

Public Assessment Report

Decentralised

Azathioprine 50mg Film-coated Tablets

UK/H/934/01/DC

Relonchem Ltd

Lay Summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Relonchem Ltd a Marketing Authorisation (licence) for the medicinal product Azathioprine 50mg Film-coated-Tablets. This is a prescription only medicine.

This medicinal product contains the active ingredient azathioprine and is used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and procedures which influence the immune response. It is a purine analogue which acts as an immunosuppressant by reducing the production of white blood cells that are an important component of the immune system. 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.

The data submitted in support of the application for Azathioprine raised no clinically significant safety concerns and it was therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation was granted.

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Module 1

| | |
|---|--|
| Product Name | Azathioprine 50mg Film-coated Tablets |
| Type of Application | Decentralised |
| Active Substance (INN) | Azathioprine |
| Pharmacotherapeutic Classification (ATC) | L04AX01 |
| Pharmaceutical Form and Strength | Film-coated tablets, 50mg |
| Procedure Numbers | UK/H/934/01/DC |
| RMS | UK |
| CMS | IE |
| Start Date | 13/10/2006 |
| End Date | 09/10/2007 |
| MA Number | PL 20395/0066 |
| Name and address of MA holder | Relonchem 27 Old Gloucester Street, London, WC1 3XX, UK |

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Azathioprine 50mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg Azathioprine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet.

Azathioprine 50 mg Tablets are pale yellow, circular, film coated, biconvex, tablets engraved with “AZA”, score-line and “50” on one face. The other face is plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Azathioprine 50mg Tablets are used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and procedures which influence the immune response. 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 50mg Tablets, in combination with corticosteroids and/or other immunosuppressive agents and procedures, is indicated to enhance the survival of organ transplants, such as renal transplants, cardiac transplants, and hepatic transplants; and to reduce the corticosteroid requirements of renal transplant recipients.

Azathioprine 50mg Tablets, either alone or more usually in combination with corticosteroids and/or other drugs and procedures, has been used with clinical benefit (which may include reduction of dosage or discontinuation of corticosteroids) in a proportion of patients suffering from the following:

severe rheumatoid arthritis;
systemic lupus erythematosus;
dermatomyositis and polymyositis;
auto-immune chronic active hepatitis;

pemphigus vulgaris;
polyarteritis nodosa;
auto-immune haemolytic anaemia;
chronic refractory idiopathic thrombocytopenic purpura.

4.2 Posology and method of administration

Transplantation - adults and children

Depending on the immunosuppressive regimen employed, a dosage of up to 5 mg/kg body weight/day may be given on the first day of therapy, either orally or intravenously.

Maintenance dosage should range from 1 to 4 mg/kg body weight/day and must be adjusted according to clinical requirements and haematological tolerance.

Evidence indicates that Azathioprine 50mg Tablets therapy should be maintained indefinitely, even if only low doses are necessary, because of the risk of graft rejection.

Dosage in other conditions - adults and children

In general, starting dosage is from 1 to 3 mg/kg body weight/day, and should be adjusted, within these limits, depending on the clinical response (which may not be evident for weeks or months) and haematological tolerance.

When therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. If no improvement occurs in the patient's condition within 3 months, consideration should be given to withdrawing Azathioprine 50mg Tablets .

The maintenance dosage required may range from less than 1 mg/kg body weight/day to 3 mg/kg body weight/day, depending on the clinical condition being treated and the individual patient response, including haematological tolerance.

In patients with renal and/or hepatic insufficiency, dosages should be given at the lower end of the normal range (see Special Warnings and Precautions for Use for further details).

Use in the elderly (see Renal and/or hepatic insufficiency)

There is limited experience of the administration of Azathioprine 50mg Tablets to elderly patients. Although the available data do not provide evidence that the incidence of side effects among elderly patients is higher than that among other patients treated with Azathioprine 50mg Tablets, it is recommended that the dosages used should be at the lower end of the range.

Particular care should be taken to monitor haematological response and to reduce the maintenance dosage to the minimum required for clinical response.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to Azathioprine 50mg Tablets.

Severe disorders of the liver, kidney or bone marrow function

Pancreatitis

Severe infections

Azathioprine 50mg Tablets therapy should not be initiated in patients who may be pregnant, or who are likely to become pregnant without careful assessment of risk versus benefit (see Special Warnings and Precautions for Use and Pregnancy and Lactation).

4.4 Special warnings and precautions for use

Monitoring

There are potential hazards in the use of Azathioprine 50mg Tablets. It should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of therapy.

It is suggested that during the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than 3 months.

Patients receiving Azathioprine 50mg Tablets should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestations of bone marrow depression.

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with Azathioprine 50mg Tablets. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Also it has been reported that decreased TPMT activity increases the risk of secondary leukaemias and myelodysplasia in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (see section 4.8 Undesirable effects).

Renal and/or hepatic insufficiency

It has been suggested that the toxicity of Azathioprine 50mg Tablets may be enhanced in the presence of renal insufficiency, but controlled studies have not supported this suggestion. Nevertheless, it is recommended that the dosages used should be at the lower end of the normal range and that haematological response should be carefully monitored. Dosage should be further reduced if haematological toxicity occurs.

