD patients with a difference of 2 patients who would have gone out of remission

within 3 months had they not been allowed to receive one short course of steroid therapy <3 months. According to the MAH, it is therefore reasonable to assume that steroid treatment of <3 months is no major factor in maintaining remission in > 12 months of treatment. Remission was maintained for 12 months after T0 in a proportion of 0.44 of the study population in *Modified* efficacy analysis set 1 (95% C.I. 0.347 – 0.538). The proportion of CD patients with maintenance of remission until 12 months after T0 was higher than the proportion of UC patients (0.484 vs. 0.368).

Modified efficacy analysis set 2 aimed to compare the historical data of 174 CD patients with MTX treatment (Seinen et al. 2013) with data of 67 CD patients with Thiosix 6-TG treatment in Efficacy analysis set 1. Upon request by the authorities, patients were excluded from this analysis when patients had previously used TNFα-inhibitors or other biological medication for the treatment of IBD. This reduced the number of CD patients in the MTX treatment set to 136 patients and in the Thiosix 6-TG treatment set to 52 patients. These groups together are defined as Efficacy analysis set 2 (n= 188). The percentage of patients who remained on MTX treatment for at least 18 months was 67% (87 out of 129 patients) versus 79% (41 out of 52 patients) in the Thiosix 6-TG treatment group.

A comparison of 6-TG to methotrexate (external control study) was made for the endpoint drug survival within 12 months. No significant difference was found in the unadjusted analysis and the mean times of drug survival of these active substances was found to be similar. Treatment differences between the clinical effects of 6-TG in CD patients in study TS-001 and those of methotrexate in CD patients in the external control study tended to become larger after adjustment for confounders. This trend was observed in separate analyses using propensity score classes, using propensity score matched pairs, and inverse probability treatment weights. In none of aforementioned analyses, the difference between the adjusted and unadjusted analysis was statistically significant.

Conclusion

In total, 61% of patients who reached steroid-free remission maintained their remission during 6 months of monotherapy in Efficacy analysis set 1, which allowed one course of steroid therapy of < 3 months. Forty five percent (45%) of 108 patients remained in corticosteroid-free remission for longer than 12 months. The group of CD patients (n= 66) had a longer remission time on 6-TG than the UC group (n= 42) with 48% of CD patients remaining in steroid-free remission for >12 months after T0 as opposed to 40% in the UC group.

The percentage of CD patients who remained on MTX treatment for at least 18 months was 67% (87 out of 129 patients) versus 79% (41 out of 52 patients) in the 6-TG treatment group. The patients in these analyses sets remained on 6-TG treatment longer than on MTX treatment (mean difference of 40 days). The comparison with a matched control group treated with MTX showed that a comparable percentage of CD patients remained on treatment after 18 months. It is concluded that the efficacy was adequately addressed and is clinically relevant.

Safety results

Adverse events

The adverse event reports are a combination of treatment failure, the known adverse events of 6-TG and those of the concomitant therapies. During the study period, a total of 2185 AEs were reported in 187 patients (93%). 1764 (81%) non-serious adverse events were reported in these 187 pateints. 421 (19%) adverse events were serious adverse events which occurred in 117 patients (58%). Six hundred forty (640) AEs (29%) in 123 (61%) patients were considered to be treatment related (possibly or probably related to Thiosix 6-TG only) by the investigator. The most frequently occurring adverse event in all treatment groups was abdominal pain in 35% of patients. Other frequently occurring adverse events were fatigue (32%) and diarrhea (26%).

108 Study patients were included in Efficacy analysis set 1 of study TS-001. Of these, 78 had adverse events on conventional thiopurines, 11 had an insufficient response to conventional thiopurines, and 19 had both adverse events and an insufficient response to conventional thiopurines at baseline.

