



Medicines & Healthcare products
Regulatory Agency



**AZATHIOPRINE 25MG FILM-COATED TABLETS
&
AZATHIOPRINE 50MG FILM-COATED TABLETS
(Azathioprine)**

UKPAR

UK Licence Numbers: PL 11311/0475-6

Tillomed Laboratories Limited.

LAY SUMMARY

AZATHIOPRINE 25MG FILM-COATED TABLETS AZATHIOPRINE 50MG FILM-COATED TABLETS

(Azathioprine, film-coated tablet, 25mg and 50mg)

This is a summary of the Public Assessment Report (PAR) for Azathioprine 25mg and 50mg film-coated Tablets. It explains how the applications for Azathioprine 25mg and 50mg film-coated Tablets were assessed and their authorisations recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Azathioprine 25mg and 50mg film-coated Tablets.

For practical information about using Azathioprine 25mg and 50mg film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Azathioprine 25mg and 50mg film-coated Tablets and what are they used for?

This medicine is the same as Azathioprine 25mg & 50mg film-coated Tablets (PL 11311/0115-6) originally granted to Tillomed Laboratories Limited. The licence holder (Tillomed Laboratories Limited) for Azathioprine 25mg & 50mg film-coated Tablets has agreed that its own scientific data can be used as a basis for the grant of identical licences for Azathioprine 25mg and 50mg film-coated Tablets (informed consent).

Azathioprine 25mg and 50mg film-coated Tablets are used to treat the following:

- To prevent the body from rejecting kidney, liver, heart, lung or pancreas transplants

If the patient is intolerant to or is dependent on steroids and (despite treatment with high doses of steroids) treatment has been ineffective, Azathioprine is used to treat severe cases of the following:

- Severe inflammatory disease of the joints (rheumatoid arthritis) that cannot be kept under control by less toxic medicines (Disease-Modifying Anti-Rheumatic Drugs [DMARDs] e.g. ciclosporin)
- Moderate to severe inflammatory intestinal diseases (Crohn's disease, ulcerative colitis)
- Long-term inflammation of skin and/or intestines (systemic lupus erythematosus)
- Inflammation of the skin and muscles (dermatomyositis, polymyositis)
- Inflammation of the liver (hepatitis)
- Inflammation of the walls of the arteries (polyarteritis nodosa)
- Increased breakdown of red blood cells due to the presence of auto-antibodies active at body temperature (warm) causing anaemia (looking pale and feeling tired)
- Autoimmune disorder where the number of platelets circulating is reduced by the immune system destroying them, causing a rash and an increased tendency to bleed, persisting longer than 6 months without a specific cause and is not responsive to conventional treatment (chronic refractory idiopathic thrombocytopenic purpura)

- Blistering of the skin (pemphigus vulgaris)

How do Azathioprine 25mg and 50mg film-coated Tablets work?

Azathioprine (the active ingredient in this medicine), belongs to a group of medicines called immunosuppressants. These work by reducing the strength of the body's immune system. Azathioprine may be taken long-term as it can take weeks or months before an effect is seen.

How are Azathioprine 25mg and 50mg film-coated Tablets used?

The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient must always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose and duration of treatment will depend on the patient's condition, weight and age. Refer to section 3 of the package leaflet for full details.

These tablets are to be taken orally and should be swallowed whole with sufficient fluid (200mls liquid). These tablets should be taken with or just after food.

Adults

The patient should be adequately monitored for toxic effects throughout the duration of treatment. Particular care should be taken to monitor their response and to reduce the maintenance dose to the lowest dose possible.

Although adverse effects on blood cell formation (haematopoiesis) occur most commonly at the beginning of treatment with azathioprine, late occurrence has been reported. Therefore, careful monitoring of the blood cell counts is recommended even if the patient is on stable long-term treatment with azathioprine.

It is recommended that a complete blood count, including platelet count, should be performed at least once a week for the first 8 weeks of treatment. After 8 weeks, the frequency may be reduced to once a month or intervals of not longer than 3 months. At the first signs of an abnormal fall in blood counts, treatment should be interrupted immediately as white blood cells and platelets may continue to fall after treatment is stopped.