Caution is necessary during the administration of Azathioprine 50mg Tablets to patients with hepatic dysfunction, and regular complete blood counts and liver function tests should be undertaken. In such patients the metabolism of Azathioprine 50mg Tablets may be impaired, and the dosage of Azathioprine 50mg Tablets should therefore be reduced if hepatic or haematological toxicity occurs.

Limited evidence suggests that Azathioprine 50mg Tablets is not beneficial to patients with hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). Therefore, given the abnormal metabolism in these patients, it is not prudent to recommend that these patients should receive Azathioprine 50mg Tablets.

Mutagenicity

Chromosomal abnormalities have been demonstrated in both male and female patients treated with Azathioprine 50mg Tablets. It is difficult to assess the role of Azathioprine 50mg Tablets in the development of these abnormalities.

Effects on fertility

Relief of chronic renal insufficiency by renal transplantation involving the administration of Azathioprine 50mg Tablets has been accompanied by increased fertility in both male and female transplant recipients.

Carcinogenicity (see also section 4.8 Undesirable Effects)

Patients receiving immunosuppressive therapy are at an increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. It has been reported that reduction or discontinuation of immunosuppression may be associated with partial or complete regression of non-Hodgkin's lymphomas and Kaposi's sarcomas.

Patients receiving multiple immunosuppressive agents may be at risk of over-immunosuppression, therefore such therapy should be maintained at the lowest effective level.

As is usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor.

4.5 Interaction with other medicinal products and other forms of interaction

Allopurinol/ oxipurinol/ thiopurinol

Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol which results in reduced conversion of biologically active 6⁻thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol, oxipurinol and/or thiopurinol are given concomitantly with 6⁻mercaptopurine or azathioprine, the dose of 6-mercaptopurine and azathioprine should be reduced to one-quarter of the original dose.

Neuromuscular blocking agents

Azathioprine 50mg Tablets can potentiate the neuromuscular blockade produced by depolarising agents such as succinylcholine and can reduce the blockade produced by non-depolarising agents such as tubocurarine. There is considerable variation in the potency of this interaction.

Warfarin

Inhibition of the anticoagulant effect of warfarin, when administered with azathioprine, has been reported.

Cytostatic/myelosuppressive agents

Where possible, concomitant administration of cytostatic drugs, or drugs which may have a myelosuppressive effect, such as penicillamine, should be avoided. There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between Azathioprine 50mg Tablets and co-trimoxazole.

ACE inhibitors

There has been a case report suggesting that haematological abnormalities may develop due to the concomitant administration of Azathioprine 50mg Tablets and captopril.

Other interactions

It has been suggested that cimetidine and indometacin may have myelosuppressive effects, which may be enhanced by concomitant administration of Azathioprine 50mg Tablets.

As there is *in vitro* evidence that aminosalicylate derivatives (eg. olsalazine, mesalazine or sulfasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent Azathioprine 50mg Tablets therapy (see Special Warnings and Special Precautions for Use).

Furosemide has been shown to impair the metabolism of azathioprine by human hepatic tissue *in vitro*. The clinical significance is unknown.

Vaccines

The immunosuppressive activity of Azathioprine 50mg Tablets could result in an atypical and potentially deleterious response to live vaccines and so the administration of live vaccines to patients receiving Azathioprine 50mg Tablets therapy is contra-indicated on theoretical grounds.

A diminished response to killed vaccines is likely and such a response to hepatitis B vaccine has been observed among patients treated with a combination of azathioprine and corticosteroids.

A small clinical study has indicated that standard therapeutic doses of Azathioprine 50mg Tablets do not deleteriously affect the response to polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration.

4.6 Pregnancy and lactation

Teratogenicity

Studies in pregnant rats, mice and rabbits using azathioprine in dosages from 5 to 15 mg/kg body weight/day over the period of organogenesis have shown varying degrees of foetal abnormalities. Teratogenicity was evident in rabbits at 10 mg/kg body weight/day.

Evidence of the teratogenicity of Azathioprine 50mg Tablets in man is equivocal. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving Azathioprine 50mg Tablets.

Mutagenicity

Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes from the off-spring of patients treated with Azathioprine 50mg Tablets. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of patients treated with Azathioprine 50mg Tablets. Azathioprine and long - wave ultraviolet light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine for a range of disorders.

The Use of Azathioprine 50mg Tablets in Pregnancy and Lactation

Azathioprine 50mg Tablets is contraindicated (see 4.3) in pregnancy. Women of childbearing potential have to use effective contraception during treatment.

Azathioprine 50mg Tablets should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit.

There have been reports of premature birth and low birth weight following maternal exposure to azathioprine, particularly in combination with corticosteroids. There have also been reports of spontaneous abortion following either maternal or paternal exposure.

Azathioprine and/or its metabolites have been found in low concentrations in foetal blood and amniotic fluid after maternal administration of azathioprine.

Leucopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took azathioprine throughout their pregnancies. Extra care in haematological monitoring is advised during pregnancy.

Lactation

6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment. The use of Azathioprine in nursing mothers is not recommended.

4.7 Effects on ability to drive and use machines

Due to the possibility of adverse drug reactions such as dizziness, and because of individually occurring different reactions, the ability to participate actively in traffic

or operate machines may be influenced adversely by azathioprine treatment. This is to be considered especially in combination with alcohol

4.8 Undesirable effects

For this product there is no modern clinical documentation that can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication. The following convention has been utilised for the classification of frequency: Very common, $\geq 1/10$; common, $\geq 1/100$ and $< 1/10$; uncommon, $\geq 1/1000$ and $< 1/100$; rare, $\geq 1/10000$ and $< 1/1000$; very rare, $< 1/10000$.

