AZAPIN

NAME OF THE MEDICINE

AZAPIN (azathioprine) 50 mg tablets

AZAPIN tablets contain azathioprine. Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). Its chemical name is 6-[(1-methyl-4-nitro-1H-imidazol-5-yl)thio]-1H-purine. MW 277.3. Structurally it is represented as:

\[ \text{Chemical Structure Image} \]

DESCRIPTION

It is a pale yellow powder, which is stable under ordinary conditions. It is practically insoluble in water, in ethanol (96%), and in chloroform and is sparingly soluble in dilute mineral acids. It dissolves in dilute solutions of alkali hydroxides.

Other ingredients of AZAPIN tablets are: cellulose microcrystalline, mannitol, maize starch, povidone, croscarmellose sodium, and sodium stearyl fumarate and Opadry™ clear OY-7240 (macrogol 400 and hypromellose).

PHARMACOLOGY

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down in vivo into 6-MP and a methyl nitro-imidazole 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 transverse 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 methyl nitroimidazole 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.

The determination of azathioprine or 6-MP plasma concentrations has no prognostic value as regards effectiveness or toxicity of these compounds.

While the precise mode of action remains to be elucidated, some suggested mechanisms include:

- The release of 6-MP which acts as a purine antimetabolite;
- The possible blockade of –SH groups by alkylation;
- The inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of immune response.
- Damage to deoxyribonucleic acid (DNA) through incorporation of purine thioanalogues.
Because of these mechanisms, the therapeutic effect of azathioprine may be evident only after several weeks or months of treatment.

Studies in mice with 35S-azathioprine showed no unusually large concentration in any particular tissue although, concentrations of 35S-azathioprine are very low in the brain.

**Pharmacokinetics.**

**Absorption** Azathioprine is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in 1 to 2 hours with a biological half-life of 5 hours following single doses.

**Distribution** After oral administration it disappears rapidly from the circulation and is extensively metabolised to mercaptopurine. Both azathioprine and mercaptopurine are about 30% bound to plasma proteins. About 10% of the dose of azathioprine is split between the sulphur and the purine ring to give 1-methyl-4-nitro-5-thioimidazole. Small amounts of unchanged azathioprine and mercaptopurine are eliminated in the urine.

**INDICATIONS**

Azathioprine is used as an immunosuppressant / antimetabolite either alone or, more commonly, in combination with the other agents (usually corticosteroids) and procedures which influence the immune response. Therapeutic effects 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, in combination with corticosteroids and / or other immunosuppressive agents and procedures, is indicated in the management of patients receiving organ transplants.

Azathioprine, 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, and chronic refractory idiopathic thrombocytopenic purpura.

**CONTRAINDICATIONS**

The use of **AZAPIN** is contraindicated in patients with a previous history of hypersensitivity to azathioprine, any other component of the preparation, or any of the excipients in this product (listed previously). Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to azathioprine.

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

Therapy with **AZAPIN** 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. (Refer precautions)

**PRECAUTIONS**

"Cytomegalovirus (CMV) disease (see ADVERSE 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 associated with the use of azathioprine. Azathioprine should be prescribed only if the patient can be adequately monitored for toxic effects throughout the entire duration of treatment.

During the first eight weeks of therapy, complete blood counts, including platelets, must be performed weekly or more frequently if high dosage is used or if a co-existent 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 be
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.

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

Patients receiving azathioprine 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.

There are individuals with an inherited deficiency of the enzyme thiopurine methltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initial treatment with AZAPIN. 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 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.

Renal and / or hepatic insufficiency
It is impossible to relate plasma levels of azathioprine or 6-mercaptopurine to therapeutic efficacy or toxicity. The 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 AZAPIN to patients with hepatic dysfunction, and regular complete blood counts and liver function tests should be undertaken. In such patients the metabolism of AZAPIN may be impaired, and the dosage of AZAPIN should therefore be reduced to the lower end of the recommended range. Dosage should be further reduced if hepatic or haematological toxicity occurs.

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

Carcinogenesis, mutagenesis, impairment of fertility
Mutagenesis Chromosomal abnormalities, which may occur independently of the influence of azathioprine, 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 AZAPIN.

Carcinogenicity
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.
Patients receiving multiple immunosuppressive agents may be at risk of over-immunosuppressive, 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.

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)
Infection with varicella zoster virus (VZV; chicken pox 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.

Use in Pregnancy (Pregnancy Category D)
The decision to maintain or discontinue azathioprine treatment during pregnancy, or to terminate the pregnancy, depends on the condition being treated, in which maternal wellbeing has to be weighed against the possible risks to the foetus. As a general rule therapy with azathioprine 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 azathioprine.

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 the maternal administration of azathioprine.

The rare possibility of neonatal leucopenia and / or thrombocytopenia that may not be clinically evident appears to be preventable by the reduction in maternal dose 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.

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 the 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.

