1. NAME OF THE MEDICINE

Azathioprine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

THIOPRINE tablets contain 50mg of the active azathioprine.

For the list of excipients, see section 6.1 List of excipients.

The tablets are gluten free.

Azathioprine is a pale yellow, odourless powder.

3. PHARMACEUTICAL FORM

The 50 mg film coated tablets are round, yellow, scored and marked “GX” above the score and “CH1” below the score on one side, plain on the other.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Azathioprine is used as an immunosuppressant anti-metabolite 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.

THIOPRINE, in combination with corticosteroids and/or other immunosuppressive agents and procedures, is indicated in the management of patients receiving organ transplants.

THIOPRINE, either alone or more usually in combination with corticosteroids and/or other 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/polymyositis,
- autoimmune chronic active hepatitis,
- pemphigus vulgaris,
- polyarteritis nodosa,
- autoimmune haemolytic anaemia,
- chronic refractory idiopathic thrombocytopenic purpura.

4.2 DOSE AND METHOD OF ADMINISTRATION

THIOPRINE tablets should be administered at least 1 hour before or 3 hours after food or milk.

Specialist medical literature should be consulted for guidance as to clinical experience in particular conditions.
**Dosage in transplantation**

**Adults and children.**

Depending on the immunosuppressive regimen adopted, a loading dose of up to 5 mg/kg/day is usually given. Maintenance dosage may range from 1 to 4 mg/kg/day and must be adjusted according to clinical requirements and haematological tolerance.

Evidence indicates that THIOPRINE therapy should be maintained indefinitely, even if only low doses are necessary, because of risk of graft rejection.

**Dosage in other conditions**

**Adults and children.**

In general, the initial dose should be approximately 1.0 mg/kg/day (50 to 100 mg) gradually increasing in increments of 0.5 mg/kg/day over several weeks, if necessary up to a maximum dose of 2.5 mg/kg/day.

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

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

**Use in the elderly**

See section 4.4 Special warnings and precautions for use – Renal and/or hepatic impairment.

The rapid in vivo cleavage of the azathioprine molecule followed by tissue fixation makes it impossible to relate plasma drug levels to toxicity. There are no specific data as to the tolerance of azathioprine in elderly patients. It is recommended that the dosages used are at the lower end of the range given for adults and children.

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

**Renal/Hepatic Impairment**

See “Section 4.4 Special warnings and precautions for use”

**4.3 CONTRAINDICATIONS**

THIOPRINE is contraindicated in patients known to be hypersensitive to azathioprine or any other component of the preparation. Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to THIOPRINE.

Patients with rheumatoid arthritis previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan or others) may have a prohibitive risk of neoplasia if treated with THIOPRINE.

THIOPRINE therapy should not be initiated in patients who may be pregnant, who are likely to become pregnant in the near future, or who are known to be pregnant (see Section 4.4 Special warnings and precautions for use).
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Co-administration of ribavirin and azathioprine is not advised. Ribavirin may reduce efficacy and increase toxicity of azathioprine.

Cytomegalovirus (CMV) disease (see Section 4.8 Adverse effects (Undesirable effects))

Cytomegalovirus (CMV) viraemia resulting in severe pneumonitis and associated haemophagocytic syndrome manifesting in patients with inflammatory bowel disease has been reported in the literature.

Caution should be exercised and specialist literature consulted when determining the risks of CMV reactivation and IBD deterioration.

Monitoring

There are potential hazards to the use of this drug. It should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of therapy.

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

During the first eight weeks of therapy, complete blood counts, including platelets, must be performed weekly, or more frequently if high dosages 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 recommended that complete blood counts are repeated at intervals of not longer than one month or more frequently if dosage alterations or other changes to therapy are made. Delayed haematological suppression may occur.

Prompt reduction in dosage or temporary withdrawal of the drug may be necessary if there is a rapid fall in, or persistently low, leucocyte count or other evidence of bone marrow depression.

Patients receiving THIOPRINE should be instructed to report immediately if there is any evidence of infection, unexpected bruising or bleeding, black tarry stools and blood in the urine or stools, or other manifestations of bone marrow depression. Bone marrow suppression is reversible if azathioprine is withdrawn early enough.

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 THIOPRINE. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (see Section 4.8 Adverse effects (Undesirable effects)). Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore, close monitoring of blood counts is still necessary.

The dosage of azathioprine may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression.

Renal and/or Hepatic Impairment

It is impossible to relate plasma levels of azathioprine or 6-mercaptopurine to therapeutic efficacy or toxicity. Conversion of 6-thioinosinic acid to 6-thiouric acid by xanthine oxidase is not dependent on intact hepatic and/or renal function. Nevertheless, it is recommended that the dosages used are at the lower end of the normal range and that haematological response is carefully monitored. Dosage should be further reduced if haematological toxicity occurs.