Infection and infestations

Transplant patients receiving Azathioprine 50mg Tablets in combination with other immunosuppressants.

Very common: Viral, fungal, and bacterial infections.

Other indications.

Uncommon: Viral, fungal and bacterial infections.

Patients receiving Azathioprine 50mg Tablets alone, or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections.

Neoplasms benign and malignant (including cysts and polyps)

Rare: Neoplasms including non-Hodgkin's lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myeloid leukaemia and myelodysplasia (see also section 4.4 Special Warnings and Special Precautions for Use).

The risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas, (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, is increased in patients who receive immunosuppressive drugs, particularly in transplant recipients receiving aggressive treatment and such therapy should be maintained at the lowest effective levels. The increased risk of developing non-Hodgkin's lymphomas in immunosuppressed rheumatoid arthritis patients compared with the general population appears to be related at least in part to the disease itself.

There have been rare reports of acute myeloid leukaemia and myelodysplasia (some in association with chromosomal abnormalities).

Blood and lymphatic system disorders

Very common: Depression of bone marrow function; leucopenia.

Common: Thrombocytopenia.

Uncommon: Anaemia.

Rare: Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia.

Azathioprine 50mg Tablets may be associated with a dose-related, generally reversible, depression of bone marrow function, most frequently expressed as leucopenia, but also sometimes as anaemia and thrombocytopenia, and rarely as agranulocytosis, pancytopenia

and aplastic anaemia. These occur particularly in patients predisposed to myelotoxicity, such as those with TPMT deficiency and renal or hepatic insufficiency and in patients failing to reduce the dose of Azathioprine 50mg Tablets when receiving concurrent allopurinol therapy.

Reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content have occurred in association with Azathioprine 50mg Tablets therapy. Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and erythroid hypoplasia are rare.

Respiratory, thoracic and mediastinal disorders

Very rare: Reversible pneumonitis.

Reversible pneumonitis has been described very rarely.

Gastrointestinal disorders

Uncommon: Pancreatitis.

Rare: Colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population.

A minority of patients experience nausea when first given Azathioprine 50mg Tablets. This appears to be relieved by administering the tablets after meals.

Serious complications, including colitis, diverticulitis and bowel perforation, have been described in transplant recipients receiving immunosuppressive therapy. However, the aetiology is not clearly established and high-dose corticosteroids may be implicated. Severe diarrhoea, recurring on re-challenge, has been reported in patients treated with Azathioprine 50mg Tablets for inflammatory bowel disease. The possibility that exacerbation of symptoms might be drug-related should be borne in mind when treating such patients.

Pancreatitis has been reported in a small percentage of patients on Azathioprine 50mg Tablets therapy, particularly in renal transplant patients and those diagnosed as having inflammatory bowel disease. There are difficulties in relating the pancreatitis to the administration of one particular drug, although re-challenge has confirmed an association with Azathioprine 50mg Tablets on occasions.

Hepato-biliary disorders

Uncommon: Cholestasis and degeneration of liver function tests.

Rare: Life-threatening hepatic damage.

Cholestasis and deterioration of liver function have occasionally been reported in association with Azathioprine 50mg Tablets therapy and are usually reversible on withdrawal of therapy. This may be associated with symptoms of a hypersensitivity reaction (see Hypersensitivity reactions).

Rare, but life-threatening hepatic damage associated with chronic administration of azathioprine has been described primarily in transplant patients. Histological findings include sinusoidal dilatation, peliosis hepatis, veno-occlusive disease and nodular regenerative hyperplasia. If veno-occlusive disease is clinically suspected, Azathioprine should be permanently withdrawn. In some cases withdrawal of azathioprine has resulted in either a temporary or permanent improvement in liver histology and symptoms.

Skin and subcutaneous tissue disorders

Rare: Alopecia

Hair loss has been described on a number of occasions in patients receiving azathioprine and other immunosuppressive agents. In many instances the condition resolved spontaneously despite continuing therapy. The relationship between alopecia and azathioprine treatment is uncertain.

Immune system disorders

Uncommon: Hypersensitivity reactions

Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following administration of Azathioprine 50mg Tablets. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis (see Hepato-biliary disorders).

In many cases, re-challenge has confirmed an association with Azathioprine 50mg Tablets.

Immediate withdrawal of azathioprine and institution of circulatory support where appropriate have led to recovery in the majority of cases.

Other marked underlying pathology has contributed to the very rare deaths reported.

Following a hypersensitivity reaction to Azathioprine 50mg Tablets, the necessity for continued administration of Azathioprine 50mg Tablets should be carefully considered on an individual basis.

4.9 Overdose

Symptoms and signs

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with Azathioprine 50mg Tablets and result from bone marrow depression which may be maximal after 9 to 14 days. These signs are more likely to be manifest following chronic overdosage, rather than after a single acute overdose. There has been a report of a patient who ingested a single overdose of 7.5 g of azathioprine. The immediate toxic effects of this overdose were nausea, vomiting and diarrhoea, followed by mild leucopenia and mild abnormalities in liver function. Recovery was uneventful.