The occurrence of non-serious adverse events (965 in total) for patients who had reported AEs on conventional thiopurines as the reason to switch to 6-TG was 86% of the total of patients in this subgroup. Furthermore, 71% of the patients belonging to the subgroup of patients who had reported insufficient effect of conventional thiopurines as the main reason for switching to 6-TG experienced non-serious adverse events. Finally, not serious AEs (82%) were reported in the subgroup of patients who had reported both AEs and insufficient effect of conventional thiopurines as the main reason for switching to 6-TG. Also the occurrence of mild-moderate adverse events (35.9 vs. 41.3-65.7%) tended to be lower in the subgroup of study patients who had experienced adverse events to conventional thiopurines compared to the subgroups of patients who had experienced an insufficient response to conventional thiopurines, or both adverse events and an insufficient response to conventional thiopurines. These findings indicate a better safety profile of 6-TG in patients who had experienced adverse events on conventional thiopurines compared to those who had experienced an insufficient response to conventional thiopurines, or both adverse events and an insufficient response to conventional thiopurines.

Overall, 65.1% of reported adverse events were recovered or resolved. Respective proportion tended to be somewhat higher in the subgroup of patients who had experienced both adverse events and an insufficient response to conventional thiopurines (74.6%) compared to study patients who had either experienced adverse events (64.3%) or an insufficient response (57.0%) to conventional thiopurines.

Submitted safety data indicate that the patients who had experienced adverse events on conventional thiopurines were more likely to experience non-serious and mild-moderate adverse events compared to the subgroups of patients who had experienced an insufficient response to conventional thiopurines, or both adverse events and an insufficient response to conventional thiopurines. However, the outcome of reported adverse events in the subgroup of study patients in whom adverse events to conventional thiopurine treatment had been observed appears to be comparable with study patients in the other subgroups. Because of this, the benefits and risks of 6-TG treatment should be assessed carefully in CD and UC patients who had been treated with azathioprine and/or 6-mercaptopurine, also in those who

had experienced adverse events upon prior treatment with azathioprine and/or 6-mercaptopurine.

Frequency of particular adverse events

The most frequently reported system organ class (SOC) was Gastrointestinal disorders with 733 events in 154 patients. Abdominal pain was the most frequently reported adverse event in this SOC (128 events (5.9%) in 80 patients (40%)).

General disorders and administration site conditions were reported second most frequently with 346 events in 143 patients with fatigue being most reported with 84 adverse events (4%) in 66 patients (33%).

Musculoskeletal and connective tissue disorders was the third most reported SOC with 173 events in 83 patients, with arthralgia being the most frequently reported adverse event (27 events (1%) in 23 patients (11%)) together with musculoskeletal discomfort (22 events (1%) in 21 patients (10%)) and arthropathy (21 events (1%) in 19 patients (10%)).

Hepatotoxicity is a well-known adverse drug reaction of thiopurine treatment (frequency: 1-10%) (SmPC 6-mercaptopurine). Among the treatment-related adverse events reported for 6-TG, the frequency of hepatotoxicity is 10 (5.0%). Such a proportion is considered reassuring with respect to the safety profile of 6-TG in a population mainly consisting of purine intolerant patients.

The nature of the observed adverse events in this section is considered transient. As reported above, over 80% of reported adverse events were not serious. Hence, the safety risks of 6-TG treatment appear to be acceptable in most study patients.

Conclusion

In study TS-001, the occurrence of non-serious and mild to moderate adverse events upon 6-TG treatment tended to be higher in study patients who had discontinued prior conventional thiopurine treatment (i.e. azathioprine and/or 6-mercaptopurine) because of adverse events compared to the study patients who had discontinued conventional thiopurine treatment because of an insufficient response, or because of both adverse events and an insufficient response. Hence, 6-TG may be tolerated well after discontinuation of conventional thiopurine treatment because of adverse events. Therefore, the safety of 6-TG medicinal product Thiosix is considered to be adequately addressed and the safety risks are acceptable.

TS-002: A 6-TG registry that explores the effectiveness and safety of 6-TG in the long-term treatment of IBD

Introduction

In the TS-002 registry, 89 IBD patients (CD: 47, UC: 41, undetermined IBD: 1) with prolonged 6-TG/Thiosix treatment were followed for longer than one year.