Caution is necessary during the administration of azathioprine to patients with hepatic dysfunction, and regular complete blood counts and liver function tests should be undertaken. In such patients the metabolism of azathioprine may be impaired, and the dosage of azathioprine further reduced if hepatic or haematological toxicity occurs.
Lesch-Nyhan syndrome

Limited evidence suggests that azathioprine 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 THIOPRINE.

Mutagenicity

Chromosomal abnormalities, which can occur independently of the influence of THIOPRINE, have been demonstrated in both male and female transplant recipients.

Chromosomal abnormalities which disappear in time have been demonstrated in offspring of transplant recipients. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in these offspring.

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.

Teratogenicity

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

Epidemiological evidence in man indicates that the frequency of occurrence of congenital abnormalities in the offspring of maternal transplant recipients is similar to that in the general population.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving THIOPRINE.

Carcinogenicity

Patients receiving immunosuppresive therapy, including azathioprine, are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder. A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

Varicella Zoster Virus Infection (see Section 4.8 Adverse effects (Undesirable effects))

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Infection with varicella zoster virus (VZV, chickenpox and herpes zoster) may become severe during the administration of immunosuppressants. Caution should be exercised especially with respect to the following:

Before starting the administration of immunosuppressants, the prescriber should check to see if the patient has a history of VZV. Serologic testing may be useful in determining previous exposure. Patients who have no history of exposure should avoid contact with individuals with chickenpox or herpes zoster. If the patient is exposed to VZV, special care must be taken to avoid patients developing chickenpox or herpes zoster, and passive immunisation with varicella-zoster immunoglobulin (VZIG) may be considered.

If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.
Progressive Multifocal Leukoencephalopathy (PML)

PML, an opportunistic infection caused by the JC virus (a type of human polyomavirus) has been reported in patients receiving azathioprine with other immunosuppressive agents. Immunosuppressive therapy should be withheld at the first sign or symptoms suggestive of PML and appropriate evaluation undertaken to establish a diagnosis (see Section 4.8 Adverse effects (Undesirable effects)).

Hepatitis B (see Section 4.8 Adverse effects (Undesirable effects))

Hepatitis B carriers (defined as patients positive for hepatitis B surface antigen [HBsAg] for more than six months), or patients with documented past HBV infection, who receive immunosuppressive drugs are at risk of reactivation of HBV replication, with asymptomatic increases in serum HBV DNA and ALT levels. Specialist medical literature should be consulted for guidance including prophylactic therapy with oral anti-HBV agents.

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD) and there could potentially be an increased susceptibility for developing the condition with the use of azathioprine. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with azathioprine should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Other Precautions

Azathioprine should be used with caution in hypersplenism.

Withdrawal of azathioprine should be gradual and performed under close supervision.

Dental work, whenever possible should be completed prior to initiation of azathioprine therapy or deferred until blood counts are normal.

Hypersensitivity

Patients suspected to have previously presented a hypersensitivity reaction to 6-mercaptopurine should not be recommended to use its pro-drug azathioprine, and vice-versa, unless the patient has been confirmed as hypersensitive to the culprit drug with allergological tests, and tested negative for the other.

Use in the elderly

The safety and efficacy of azathioprine have not been established (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Use in the elderly).

Paediatric use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Allopurinol/oxypurinol/thiopurinol.

Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol which results in reduced conversion of biologically active 6-thiinoisinic acid to biologically inactive 6-thiouric acid. When allopurinol, oxipurinol and/or thiopurinol are given concomitantly with 6-mercaptopurine (6-MP) or azathioprine, the dose of 6-MP and azathioprine should be reduced to one quarter of the original dose.
Other xanthine oxidase inhibitors, such as febuxostat may decrease the metabolism of azathioprine. Concomitant administration is not recommended as data is insufficient to determine an adequate dose reduction.

**Neuromuscular blocking agents.**

Azathioprine can potentiate the neuromuscular blockade produced by depolarising agents such as succinylcholine and reduce the blockade produced by non-depolarising agents such as tubocurarine.

**Anticoagulants.**

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with azathioprine. Therefore, higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with azathioprine.

**Cytostatic agents/myelosuppressive agents.**

Azathioprine should be used with caution in patients receiving, or who have recently received, other bone marrow suppressive 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 and the combination of sulfamethoxazole/trimethoprim.

There have been case reports suggesting that haematological abnormalities may develop due to the concomitant administration of azathioprine and ACE inhibitors.

It has been suggested that cimetidine and indomethacin may have myelosuppressive effects which may be enhanced by concomitant administration of azathioprine.