Treatment

There is no specific antidote. Gastric lavage has been used. Subsequent monitoring, including haematological monitoring, is necessary to allow prompt treatment of any adverse effects which may develop. The value of dialysis in patients who have taken an overdose of Azathioprine 50mg Tablets is not known, though azathioprine is partially dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic Group: Antineoplastic and 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 a methylnitroimidazole moiety. The 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 rate of conversion varies from one person to another. Nucleotides do not traverse cell membranes and therefore do not circulate in body fluids. Irrespective of whether it is given directly or is derived *in vivo* from azathioprine, 6-MP is eliminated mainly as the inactive oxidised metabolite thiouric acid. This oxidation is brought about by xanthine oxidase, an enzyme that is inhibited by allopurinol. The activity of the methylnitroimidazole moiety has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP. Determination of plasma concentrations of azathioprine or 6-MP have no prognostic values as regards effectiveness or toxicity of these compounds.

While the precise modes of action remain to be elucidated, some suggested mechanisms include:

1. the release of 6-MP which acts as a purine antimetabolite.
2. the possible blockade of -SH groups by alkylation.
3. the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response.
4. damage to deoxyribonucleic acid (DNA) through incorporation of purine thio-analogues.

Because of these mechanisms, the therapeutic effect of Azathioprine 50mg Tablets may be evident only after several weeks or months of treatment.

Azathioprine 50mg Tablets appears to be well absorbed from the upper gastro-intestinal tract.

Studies in mice with [³⁵S]-azathioprine showed no unusually large concentration in any particular tissue, and there was very little [³⁵S]-label found in brain.

Plasma levels of azathioprine and 6-MP do not correlate well with the therapeutic efficacy or toxicity of Azathioprine 50mg Tablets.

5.2 Pharmacokinetic properties

Azathioprine is well absorbed following oral administration. After oral administration of [³⁵S]-azathioprine, the maximum plasma radioactivity occurs at 1-2 hours and decays with a half-life of 4-6 hours. This is not an estimate of the half-life of azathioprine itself, but reflects the elimination from plasma of azathioprine and the [³⁵S]-containing metabolites of the drug. As a consequence of the rapid and extensive metabolism of azathioprine, only a fraction of the radioactivity measured in plasma is comprised of unmetabolised drug. Studies in which the plasma concentration of azathioprine and 6-MP have been determined following intravenous administration of azathioprine have estimated the mean plasma T^{1/2} for azathioprine to be in the range of 6-28 minutes and the mean plasma T^{1/2} for 6-MP to be in the range 38-114 minutes after i.v. administration of the drug.

Azathioprine is principally excreted as 6-thiouric uric acid in the urine. 1-methyl-4-nitro-5-thioimidazole has also been detected in urine as a minor excretory product. This would indicate that, rather than azathioprine being exclusively cleaved by nucleophilic attack at the 5-position of the nitroimidazole ring to generate 6-MP and 1-methyl-4-nitro-5-(S-glutathionyl)imidazole. A small proportion of the drug may be cleaved between the sulphur-atom and the purine ring. Only a small amount of the dose of azathioprine administered is excreted unmetabolised in the urine.

5.3 Preclinical safety data

No additional data of clinical relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose,

Mannitol,

Maize starch,

Povidone K25,

Croscarmellose sodium,

Sodium stearyl fumarate,

Tablet coat:

Hypromellose,

Macrogol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the outer carton.

6.5 Nature and contents of container

PVDC/PVC/Al Blister strips in a pack.

Pack sizes: 56 and 100 film-coated tablets.

6.6 Special precautions for handling and disposal

The tablets are not intended to be broken.

Provided that the film-coating is intact, there is no risk in handling film-coated Azathioprine 50mg Tablets. Azathioprine 50mg Tablets should not be divided and, provided the coating is intact, no additional precautions are required when handling them.

Health professionals who handle Azathioprine 50mg Tablets should follow guidelines for the handling of cytotoxic drugs according to prevailing local recommendations and/or regulations.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Relonchem Limited

27 Old Gloucester Street

London

WC1 3XX

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20395/0066

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

09/10/2007

10 DATE OF REVISION OF THE TEXT

09/10/2007

Module 3

Product Information Leaflet

Azathioprine 50mg Film-coated Tablets

(Azathioprine)

RelonChem**PACKAGE LEAFLET: INFORMATION FOR THE USER****Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What are Azathioprine 50mg Tablets and what are they used for
2. Before you take Azathioprine 50mg Tablets
3. How to take Azathioprine 50mg Tablets
4. Possible side effects
5. How to store Azathioprine 50mg Tablets
6. Further information

1. WHAT ARE AZATHIOPRINE 50MG TABLETS AND WHAT ARE THEY USED FOR

Azathioprine 50mg Tablets belong to a group of medicines called immunosuppressives. This means that they reduce the strength of your immune system. Immunosuppressive medicines are sometimes necessary to help your body accept an organ transplant, or to treat some diseases where your immune system is reacting against your own body (autoimmune diseases).

2. BEFORE YOU TAKE AZATHIOPRINE 50MG TABLETS**Do not take Azathioprine 50mg Tablets**

- If you are allergic (hypersensitive) to azathioprine, mercaptopurine or any of the other ingredients of Azathioprine 50mg Tablets.
- if you are pregnant or breast-feeding
- if you are planning to have a baby (This applies to both men and women).
- if you are being treated for a severe infection
- if you have severe liver problems
- if you have an inflamed pancreas (pancreatitis)
- if you suffer from a weak immune system.