Study objectives

The primary endpoint of registry study TS-002 was the evaluation of reported adverse events during 6-TG treatment, and the occurrence of NRH in particular. Furthermore, clinical scores (SCCAI, HBI) were also investigated.

Results

The primary objective of this study was to monitor the incidence of NRH (confirmed by biopsy as stated in the protocol). One case of presumably NRH was identified within the study. However, given that NRH was not confirmed by biopsy, the MAH described that the incidence of NRH in this study was 0%. It is however noted that signs of NRH were reported in three patients in study TS-001 (see discussion above). In two of these cases, NRH was histologically confirmed. Because of this, NRH is still considered an important adverse drug reaction, as it is associated with portal hypertension (Vernier-Massouille et al. 2007).

The reported adverse advents regarding gastrointestinal disorders, general disorders and administration site conditions, and hepatobiliary disorders are generally in line with the known safety profile of 6-TG or could be attributed to the underlying disease, and are currently adequately reflected in the product information.

Within the SOC skin and subcutaneous tissue disorders, the adverse events erythema and pruritus were each reported twice. Currently, these adverse event are not reflected in the product information. No further information on these cases was provided by the MAH. The MAH provided a cumulative review of cases reporting pruritus and urticaria. Erythema was a co-reported with pruritis in a few cases. Based on the cumulative review of pruritus and urticaria, there is currently insufficient evidence to support a causal relation with the use of thioguanine. No further regulatory action is needed.

Photosensitivity as a known ADR of AZA and 6-MP are not reported for 6-TG in study TS-002. Notwithstanding this lack of reports photosensitivity is included in the product information of 6-TG medicinal product Thiosix (SmPC sections 4.4 and 4.8).

Clinical scores for disease activity and severity (i.e. SCCAI, HBI) improved slightly between baseline and month 12. All patients (N= 74) were in clinical remission at 12 months (100%).

Conclusion

The primary objective of this study was to monitor the incidence of NRH (confirmed by biopsy), which was reported to be 0%, whereas signs of NRH were observed in 3 patients in study TS-001. Furthermore, information was provided on the nature of the other (serious) adverse events.

As for the secondary objective of this study; the reported serious adverse advents are generally in line with the known safety profile of 6-TG medicinal product Thiosix or could be attributed to the underlying disease, and are currently adequately reflected in the product information.

Benefit-risk assessment and overall conclusion on long-term efficacy and safety

The clinical efficacy and safety of maintenance treatment with 6-TG medicinal product Thiosix have been evaluated in CD and UC patients in remission who had not sufficiently responded to or were intolerant to prior conventional thiopurine treatment (i.e. azathioprine and/or 6-mercaptopurine) in two prospective, observational registry studies. 6-TG was dosed as recommended in the SmPC of 6-TG medicinal product Thiosix.

Both the study population and 6-TG dose in these studies are considered appropriate for the target population. However, the study design does not allow a direct comparison with active control or placebo treatment. Because of this, the clinical effects of 6-TG relative to those of another study treatment in the same study population are unknown. Therefore, caution is needed with respect to the interpretation of the observed clinical efficacy and safety in conducted registry studies.