**Aminosalicylates.**

As there is *in vitro* and *in vivo* evidence that aminosalicylate derivatives (e.g. olsalazine, meslazine or sulfasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent azathioprine therapy (see Section 4.4 Special warnings and precautions for use).

**Methotrexate.**

When azathioprine is administered concomitantly with high dose methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.

**Vaccines.**

The immunosuppressive activity of azathioprine could result in an atypical and potentially deleterious response to live vaccines and so the administration of live vaccines to patients receiving azathioprine therapy is contraindicated 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 do not deleteriously affect the response to polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration.

**Ribavirin.**

Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin; therefore co-administration is not advised.
Infliximab.

An interaction has been observed between azathioprine and infliximab. Patients receiving ongoing azathioprine experienced increase in 6-TGN (6-thioguanine) nucleotide, an active metabolite of azathioprine) levels and a decrease in the mean leukocyte count following infliximab infusion.

Miscellaneous.

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

Drugs known to induce (phenytoin, phenobarbital, rifampicin) or inhibit (ketoconazole, erythromycin) hepatic microsomal enzymes may alter the clearance of THIOPRINE.

Co-administration of THIOPRINE and captopril may result in increased susceptibility to leucopenia.

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in Pregnancy (Category D)

The decision to maintain or discontinue THIOPRINE during pregnancy, or to terminate the pregnancy, depends on the condition under treatment in which the maternal wellbeing has to be weighed against possible risks to the foetus. As a general rule, THIOPRINE therapy should not be initiated in patients known to be pregnant.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving THIOPRINE.

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.

The rare possibility of neonatal leucopenia and/or thrombocytopenia which may not be clinically evident appears to be preventable by reducing maternal dosage of azathioprine if, at 32 weeks' gestation, the maternal leucocyte count is at or below 8.6 x 10^9/L. The possibility of neonatal immunosuppression is a serious and potentially fatal complication. Extra care in haematological monitoring is advised during pregnancy.

Effects on Fertility

Relief of chronic progressive renal failure by renal transplantation involving the use of azathioprine has been accompanied by increased fertility in both male and female transplant recipients.

Use in Lactation

6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment. Nursing mothers should be advised to consult their physician, since use by nursing mothers is not recommended because of possible adverse effects on the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person’s ability drive and use machines were not assessed as part of its registration.
4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Hypersensitivity reactions.

Several different clinical syndromes, which appear to be of an idiosyncratic hypersensitivity nature, have been described occasionally. They include general malaise, headache, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, vasculitis, myalgia, muscular pains, arthralgia, hypotension, disturbed hepatic function, cholestatic jaundice, pancreatitis, cardiac dysrhythmia, and renal dysfunction. In many cases, rechallenge has confirmed an association with azathioprine.

Additional adverse reactions of low frequency have been reported. These include skin rashes (approximately 2%), steatorrhoea, negative nitrogen balance, Stevens-Johnson syndrome and toxic epidermal necrolysis (all less than 1%).

It has been suggested that the imidazole side chain gives rise to hypersensitivity, whereas the 6-mercaptopurine (6-MP) molecule gives rise to cholestasis.

Immediate withdrawal of azathioprine and supportive circulatory measures has led to recovery in the majority of cases. Other marked underlying pathology has contributed to the very rare deaths reported.

THIOPRINE should be PERMANENTLY withdrawn after any such clinical syndrome.

Benign, malignant and unspecified neoplasms (including cysts and polyps).

The risk of developing lymphomas and other malignancies, notably skin cancers 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 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).

Rare: neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ (see section 4.4 Special warnings and precaution for use).

Haematopoiesis.

Azathioprine 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 thiopurine methyltransferase (TMPT) deficiency and renal or hepatic insufficiency, and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol therapy.

Therapeutic use of azathioprine is associated with a reversible, dose related reduction in numbers of circulating total white cells, granulocytes and lymphocytes together with increases in mean corpuscular volume and red cell haemoglobin content. Megaloblastic bone marrow changes have been observed, but severe megaloblastic anaemia and erythroid hypoplasia are rare.

THIOPRINE may produce thrombocytopenia which is dose related and may be delayed.

Alopecia.

Hair loss has been described in 50% of renal transplant recipients receiving azathioprine and corticosteroids, but does not appear to be a major problem when azathioprine is used for other indications. It is reversible in over 80% of cases despite continuing immunosuppression.
Susceptibility to infection.

Patients receiving azathioprine alone or in combination with other immunosuppressants, particularly corticosteroids have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection and reactivation with vZV, hepatitis B and other infectious agents. Viral, fungal and bacterial infections are very common in transplant patients receiving azathioprine in combination with other immunosuppressants.