Take special care with Azathioprine 50mg Tablets**Please consult your doctor**

- if you are going to have a vaccination while you are taking Azathioprine 50mg Tablets
- if you suffer from liver or kidney disease
- if you have a condition where your body produces too little of a natural chemical called thiopurine methyltransferase (TPMT)
- if you suffer from a condition known as Lesch-Nyhan Syndrome

Taking other medicines

It is important that you tell your doctor if you are taking or likely to be taking any of the following medicines before taking Azathioprine 50mg Tablets as they may harm you:

- allopurinol (used mainly to treat gout)
- tubocurarine, succinylcholine (used mainly during surgical operations)
- penicillamine (used mainly in the treatment of rheumatoid arthritis)
- captopril, furosemide (used mainly to treat high blood pressure)
- warfarin (used to prevent blood clots)
- cimetidine (used to treat stomach ulcers and indigestion)
- indometacin (used as a pain killer and anti-inflammatory)
- cytostatic drugs (includes some antibiotics and also medicinal products used to treat various types of cancer)
- balsalazide, mesalazine, olsalazine or sulfasalazine (used mainly to treat ulcerative colitis)
- co-trimoxazole (an antibiotic)

Please also tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Azathioprine 50mg Tablets with food and drink

You should swallow your tablets with some water.

Pregnancy and breast-feeding

Do not take Azathioprine 50mg Tablets if you are pregnant or breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You are safe to drive or operate machinery when taking Azathioprine 50mg Tablets, unless you experience dizziness. Dizziness may be made worse by alcohol and you should not drive or operate machinery if you have been drinking alcohol.

Important information about some of the ingredients of Azathioprine 50mg Tablets

These tablets contain Mannitol which may have a mild laxative effect.

3. HOW TO TAKE AZATHIOPRINE 50MG TABLETS

Always take Azathioprine 50mg Tablets exactly as your doctor has told you. It is important to take your medicine at the right times. The label on your pack will tell you how many tablets to take and how often to take them. You should check with your

doctor or pharmacist if you are not sure. The number of Azathioprine 50mg Tablets people take can be very different. Your doctor may change your dose from time to time. The usual dose for adults is 1-5mg per kilogram body weight per day and for children, 1-3mg per kilogram of body weight per day. The usual dosage for elderly patients should be at the lower end of the dosage range for adults. If you are not sure how many tablets to take, or if the dose on the label has changed for no reason, ask your doctor.

From time to time, while you are taking Azathioprine 50mg Tablets, your doctor will want you to have a blood test. This is to check your blood cell count and to change your dose if necessary.

If you take more Azathioprine 50mg Tablets than you should

If you take too many tablets, or if someone else takes your medicine by mistake, tell your doctor immediately.

If you forget to take Azathioprine 50mg Tablets

If you forget to take a dose, tell your doctor. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Azathioprine 50mg Tablets

If your doctor tells you to stop taking the tablets, please return any which are left over to your pharmacist. Only keep them if your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Azathioprine 50mg Tablets can cause side effects, although not everybody gets them.

Patients receiving immunosuppressives such as Azathioprine may be more likely to develop different types of cancers including skin cancers. You should take care to avoid too much sun and wear protective clothing and sunscreen. A few people may be allergic to Azathioprine 50mg Tablets. See your doctor **immediately** if you develop any of the following symptoms:

- Feeling sick and/or being sick
- Diarrhoea
- Fever, shivering/chill and skin rash
- Muscle and bone pain
- Kidney problems (symptoms may include changes in the amount of urine passed and changes in the colour of the urine).
- Tiredness
- Dizziness.

Tell your doctor immediately if any of the following happen to you while you are taking Azathioprine 50mg Tablets:

- You start to notice any signs of a fever or an infection
- You have any unexpected bruising or bleeding
- You develop bad diarrhoea and/or abdominal pain
- You develop jaundice (skin or whites of the eyes turn yellow)
- You develop a chest infection (pneumonitis)
- If you develop lumps on the body or patches on the skin.

You may notice some hair loss while taking Azathioprine 50mg Tablets. This is a rare side effect of Azathioprine that could happen in less than 1 in 1,000 patients. Often hair does grow again, even if you carry on taking Azathioprine 50mg Tablets. If you are worried ask your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE AZATHIOPRINE 50MG TABLETS

Store in the outer carton in order to protect from light.

Keep out of the reach and sight of children.

Do not use Azathioprine 50mg Tablets after the expiry date which is stated on the carton and blister foil.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Azathioprine 50mg Tablets contain

- The active substance is Azathioprine.
- Each tablet contains 50mg of azathioprine.
- The other ingredients are Microcrystalline cellulose, Mannitol, Maize starch, Povidone K25, Croscarmellose sodium, Sodium stearyl fumarate, Hypromellose and Macrogol.

What Azathioprine 50mg Tablets look like and contents of the pack

Azathioprine 50mg Tablets are pale yellow, circular coated tablets. On one side of each tablet are the letters 'AZA', then a score line and the number "50".