The 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.
ADVERSE EFFECTS

Hypersensitivity reactions
There have been occasional reports of several different clinical syndromes that appear to be of an idiosyncratic hypersensitivity nature. These include general malaise, headache, dizziness, nausea, vomiting, diarrhoea, fever, rigours, exanthema, rash, vasculitis, myalgia, muscular pain, 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 have been reported at a low frequency. 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.

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

Azathioprine use should be permanently withdrawn after any such clinical hypersensitivity syndrome.

Neoplasms benign and malignant (including cysts and polyps)
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 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).

Haematopoiesis
AZAPIN 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 AZAPIN when receiving concurrent allopurinol therapy.

The therapeutic use of azathioprine has also been associated with 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.

Azathioprine may produce thrombocytopenia that 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 with varicella, herpes zoster Cytomegalovirus (CMV) and other infectious agents (see PRECAUTIONS). Viral, fungal and bacterial infections are very common in transplant patients receiving azathioprine in combination with other immunosuppressants.

Gastrointestinal
Nausea, vomiting and gastrointestinal discomfort may occur during the first few months of therapy with azathioprine. 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 receiving immunosuppressive therapy. However, the aetiology is not clearly established and high-dose corticosteroids may be implicated. 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 medicine-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 medicine, although rechallenge has confirmed an association with azathioprine on occasions.

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

**Respiratory**
Reversible pneumonitis has been described very rarely.

**Hepatotoxicity**
Hepatotoxicity may manifest by the elevation of serum alkaline phosphatase, bilirubin and / or serum transaminases and is generally reversible after interruption of azathioprine. The periodic measurement of serum transaminases, alkaline phosphatase and bilirubin is indicated for the 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 dilatation, 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. AZAPIN should be permanently withdrawn in patients with hepatic veno-occlusive disease.

**Other**
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 and taste.

**INTERACTIONS WITH OTHER MEDICINES**

**Allopurinol / oxypurinol / thiopurinol**
The activity of the enzyme xanthine oxidase is inhibited by allopurinol, oxipurinol and thiopurinol. This results in the reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol, oxypurinol 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 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.

**Cytostatic/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 AZAPIN and co-trimoxazole.

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

**Warfarin**
Inhibition of the anticoagulant effect of warfarin, when administered with azathioprine, has been reported.
**Aminosalicylates**
As there is *in vitro* evidence that aminosalicylate derivatives (e.g. olsalaxine, meslazine or sulfasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent azathioprine therapy (see Precautions).

**Vaccines**
The immunosuppressive activity of AZAPIN could result in an atypical and potentially deleterious response to live vaccines and so the administration of live vaccines in patients receiving AZAPIN 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.

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

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

The co-administration of azathioprine and captopril may result in increased susceptibility to leucopenia.

**DOSE AND ADMINISTRATION**

**AZAPIN** tablets are intended for oral administration only.

**Transplantation – Adults and Children**
Depending on the immunosuppressive regimen employed, a dosage of up to 5 mg / kg bodyweight / day may be given orally on the first day of therapy.

The maintenance dosage should range from 1 to 4 mg / kg / day orally, and must be adjusted according to clinical requirements and haematological tolerance.

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

**Other Conditions – Adults and Children**
In general, the starting dose is from 1 mg / kg / day, gradually increasing in increments of 0.5 mg / kg per day over several weeks, if necessary up to a maximum 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 the maintenance of that response. If no improvement occurs in the patient’s condition within 3 months, consideration should be given to withdrawing azathioprine.

The maintenance dosage required may range from less than 1 mg / kg per day, to 3 mg / kg per 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 levels to drug toxicity. There are no specific data as to the tolerance of elderly patients to azathioprine. It is recommended that the dosages used be 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.

**OVERDOSAGE**
The oral LD$_{50}$ for single doses of azathioprine in mice and rats is 2500 mg / kg and 400 mg / kg respectively.
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 overdose. Occasional reports describe ingestion of azathioprine from 0.5 to 7.5 g on a single occasion with apparent uneventful recovery.

Treatment
Symptomatic; it 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.

PRESENTATION AND STORAGE
AZAPIN 50 mg tablet: A pale yellow, round, film coated, biconvex, tablet engraved with “AZA”, breakline & “50” on one face. The other face is plain.

AZAPIN tablets are available in blister packs of 100 tablets.

Storage: Store below 30°C. Protect from light and moisture.

Safe Handling of Azathioprine Tablets
Azathioprine tablets should not be divided, crushed or broken. Provided that the film coating is intact, there is no risk in handling film coated tablets.

POISONS SCHEDULE
Prescription Medicine (S4)

NAME AND ADDRESS OF THE SPONSOR
Arrow Pharma Pty Ltd
15 – 17 Chapel Street
Cremorne VIC 3121

AZAPIN 50 mg AUST R 92801

DATE OF FIRST INCLUSION ON THE AUSTRALIA REGISTER OF THERAPEUTIC GOODS (ARTG)
26 March 2003

DATE OF MOST RECENT AMENDMENT
3 July 2017