This count should be performed more frequently if:

- Higher doses are used
- The patient is elderly
- Kidney function is impaired or in severe kidney disorders
- Liver function is mildly to moderately impaired or in liver disorders
- Bone marrow function is mildly to moderately impaired
- The patient suffers from an overactive spleen (hypersplenism)
- The patient is taking the following medicines in addition to Azathioprine (see section 2 "Other medicines and azathioprine" of the package leaflet):
 - allopurinol, oxipurinol, thiopurinol
 - mesalazine, olsalazine or sulfasalazine
 - ACE inhibitors

- trimethoprim/sulphamethoxazole
- cimetidine
- indomethacin
- cytostatic/myelosuppressive medicines

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Azathioprine 25mg and 50mg film-coated Tablets can only be obtained with a prescription.

What benefits of Azathioprine 25mg and 50mg film-coated Tablets have been shown in studies?

The applications for Azathioprine 25mg and 50mg film-coated Tablets are considered to be identical to the previously authorised licences for Azathioprine 25mg & 50mg film-coated Tablets (PL 11311/0115-6), with the same benefits and risks. So, no new studies have been provided for Azathioprine 25mg and 50mg film-coated Tablets. However, reference is made to the studies for Azathioprine 25mg & 50mg film-coated Tablets (PL 11311/0115-6).

What are the possible side effects from Azathioprine 25mg and 50mg film-coated Tablets?

Like all medicines, Azathioprine 25mg and 50mg film-coated Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Azathioprine 25mg and 50mg film-coated Tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why was Azathioprine 25mg and 50mg film-coated Tablets approved?

No new or unexpected safety concerns arose from these applications. The MHRA, therefore, considered that the benefits of Azathioprine 25mg and 50mg film-coated Tablets outweigh its risks; and the grant of Marketing Authorisations was recommended.

What measures are being taken to ensure the safe and effective use of Azathioprine 25mg and 50mg film-coated Tablets?

Safety information has been included in the Summaries of Product Characteristics and the package leaflet for Azathioprine 25mg and 50mg film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Azathioprine 25mg and 50mg film-coated Tablets.

Marketing Authorisations were granted in the UK to Roger Oakes Limited on 30 December 2008.

The Marketing Authorisations underwent a change of ownership procedure from the company Roger Oakes Limited (PL 32019/0021-22) to the company, Tillomed Laboratories Limited (PL 11311/0475-6) on 03 September 2009.

A pack size of 28 tablets was approved for addition to the product licence Azathioprine 25mg film-coated Tablets (PL 11311/0475) on 13 January 2015.

A pack size of 56 tablets was approved for addition to the product licence Azathioprine 50mg film-coated Tablets (PL 11311/0476) on 13 January 2015.

The full PAR for Azathioprine 25mg and 50mg film-coated Tablets follows this summary.

For more information about treatment with Azathioprine 25mg and 50mg film-coated Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2016.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Roger Oakes Limited Marketing Authorisations for the medicinal products Azathioprine 25mg film-coated Tablets (PL 32019/0021) and Azathioprine 50mg film-coated Tablets (PL 32019/0022) on 30th December 2008. The products are prescription-only medicines.

These applications were submitted as simple abridged ‘informed consent’ applications according to article 10c of Directive 2001/83/EC (as amended), cross-referring to the Marketing Authorisations Azathioprine 25mg & 50mg film-coated Tablets (PL 11311/0115-6), originally granted to Tillomed Laboratories Limited on 25th October 2002 and subsequently underwent a change of ownership to the company Sandoz Limited (PL 04416/1247-8) on 09 November 2010. These abridged applications had been approved as generic medicinal products of Imuran 25mg Tablets (PL 00003/0225) and Imuran 50mg Tablets (PL 00003/0226) respectively, granted to The Wellcome Foundation Limited on 3rd October 1986.

Azathioprine Tablets contain the active ingredient azathioprine, which belongs to the pharmacotherapeutic group ‘other immunosuppressive agents’ (ATC code: L04AX01). Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down *in vivo* into 6-MP and 1-methyl-4-nitro-5-thiomidazole. 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid. The activity of the methylnitroimidazole moiety has not been defined clearly. However, in various systems it appears to modify the activity of azathioprine, compared with that of 6-MP. Azathioprine has an effect on both immunological reaction and tumour growth. Its major role has been as an agent for suppressing the immune response, although the precise mechanism by which this effect is achieved is not known.