Your Azathioprine 50mg Tablets come in blister packs of 56 and 100 tablets

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is:-

Relonchem Limited

27 Old Gloucester Street, London, WC1 3XX, United Kingdom

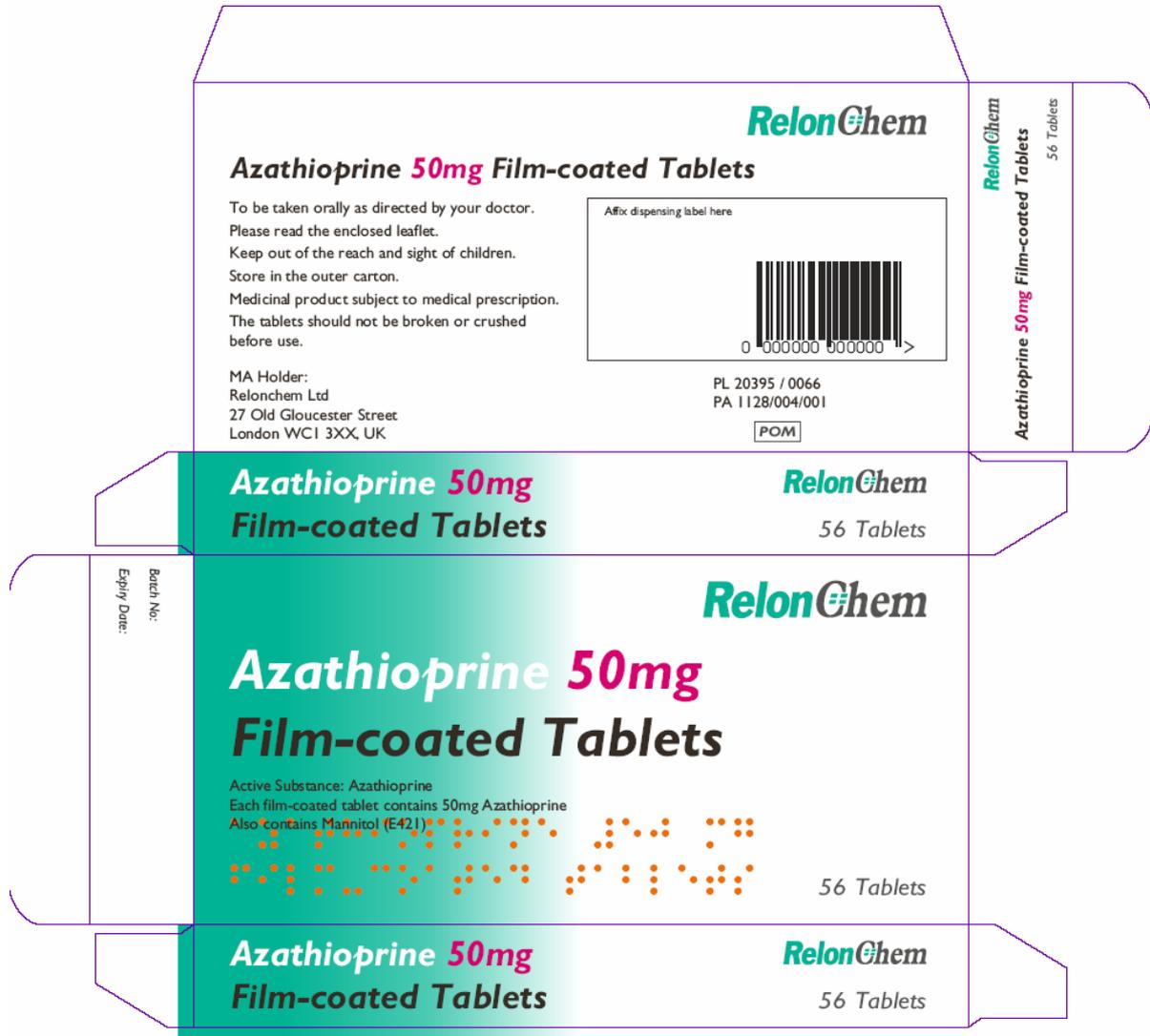
The Manufacturer is:-

Actavis hf, Reykjavikurvegur 78, IS - 220, Hafnarfjordur, Iceland.

This leaflet was last approved in September 2007.

Module 4

Labelling



| | | |
|------------------|--|---|
| RelonChem | Azathioprine 50mg Film-coated Tablets | PL 20395 / 0066 PA 1/28/004/001 POM |
| RelonChem | Azathioprine 50mg Film-coated Tablets | |
| RelonChem | Azathioprine 50mg Film-coated Tablets | MA Holder: Relonchem Ltd United Kingdom |
| RelonChem | Azathioprine 50mg Film-coated Tablets | PL 20395 / 0066 PA 1/28/004/001 POM |
| RelonChem | Azathioprine 50mg Film-coated Tablets | |
| RelonChem | Azathioprine 50mg Film-coated Tablets | MA Holder: Relonchem Ltd United Kingdom |
| RelonChem | Azathioprine 50mg Film-coated Tablets | PL 20395 / 0066 PA 1/28/004/001 POM |
| RelonChem | Azathioprine 50mg Film-coated Tablets | |
| RelonChem | Azathioprine 50mg Film-coated Tablets | MA Holder: Relonchem Ltd United Kingdom |

Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Azathioprine 50 mg Tablets, in the treatment of rheumatoid arthritis, Crohns disease and other autoimmune diseases, can be approved.