Overall, 45.4% of CD and UC patients in corticosteroid-free remission at baseline were also in corticosteroid-free remission after 12 months of 6-TG maintenance treatment in study TS-001. No major differences in effects were observed between patients for whom adverse events and/or an insufficient response to conventional thiopurine treatment had been reported. A corticosteroid-free remission rate of 45% is lower than the targeted corticosteroid-free remission rate of 55% in the sample size calculations. However, publications from medical literature indicate that observed corticosteroid-free remission rate is still clinically relevant. In addition, most of submitted publications did not concern studies in CD and/or UC patients who had experienced adverse events or an insufficient response to azathioprine and/or 6-mercaptopurine. Moreover, the precise endpoints and the scales used for the evaluation of the endpoints in studies from medical literature differ from those in the registry studies. For example, maintenance of corticosteroid-free remission was not evaluated in all submitted studies from medical literature. However, remission, the (near) absence of disease activity, is an objective endpoint irrespective of the scale used to evaluate this. As far as reported, comparable corticosteroid-free remission rates were observed after 12 months (43 up to 65% (Ward et al. 2017, Savelkoul et al. [manuscript], Bayoumi et al. 2020)) in other studies on 6-TG. As indicated by the MAH, comparable or lower (corticosteroid-free) remission rates after about 12 months of treatment were also observed in CD and UC patients for other active substances of medicinal products which are authorized for marketing such as azathioprine and/or mercaptopurine (24.1 up to 76%), infliximab (18 up to 37.9%), vedolizumab (29-46%), and ustekinumab (37-53%).

Two Dutch associations of gastrointestinal specialists (Nederlandse Vereniging van Maag-Darm- en Leverartsen (NVDML), and the Initiative on Crohn and Colitis (ICC)), and also the Dutch patient association for Crohn and Colitis patients consider a corticosteroid-free remission rate of 45% after 12 months of maintenance treatment also clinically relevant for CD and UC patients in remission. (RICHTLIJN DIAGNOSTIEK EN BEHANDELING VAN INFLAMMATOIRE DARMZIEKTEN BIJ VOLWASSENEN, Albersnagel et al., 2008)

The most frequently reported adverse events in all treatment groups were abdominal pain (35% of patients), fatigue (32%) and diarrhoea (26%). Most adverse events with an attributed severity were reported as mild or moderate in severity (60%). Six percent of all adverse events were reported as severe.

Submitted safety data of study TS-001 indicate that the patients who had discontinued prior conventional thiopurine treatment with azathioprine and/or 6-mercaptopurine because of adverse events were more likely to experience non-serious and mild to moderate adverse events compared to the subgroups of patients who had discontinued prior thiopurine treatment because of an insufficient response, or both adverse events and an insufficient response. Hence, 6-TG was tolerated well in a considerable proportion of CD and UC patients after discontinuation of conventional thiopurine treatment because of adverse events. However, the outcome of reported adverse events in this subgroup of study patients is not necessarily better compared to study patients in the other subgroups. Because of this, the benefits and risks of 6-TG treatment should be assessed carefully in CD and UC patients who had been treated with azathioprine and/or 6-mercaptopurine, also in those who had discontinued prior treatment with azathioprine and/or 6-mercaptopurine because of adverse events.

The incidence of nodular regenerative hyperplasia was low and its risk with the current dosage recommendations is considered low. The current SmPC labelling (in sections 4.2, 4.4 and 4.8) regarding hepatotoxicity and nodular regenerative hyperplasia is considered adequate.

Maintenance treatment with thiopurines such as 6-TG, azathioprine, and 6-mercaptopurine is recommended in patients with steroid-dependent moderate-to-severe UC or in UC patients who are intolerant to 5-aminosalicylic acid in current UC treatment guidelines of the European Crohn's and Colitis Organisation (ECCO)(Raine et al. 2021). In the ECCO treatment guidelines on CD, continuation of thiopurine maintenance treatment in CD patients in long-term remission is suggested, as the risk of relapse is higher when the treatment is discontinued (Torres et al. 2020). Since maintenance treatment with thiopurines as a drug class is advised in current ECCO treatment guidelines on CD and UC, 6-TG maintenance treatment may be used in CD and UC patients in remission according to respective guidelines.

In summary, although comparative data are lacking, the submitted studies support earlier literature data that 6-TG medicinal product Thiosix may have a significant and clinically relevant effect in CD and UC patients in remission who had not sufficiently responded to or were intolerant to prior conventional thiopurine treatment. As such, it fits within the drug class of thiopurines that is advised for these patients in current ECCO treatment guidelines.

The benefit-risk assessment is therefore considered to be positive.