Name of the Medicine

Active ingredient: Azathioprine.
Chemical name: 6-[(1-methyl-4-nitro-1H-imidazol-5-yl) thio]-1H-purine.
Structural formula:

![Structural formula of Azathioprine]

Molecular formula: C₉H₇N₇O₂S  Molecular weight: 277.3
CAS Registry No: 446-86-6

Description

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). Azathioprine is used for the suppression of the immune response.

It is a pale yellow, odourless powder which 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.

The active ingredient in Thioprine is azathioprine. Each Thioprine tablet contains 50 mg of azathioprine. The tablets also contain the following inactive excipients: lactose, starch - maize, starch - pregelatinised maize, stearic acid, povidone, magnesium stearate, hypromellose and macrogol 400. The tablets are gluten free.

Pharmacology

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 $^{35}$S-azathioprine showed no unusually large concentration in any particular tissue, but there was very little $^{35}$S found in the brain.

**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: systemic lupus erythematosus, severe rheumatoid arthritis, chronic refractory idiopathic
thrombocytopenic purpura, autoimmune haemolytic anaemia, autoimmune chronic active hepatitis, pemphigus vulgaris, dermatomyositis/polymyositis, polyarteritis nodosa.

**Contraindications**

Hypersensitivity 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 **Precautions**).

**Precautions**

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

**Monitoring**

There are potential hazards to the use of this drug. Therefore, 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 are 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 thioprine 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 myelodysplasias has been reported in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (see **Adverse 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 humans 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 (see Adverse Reactions)**

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.

**Varicella Zoster Virus Infection (see Adverse Reactions)**

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 Adverse Effects).

**Hepatitis B (see ADVERSE 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.

**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 $8.6 \times 10^9/L$. 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.

**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.

**Interactions with Other Medicines**

*Allopurinol/oxypurinol/thiopurinol.* Xanthine oxidase activity is inhibited by allopurinol, oxypurinol 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 (6-MP) or azathioprine, the dose of 6-MP and azathioprine should be reduced to one quarter of the original dose.

*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 Precautions).

*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 myelosupression has been reported following concomitant administration of azathioprine and ribavirin; therefore co-administration is not advised.

*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.
Adverse 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.

_Neoplasms benign and malignant (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 patients 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).

_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 _Precautions_).

_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 _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 hepatis, 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. 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.

Dosage and Administration

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

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

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 $1 \text{ mg/kg/day}$, to $3 \text{ mg/kg/day}$, depending on the clinical condition being treated and the individual patient response, including haematological tolerance.

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

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.

**Safe handling of Thioprine tablets**

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.

**Overdosage**

**Symptoms.** 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 $7.5 \text{ g}$ 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.

In cases of overdosage, immediately contact the Poisons Information Centre on 131126 for advice on management.
Presentation and Storage Conditions

*Thioprine*, 50 mg tablet: round, yellow, film coated tablet, scored and marked “GX” above the score and “CH1” below the score on one side, plain on the other; blister packs of 100 tablets.

Store below 30°C. Protect from light.

Poison Schedule of the Medicine

S4

Name and Address of the Sponsor

Alphapharm Pty Limited

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

www.alphapharm.com.au

Date of First Inclusion on the Australian Register of Therapeutic Goods (the ARTG)

30th September 1996

Date of Most Recent Amendment

24 April 12