EXECUTIVE SUMMARY

Problem statement

This decentralised application concerns a generic version of Azathioprine, submitted under Article 10(1) of Directive 2001/83/EC. In this Assessment Report, the name Azathioprine 50 mg Tablets is used. The originator product is Imuran (50 mg tablets) by GlaxoSmithKline Limited, registered since 11/04/1979 in the EU (Ireland).

With the UK as the Reference Member State in this Decentralised Procedure, Relonchem Limited is applying for the Marketing Authorisations in IE.

About the product

Azathioprine is a mercaptopurine derivative which has cytotoxic and immunosuppressive effects. The main uses of azathioprine include the treatment of active progressive severe rheumatoid arthritis, Crohns disease and other autoimmune diseases. Azathioprine is also used as an immunosuppressive agent in preventing rejection of transplanted organs. Azathioprine is metabolised to mercaptopurine and then to thioinosinate which interferes with purine metabolism. The enzyme thiopurine S-methyltransferase (TPMT) deactivates 6-mercaptopurine. Genetic polymorphisms of TPMT can lead to excessive drug toxicity. The most common side-effects of azathioprine are myelosuppression and opportunistic infections in the immunocompromised. Mercaptopurine interacts with several medicinal products including allopurinol and warfarin. The dose of azathioprine should be reduced if allopurinol is to be prescribed simultaneously.

General comments on the submitted dossier

The application is in accordance with Article 10 (1) Directive 2001/83/EC as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, non-clinical and clinical overviews have been submitted. They represent an adequate summary of the dossier.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product.

A Risk Management Plan and other documentation relating to a Pharmacovigilance system have not been provided and are not required for this generic application.

The package leaflet of Azathioprine 50 mg Tablets has been tested in two test rounds of face-to-face interviews with a total of 20 test participants in order to ensure that potential users could locate, understand and act appropriately upon the information provided in the leaflet. The 90% acceptance criterion was met for all 16 questions.

Assessor's comment

The applicant has carried out two test rounds of face to face interviews and readability of the package leaflet was demonstrated.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for the production at the sites responsible for the manufacture and assembly of this product. The stated manufacturing site for the finished product is outside the Community, the finished product is then shipped and then batch release inside the Community.

The RMS has accepted copies of inspection letter issued by inspection services of New Zealand where an MRA with the EU is in operation as certification that acceptable standards of GMP are in place at the specified finished product manufacturing site. A copy of the current manufacturing authorisation for the batch release site in Iceland has been accepted.

Assurance has been provided of compliance to GCP for the clinical trial site.

SCIENTIFIC OVERVIEW AND DISCUSSION**Quality aspects****Drug Substance**

The chemical-pharmaceutical documentation and Quality overall summary in relation to Azathioprine 50mg tablet are of an acceptable quality in view of the present European regulatory requirements. The active substance Azathioprine is described in the European Pharmacopoeia but a detailed description of the physiochemical properties and structure elucidation process has been provided. The drug substance is manufactured by Fermion Oy, Finland and Fine Chemicals Corporation (Pty) Ltd, 15 Hawkins Avenue, Epping 1, 7460, Cape Town, South Africa. Two manufacturing sites are responsible for Azathioprine manufacture by Fermion Oy, Hanko Plant, Orioninkatu 2, FIN-10900 Hanko and the Oulu Plant, Laaketehtaantie 2, FIN-90650 Oulu. Both manufacturers possess European Drug Master File and letters of access have been provided. A copy of the of Fermion Oy's and Fine Chemical's DMF has been provided for assessment. The specification provided is adequate and batch data provided are in compliance with the Ph Eur specification. Stability data provided demonstrates that Azathioprine manufactured by Fermion Oy is relatively stable and the proposed re-test period of 60 months is acceptable. The proposed 36 months re-test period for Fine Chemicals is also supported by the stability data.

Drug Product

The development of the Azathioprine 50mg tablet has been satisfactory described. Dissolution data have demonstrated that shape of the dissolution profile of the proposed product is comparable to the originator product, Imuran 50mg tablet manufactured by GSK, but the rate of dissolution is different. However, bioequivalence to the originator product has been demonstrated. The product specifications adequately cover appropriate parameters for this dosage form. The analytical methods used are suitably validated. Batch analysis has been performed on three batches of 50mg tablet at commercial production scale and shows the finished product meet the proposed specification. The conditions used in the stability studies are in accordance to the ICH stability guideline. Production scale stability data for six batches has also been provided up to 60 months. No significant change to the product with the exception of the assay value was observed in all ICH conditions. The stability data demonstrate that the proposed shelf-life of 36 months can be accepted. The product has been shown to be sensitive to light and a storage condition of "store in the outer carton" is recommended.

Non clinical aspects**Critical evaluation of the Non-clinical Overview and Summary**

The pharmacodynamic, pharmacokinetic and toxicological properties of azathioprine are well known. Azathioprine has been in clinical use for more than 30 years. As azathioprine is a well known active substance, the applicant has not provided additional non-clinical studies and further studies are not required. An overview based on the literature reviews is appropriate. There is no indication that the safety profile of azathioprine has substantially changed during its period of clinical use.