Azathioprine is indicated in combination with other immunosuppressive agents for the prophylaxis of transplant rejection in patients receiving allogenic kidney, liver, heart, lung or pancreas transplants. Therapeutic effect may be evident only after weeks or months and can include a steroid-sparing effect, thereby reducing the toxicity associated with high dosage and prolonged usage of corticosteroids.

Azathioprine is indicated in severe cases of the following diseases in patients who are intolerant to steroids or who are dependent on steroids and in whom the therapeutic response is inadequate despite treatment with high doses of steroids:

- Severe active rheumatoid arthritis that cannot be kept under control by less toxic agents (disease-modifying anti-rheumatic drugs (DMARDs);
- Severe or moderately severe inflammatory intestinal diseases (Crohn’s disease or ulcerative colitis),
- Systemic lupus erythematosus;
- Dermatomyositis and polymyositis;
- Auto-immune hepatitis;
- Polyarteritis nodosa;
- Refractory warm auto-immune haemolytic anaemia;

- Chronic refractory idiopathic thrombocytopenic purpura.

No new data were submitted nor was it necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PAR was generated for them.

These applications for Azathioprine 25mg & 50mg film-coated Tablets were submitted at the same time and were assessed concurrently. Consequently, all sections of this Scientific Discussion refer to both products.

The licences underwent a change of ownership procedure from the marketing authorisation holder (MAH) Roger Oakes Limited (PL 32019/0021-22) to the current MAH, Tillomed Laboratories Limited (PL 11311/0475-6) on 03 September 2009.

A pack size of 28 tablets was approved for addition to the product licence Azathioprine 25mg film-coated Tablets (PL 11311/0475) on 13 January 2015.

A pack size of 56 tablets was approved for addition to the product licence Azathioprine 50mg film-coated Tablets (PL 11311/0476) on 13 January 2015.

II QUALITY ASPECTS

LICENCE NUMBERS:	PL 32019/0021 & 0022
PROPRIETARY NAME:	Azathioprine 25mg & 50mg film-coated Tablets
ACTIVE INGREDIENTS:	Azathioprine
COMPANY NAME:	Roger Oakes Limited
E.C. ARTICLE:	Article 10c of Directive 2001/83/EC (as amended)
LEGAL STATUS:	POM

II.1 Introduction

These are simple abridged applications, submitted under Article 10c of Directive 2001/83/EC (as amended) for Azathioprine 25mg & 50mg film-coated Tablets. The proposed MA holder is 'Roger Oakes Limited, Allstoe House, Church Lane, Greetham, Rutland LE15 7NF'.

The reference products are Azathioprine 25mg & 50mg film-coated Tablets (PL 11311/0115-6), granted to Tillomed Laboratories Limited on 25th October 2002. The test and reference products are identical.

II.2. Drug Substance

Drug substance specification

The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

II.3. Medicinal Product

The proposed names of the products are Azathioprine 25mg film-coated Tablets and Azathioprine 50mg film-coated Tablets. The products have been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes

Each film-coated tablet contains 25mg or 50mg of the active ingredient azathioprine. The tablets are marketed in either polypropylene-aluminium blisters or PVC (polyvinylchloride) /PVDC (polyvinylidene chloride) -aluminium blisters. The blisters are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons and presented in pack sizes of pack sizes of 20 (25mg strength tablet only), 30, 50 or 100 tablets. The MAH has stated that not all pack sizes may be marketed.

The proposed shelf-life (3 years) and storage conditions (No special storage conditions) are consistent with the details registered for the cross-reference products.

Legal status

The products are available by supply through pharmacies, subject to a medical prescription.

Marketing authorisation holder / Contact Persons/Company

The proposed Marketing Authorisation holder is 'Roger Oakes Limited, Allstoe House, Church Lane, Greetham, Rutland LE15 7NF'.

The QP responsible for pharmacovigilance is stated and their CV is included.

Manufacturers

The proposed manufacturing site is consistent with that registered for the cross-reference products and evidence of GMP compliance has been provided.

Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the cross-reference products.

Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

Finished product / shelf-life specification

The proposed finished product specifications are in line with the details registered for the cross-reference products.

Drug substance specification

The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

TSE Compliance

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

EXPERT REPORTS

Satisfactory expert reports and curriculum vitae of experts are provided.

Product name and appearance

See Section II.3 'Medicinal Product; Name' for details of the proposed product names. The appearance of the products is consistent with that of the cross-reference product.

SUMMARY OF PRODUCT CHARACTERISTICS

The approved SmPCs are consistent with the details registered for the cross-reference products.

PATIENT INFORMATION LEAFLET (PIL) / CARTON PIL

The patient information leaflet has been prepared in the user tested format and in line with the details registered for the cross-reference products. The approved PIL is satisfactory.

Cartons

Colour mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In line with current legislation the applicant has included the name of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The data submitted with the applications is acceptable. The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

The applications were submitted as simple abridged applications according to article 10c of Directive 2001/83/EC (as amended).

As these are duplicate applications for of PL 11311/0115 and PL 11311/0116, no new clinical data have been supplied with the applications, and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory.

IV CLINICAL ASPECTS

The applications were submitted as simple abridged applications according to article 10c of Directive 2001/83/EC (as amended).

As these are duplicate applications of PL 11311/0115 and PL 11311/0116, no new clinical data have been supplied with the applications, and none are required for applications of this type. A clinical overview has been written by a suitably qualified person and is satisfactory.

V OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The data for these applications are consistent with that previously assessed for the cross-reference products and as such has been judged to be satisfactory.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

Medicinal products containing azathioprine have been available in the UK for much more than ten years. Their use is well-established with recognised efficacy and acceptable safety.

These applications are identical to the cross-reference products Azathioprine 25mg & 50mg film-coated Tablets (PL 11311/0115 & 0116, Tillomed Laboratories Limited), which were demonstrated to be generic medicinal versions of the innovator products Imuran 25mg and 50mg Tablets (PL 00003/0225 & 0226), respectively.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed. However, they have committed to submitting mock-ups for all packaging for assessment before they are commercially marketed.

BENEFIT/RISK ASSESSMENT

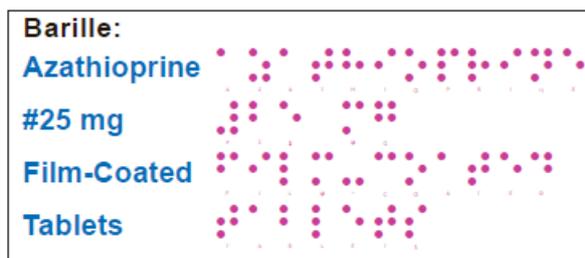
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with azathioprine is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