Very rare cases of JC virus associated PML have been reported following the use of azathioprine in combination with other immunosuppressants (see section 4.4 Special warnings and precautions for use).

Gastrointestinal reactions.

Nausea, vomiting and gastrointestinal discomfort may occur during the first few months of THIOPRINE therapy. These effects are usually reduced by dosage adjustment and by administering the tablets in divided doses and/or after meals.

Serious complications, including colitis, diverticulitis and bowel perforation, have been described in transplant recipients and appear to relate to high dosage of corticosteroids rather than to azathioprine per se.

Severe diarrhoea, recurring on rechallenge, has been reported in patients treated with azathioprine 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 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 rechallenge has confirmed an association with azathioprine on occasions.

Pulmonary reactions.

Reversible pneumonitis has been described very rarely.

Hepatotoxicity.

Cholestasis and deterioration of liver function have occasionally been reported in association with azathioprine therapy and are usually reversible on withdrawal of therapy. This may be associated with symptoms of hypersensitivity (see section 4.8 Adverse Effects - Hypersensitivity reactions).

Hepatotoxicity may manifest by elevation of serum alkaline phosphatase, bilirubin and/or serum transaminases and is generally reversible after interruption of azathioprine. Periodic measurement of serum transaminases, alkaline phosphatase and bilirubin is indicated for early detection of hepatotoxicity. Hepatotoxicity has been uncommon (less than 1%) in patients with rheumatoid arthritis.

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

Others adverse effects

Other adverse reactions include sores in the mouth and on the lips, meningitis, formication, exacerbation of myasthenia gravis and dermatomyositis and alterations in the senses of smell or taste.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.
4.9 OVERDOSE

Signs

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with azathioprine 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 overdosage. Occasional reports describe ingestion of from 0.5 to 7.5 g azathioprine on a single occasion with apparent uneventful recovery.

Treatment

Treatment is symptomatic and has included gastric lavage. If overdosage occurs, the blood picture and hepatic function in particular should be monitored. Azathioprine is dialysable but the procedure is of doubtful value since azathioprine is rapidly metabolised with entry of metabolites into tissue cells.

For information on the management of overdose, immediately contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). Azathioprine is used for the suppression of the immune response. Azathioprine 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 which 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. Determinations of plasma concentrations of azathioprine or 6-MP have no prognostic value as regards effectiveness of 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 immune response.
4. Damage to deoxyribonucleic acid (DNA) through incorporation of purine thioanalogues.

Because of these mechanisms, the therapeutic effect of THIOPRINE may be evident only after several weeks or months of treatment.

THIOPRINE appears to be well absorbed from the upper gastrointestinal tract.

Studies in mice with 35S-azathioprine showed no unusually large concentration in any particular tissue, but there was very little 35S found in the brain.
Clinical trials
No data available

5.2 PHARMACOKINETIC PROPERTIES
No data available.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
See Section 4.4 Special warnings and precaution for use

Carcinogenicity
See Section 4.8 Adverse effects (Undesirable effects).

Patients receiving immunosuppressive therapy are at an increased risk of developing lymphomas and other malignancies, notably skin cancers. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

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 by wearing protective clothing and using a sunscreen with a high sun protection factor (SPF).

Renal transplant recipients in some geographical areas are at greater risk of skin cancers than those in other areas.

Other neoplasms reportedly associated with azathioprine include carcinoma of the urinary bladder and adenocarcinoma of the lung.

6. PHARMACEUTICAL PROPERTIES

6.1 LIST OF EXCIPIENTS
The tablets also contain the following inactive excipients: lactose, starch - maize, starch - pregelatinised maize, stearic acid, povidone, magnesium stearate, hypromellose and macrogol 400.

6.2 INCOMPATIBILITIES
No data available.

6.3 SHELF LIFE
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER
Pack sizes: blister packs of 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Film-coated Thioprine tablets should not be divided, crushed or broken.

Provided that the film-coating is intact, there is no risk in handling film-coated Thioprine tablets.
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical name: 6-[(1-methyl-4-nitro-1H-imidazol-5-yl) thio]-1H-purine

Chemical structure:

![Chemical structure](image)

CAS#: 446-86-6

Molecular formula: C₉H₇N₇O₂S

Molecular weight: 277.3

Azathioprine is practically insoluble in water, in ethanol (96%) and in chloroform and sparingly soluble in dilute mineral acids. It dissolves in dilute solutions of alkali hydroxides.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Alphapharm Pty Limited

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 73

www.mylan.com.au

9. DATE OF FIRST APPROVAL

30/09/1996

10. DATE OF REVISION

17/09/2018
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