The overview is based on major international drug manuals and reviews. It is a critical summary of the literature reviewed. It has been written by Dr. rer. Nat. Ingo Janz, a pharmacist by training with some limited experience of scientific research but the majority of work experience in regulatory affairs and subsequently in management. In view of the well known properties of azathioprine, the lack of any formal training or experience in toxicology of the author is not an impediment to its acceptability. The overview refers to 52 publications up to the year 2004. The overview is adequate.

In view of the well documented clinical profile of azathioprine and the extensive description of potential treatment related adverse effects in the SPC, Section 5.3 of the SPC is acceptable.

Conclusions

There are no objections to the approval of azathioprine from the non-clinical point of view.

Clinical aspects

Pharmacokinetics

A bioequivalence study comparing the pharmacokinetic profile of Azathioprine 50 mg tablets (Test) compared to Imurek (Reference) in healthy adult volunteers has been conducted.

The primary objective of the study was to compare the bioequivalence of Azathioprine 50 mg tablets (Test, Douglas, New Zealand) as compared to the pharmaceutical alternative of Imurek (GlaxoSmithKline, Germany) after a single oral dose of 150 mg Azathioprine from the two dosage forms at time zero. The applicant presents a randomised single-centre; single-dose, two-way, cross-over design bioequivalence study conducted in 30 adult healthy volunteers. Volunteers were aged between 18-25 years and were randomly assigned to sequence groups. The study was conducted under GCP guidelines.

The study was carried out with a washout period of 14 days. Administration of the product was on Day 1 and 15 in fasted volunteers at approximately 08:00 hours. 3 x 50 mg tablets of either the test or reference drug were taken with 240 ml of water. Blood samples were taken for the determination of the analytes Azathioprine and its major metabolite 6-mercaptopurine by HPLC methods. Blood was taken at frequent intervals up to 8 hours post-dosing.

Statistical analysis of AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} was carried out using ANOVA, power test and 90% confidence intervals of untransformed and log-transformed data. The Test product was considered bioequivalent to the Reference products if the 90% confidence intervals for the AUC and C_{max} were between 80-125% (CPMP guidelines).

Assessor's comment

The study design is satisfactory and adheres to GCP.

Results

Table 1. Pharmacokinetic parameters for Azathioprine (Test Vs Reference)

| Treatment | AUC _{0-∞} ng hr/ml | AUC _{0-t} ng/ml/h | C _{max} ng/ml | T _{max} hr | t _{1/2} hr |
|---|--------------------------------|-------------------------------|---------------------------|------------------------|------------------------|
| Test (Azathioprine) | 38.1-109.7 | 34.1-103.7 | 20.2-61.9 | 0.40-3.00 | 0.51-1.65 |
| Reference (Imurek) | 41.4-133.0 | 36.8-122.3 | 23.2-67.1 | 0.47-2.52 | 0.38-2.13 |
| *Ratio (90% CI) *log-transformed values | 0.898-1.006 | 0.897-1.015 | 0.932-1.057 | - | - |

AUC_{0-∞} 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

Table 2. Pharmacokinetic parameters for 6-mercaptopurine (Test Vs Reference)

| Treatment | AUC _{0-∞} ng/ml/h | AUC _{0-t} ng/ml/h | C _{max} ng/ml | T _{max} hr | t _{1/2} hr |
|---|-------------------------------|-------------------------------|---------------------------|------------------------|------------------------|
| Test (Azathioprine) | 68.9-210.6 | 62.8-205.0 | 31.6-98.5 | 0.48-3.48 | 0.76-1.68 |
| Reference (Imurek) | 76.5-216.2 | 67.8-210.9 | 28.6-94.6 | 0.47-4.00 | 0.76-2.10 |
| *Ratio (90% CI) *log-transformed values | 0.902-1.055 | 0.901-1.066 | 0.981-1.158 | - | - |

Adverse Events

A total of four adverse events were seen in 4 out of the 30 subjects. These included tiredness, dizziness and dry eyes and were of mild severity. 3 of the adverse events occurred with the reference product and 1 adverse event occurred with the Test product. All adverse events resolved without sequelae or medical intervention. No deaths, other serious or significant adverse events occurred during the study.

Conclusion on Bioequivalence

The 90% confidence intervals for AUC and C_{max} lie within the acceptance criteria of 80-125% for both Azathioprine and 6-mercaptopurine. Therefore, Azathioprine 50 mg tablets (Test) were shown to be bioequivalent to the Imurek (Reference).

Assessor's comment The results of the study showed that the Test product and Reference product are bioequivalent as the confidence intervals for AUC and C_{max} fall within the acceptance criteria ranges of 80-125%, in line with current guidelines.

Pharmacodynamics

No novel pharmacodynamic data are supplied or required for this application. The pharmacodynamic claims in the SPC are appropriately consistent with the innovator product.

Clinical efficacy

No novel efficacy data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the efficacy of Azathioprine.

Clinical safety

No novel safety data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the safety of Azathioprine. No new safety data have been identified.

BENEFIT RISK ASSESSMENT

The use of Azathioprine is well established. It has recognised efficacy and acceptable safety. With regards to the current application, sufficient clinical information has been submitted which includes adequate review of published clinical data. The claim of essential similarity can be accepted. Overall the risk: benefit analysis for Azathioprine 50 mg Tablets is considered favourable and the product is approvable.

Module 6

Steps taken after procedure

None