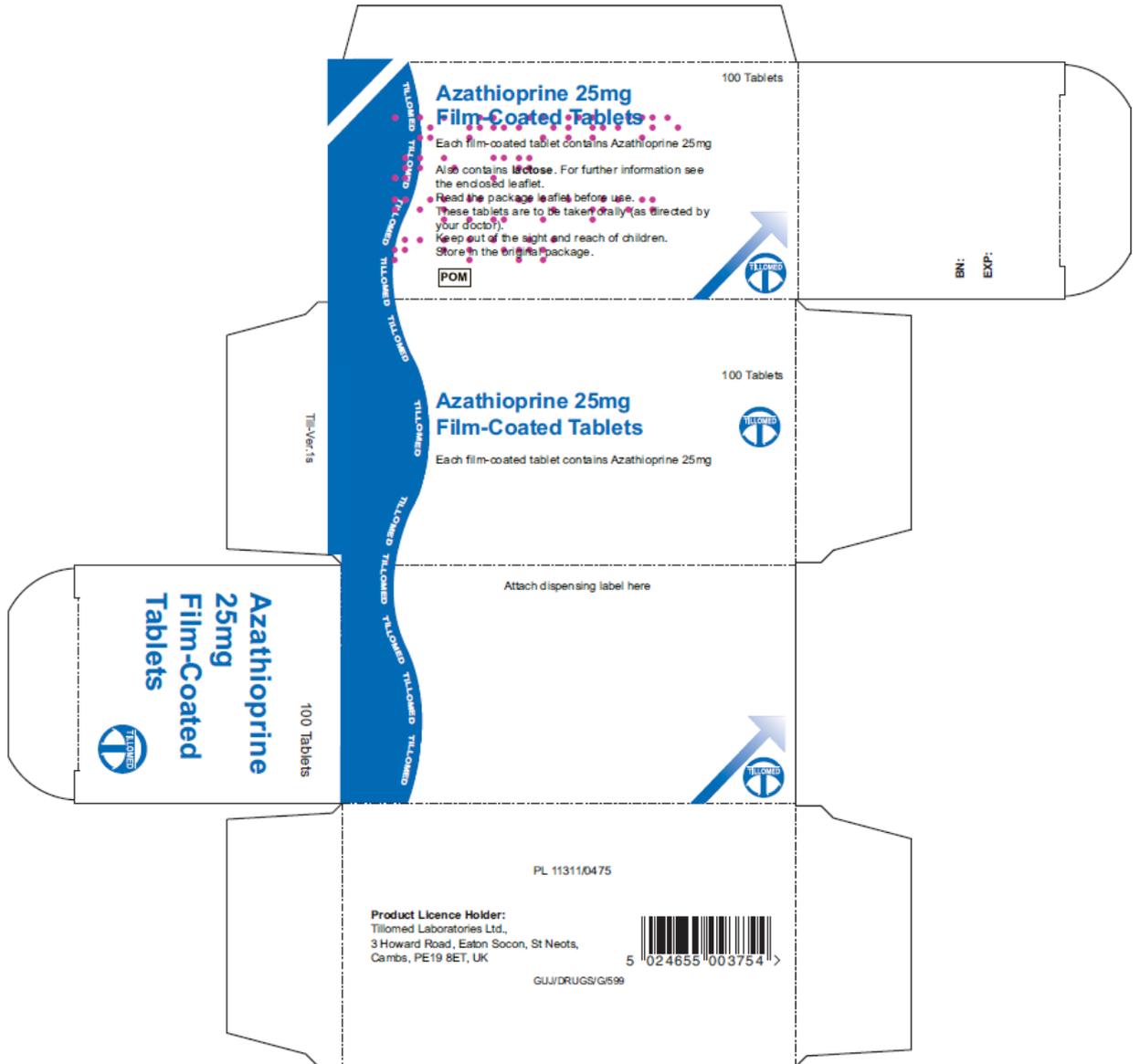
Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and Labels

The Summaries of Product Characteristics and Patient Information Leaflet (PIL) are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:

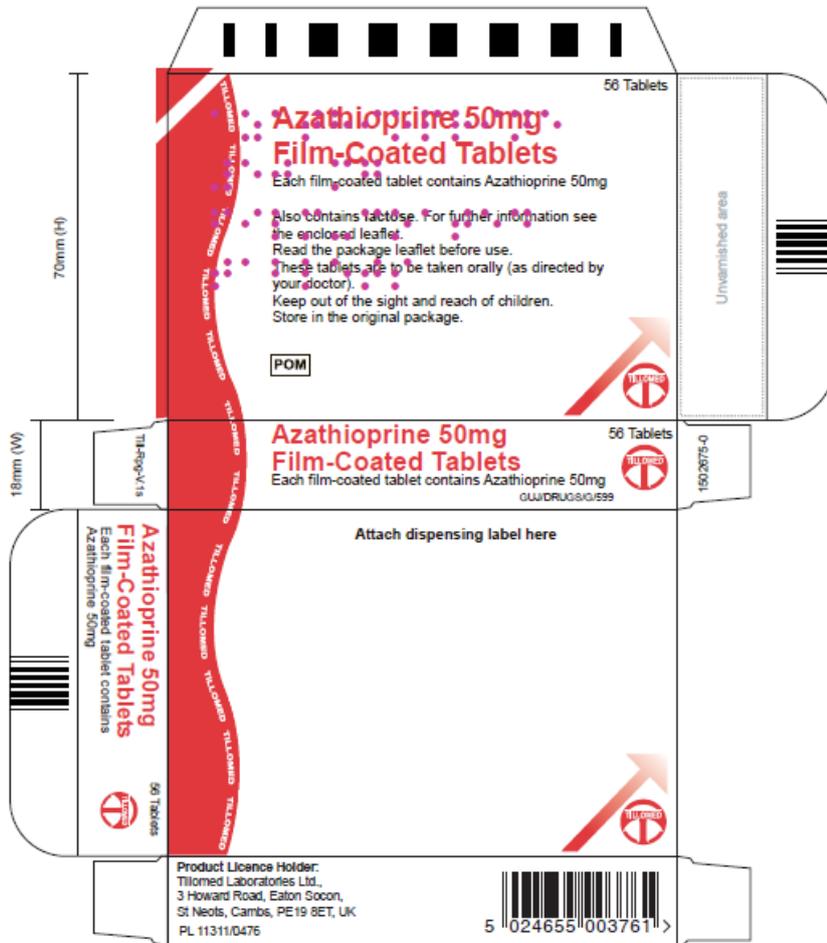


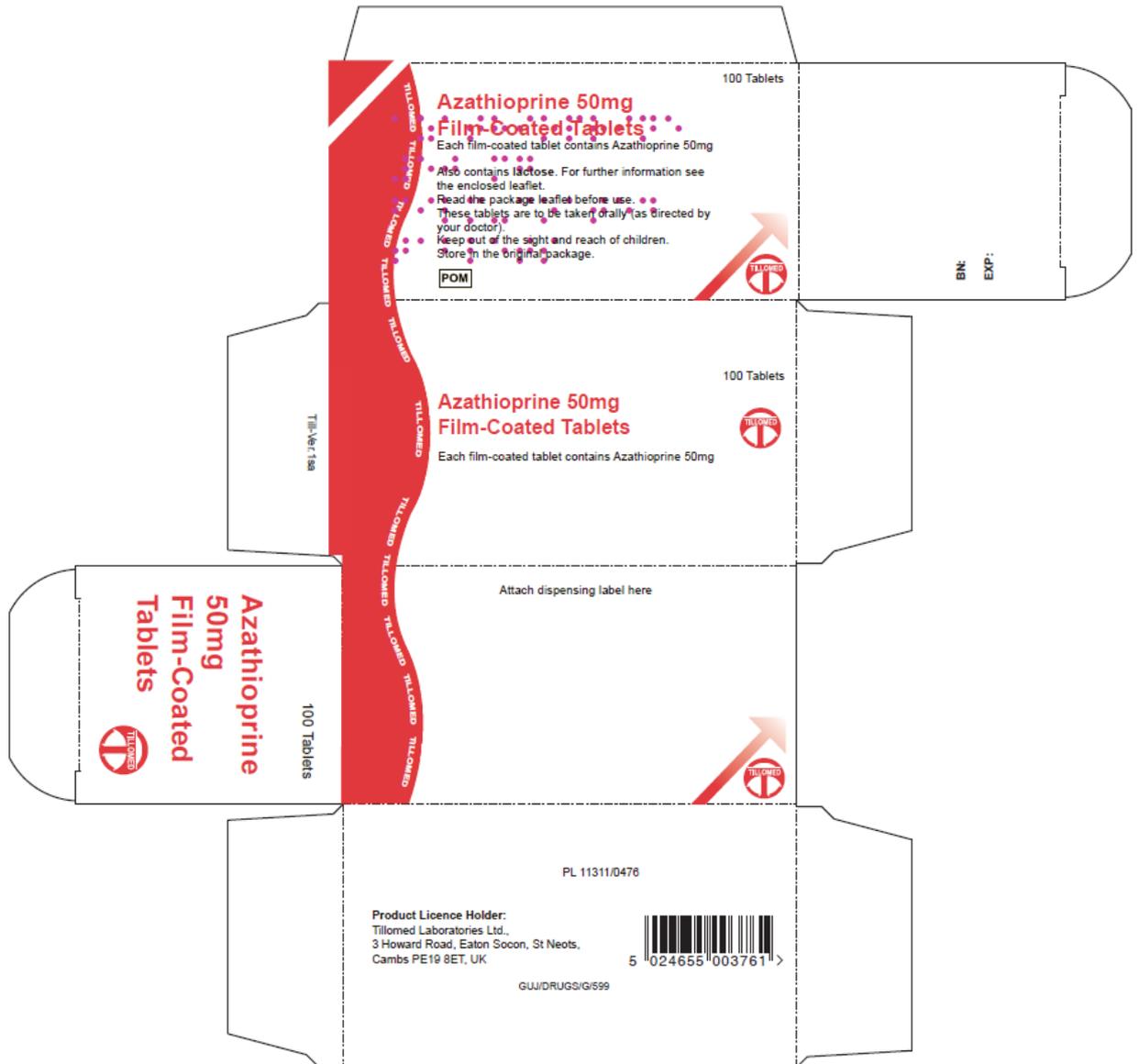


Batch No. / EXP will be printed / embossed during production.

<p>Azathioprine 25mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0475 GUJ/DRUGS/G/599 15/02/875-0</p>	<p>Azathioprine 25mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0475 GUJ/DRUGS/G/599 15/02/875-0</p>
<p>Azathioprine 25mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0475 GUJ/DRUGS/G/599 15/02/875-0</p>	<p>Azathioprine 25mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0475 GUJ/DRUGS/G/599 15/02/875-0</p>
<p>Azathioprine 25mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0475 GUJ/DRUGS/G/599 15/02/875-0</p>	<p>Azathioprine 25mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0475 GUJ/DRUGS/G/599 15/02/875-0</p>

Till-Ppg-V.1sa





Batch No. / EXP will be printed / embossed during production.

<p>Azathioprine 50mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0476 GUJ/DRUGS/G/599 1502676-0</p>	<p>Azathioprine 50mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0476 GUJ/DRUGS/G/599 1502676-0</p>
<p>Azathioprine 50mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0476 GUJ/DRUGS/G/599 1502676-0</p>	<p>Azathioprine 50mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0476 GUJ/DRUGS/G/599 1502676-0</p>
<p>Azathioprine 50mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0476 GUJ/DRUGS/G/599 1502676-0</p>	<p>Azathioprine 50mg Film-Coated Tablets Tillomed Laboratories Ltd. PL 11311/0476 GUJ/DRUGS/G/599 1502676-0</p>

Til-Rpg-V.1sa

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

The following table lists non- safety variations of clinical significance to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Date submitted	Application type	Scope	Outcome
19/02/2016	Type IB	PL 11311/0475-0025 & PL 11311/0476-0024: To update section 4.2 (Posology and method of administration) of the SmPC and consequentially the leaflet by including the information about taking the drug with food in line with the British National Formulary (BNF).	Approved on 10/03/2016-see Annex 1

ANNEX 1

Our Reference:	PL 11311/0475-0025 PL 11311/0476-0024
Product:	Azathioprine 25 mg film-coated tablets Azathioprine 50 mg film-coated tablets
Marketing Authorisation Holder:	Tillomed Laboratories Ltd
Active Ingredient(s):	Azathioprine.
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	Not applicable

Reason:

To update section 4.2 (Posology and method of administration) of the SmPC and consequentially the leaflet by including the information about taking the drug with food in line with the BNF.

Supporting Evidence

Revised SmPC fragments and PIL.

Evaluation

The BNF states the following in relation to administration of azathioprine with food in the 'Medicinal forms' section:

- There can be variation in the licensing of different medicines containing the same drug.
- Cautionary and advisory labels Label 21 - Take with or just after food, or a meal

The UK reference product is Azathioprine Imuran tablets (PL 39699/0004) and the SmPC states 'A minority of patients experience nausea when first given Imuran. This appears to be relieved by administering the tablets after meals'. Other azathioprine SmPCs state that 'The tablets should be taken during meals' (e.g. PL 30306/0520). In a Decentralised Procedure (DCP) where the reference member state (RMS) was the UK (UK/H/2846/01-03/DC), the following recommendation is found in Section 4.2 'The tablets should be taken during meals in order to decrease the risk of nausea'.

Conclusion

There is no consistent recommendation in the UK product literature with regards to administration of azathioprine with food. However, the proposed changes are acceptable and broadly in line with agreed text found in authorised products SmPCs and the BNF.

The proposed changes to the SmPCs and PIL are acceptable. The updated SmPC fragments and PIL have been incorporated into the Marketing Authorisations.

Decision- Approved on 10 March 2016.