AZAMUN™

Consumer Medicine Information

Azathioprine 50 mg tablets

Presentation
A light yellow, circular, biconvex tablet, engraved with 'AZA' and '50' separated by a line on one side and plain on the other side.

Uses
Actions
Azathioprine is an imidazolyl derivative of mercaptopurine. It acts as an immunosuppressant and anti-neoplastic agent with similar actions to those of mercaptopurine, to which it is converted in the body. Its effects may not be seen for several weeks after administration.
The exact mechanism of its immunosuppressive action is not clear. However many of its effects are believed to be attributable to competitive inhibition of hypoxanthine - guanine phosphoribosyltransferase by thioinosic acid, the product of transformation. This competition inhibits nucleic acid and protein synthesis.
In addition, methylated derivatives of 6-mercaptopurine may potentiate the suppressive effects of other 6-mercaptopurine derivatives.
Comparative studies utilising 6-mercaptopurine and azathioprine suggest that 6-mercaptopurine is responsible for most of the immunosuppressive effects of azathioprine. Azathioprine suppresses T-cell more than B-cell activity; it has limited anti-inflammatory properties. Clinically, the number of mononuclear and granulocytic cells available for migration to an area of inflammation is decreased. It also inhibits the proliferation of promyelocytes within bone marrow, thus decreasing the number of circulating monocytes available to become macrophages in the peripheral blood.
Azathioprine exerts its maximum immunosuppressive effect when given immediately after immunologic challenge (induction phase). When given prior to antigen challenge (preinduction phase), it may augment antibody response in specific immunoglobulin classes. Azathioprine is not effective when given in the effector phase (proliferation and maturation phases). Therefore, the compound has no effect on established graft rejections or secondary responses.
Azathioprine has been used extensively in allotransplantation procedures; it also has been administered in systemic lupus erythematosus, rheumatoid arthritis, polymyositis, Crohn's disease, and other collagen, vascular, and systemic inflammatory states.
It is at least as effective as the alkylating agents and is less toxic. Usual daily doses do not have pronounced effects on immunologic responses per se. A clinical response is not noted for two to four weeks.

Pharmacokinetics
Azathioprine is slowly but completely absorbed from the gastrointestinal tract when given by mouth. It disappears rapidly from the circulation and its major, active metabolite, 6-mercaptopurine is detectable one hour after oral administration.
Azathioprine is cleaved to 6-mercaptopurine and methylnitroimidazole. 6-mercaptopurine is further metabolised to methylated derivatives, thioinosinic acid and 6-thiouric acid, the latter by xanthine oxidase in the liver.
The half-life of the resultant metabolite, 6-mercaptopurine ranges from thirty minutes to four hours.
The wide variation in 6-mercaptopurine half-life after oral azathioprine administration probably reflects important differences in the disposition and metabolism of 6-mercaptopurine. 6-mercaptopurine is rapidly absorbed by cells and converted into 6-mercaptopurine ribonucleotide. Intracellular dephosphorylation can permit 6-mercaptopurine to be released back into the bloodstream.
The release phase may explain the longer half-life of plasma 6-mercaptopurine compared to azathioprine and the clinical effect may persist for long periods after the medication is eliminated.
Several studies have suggested that azathioprine dosage has a direct relationship to toxicity. However current studies refute this correlation, based on the similarly of the kinetics of rosette inhibition activity (RIA) for patients with poor renal function compared with patients with good renal function.
Azathioprine is mainly eliminated by metabolic degradation. Small amounts of unchanged drug and mercaptopurine are eliminated by the kidney. Following oral administration, no azathioprine or mercaptoprine is detectable in the urine after 8 hours.
Mercaptopurine is widely distributed in body tissues, but only a small percentage enters the cerebrospinal fluid. About 30% of both azathioprine and mercaptopurine is bound to serum protein.

Indications
AZAMUN is used as an immunosuppressant antimetabolite either alone, or more commonly in combination with other agents (usually corticosteroids) and procedures that influence the immune response. The therapeutic effect of **AZAMUN** may be evident only after weeks or months and can include a steroid-sparing effect, thereby reducing the toxicity associated with high dosage and the prolonged use of corticosteroids.
AZAMUN, in combination with corticosteroids and/ or other immuno-suppressive agents and procedures is indicated to enhance the survival or organ transplants, such as renal, cardiac and hepatic transplants; and to reduce the corticosteroid requirements of renal transplant recipients. **AZAMUN**, either alone or in combination withcorticosteroids and/or other medicines and procedures has been used with clinical benefit (which may result in a dose reduction to/or the discontinuation of corticosteroid therapy) in a proportion of patients suffering from: severe rheumatoid arthritis; systemic lupus erythematosus; dermatomyositis and polymyositis; auto-immune chronic active hepatitis; pemphigus vulgaris; polyarteritis nodosa; auto-immune haemolytic anaemia and chronic refractory idiopathic thrombocytopenic purpura.

Dosage and Administration
Azathioprine is a potent immuno-suppressive agent and should be used under the direction of a physician familiar with the risk associated with this type of therapy. The patient should be evaluated carefully and monitored adequately during treatment.
Transplantation: Adults and Children: Depending on the immuno-suppressive regimen adopted, a loading dose of up to 5mg/kg bodyweight/day is usually given.
Maintenance dosage may range from 1 to 4mg/kg bodyweight/day orally and must be adjusted according to clinical requirements and haematological tolerance.
Other Conditions: Adults and Children: In general, starting dosage rarely exceeds 3mg/kg bodyweight/day, and should be reduced 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 maintenance of that response. If no improvement occurs in the patient's condition within three months, consideration should be given to withdrawing Azamun.
The maintenance dosage required may range from less than 1mg/kg bodyweight/day to 3mg/kg bodyweight/ day, depending on the clinical condition being treated and the individual patient response, including haematological tolerance.
Use in the Elderly: 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 and/or Hepatic Insufficiency: 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 haemotological response is carefully monitored.
The maintenance dosage used for the treatment of liver disorders is at the low end of the recommended range.

Contraindications
- Hypersensitivity to azathioprine or 6-mercaptopurine
- Chickenpox, existing or recent (including recent exposure).
- Herpes zoster.
- Pregnancy should be considered a contraindication

Warnings and precautions
Azathioprine should be used with care in patients with liver damage or a history of liver disease.
The bone marrow depressant effects of azathioprine may result in an increased incidence of microbial infection, delayed healing and gingival bleeding. Dental work, wherever possible, should be completed prior to initiation of therapy or deferred until blood counts have returned to normal. Patients should be instructed in proper oral hygiene during treatment. In addition, azathioprine rarely causes sores in the mouth and on the lips.
Use in Elderly:
Although appropriate studies have not been performed in the geriatric population, geriatrics-specific problems that would limit the usefulness of this medication in the elderly are not expected. However, elderly patients are more likely to have age-related renal function impairment, which may require reduced dosage in patients receiving azathioprine.
Use in Children:
Studies performed to date have not demonstrated paediatrics-specific problems that would limit the usefulness of azathioprine in children.
Use in Lactating Women:
Azathioprine and/or its metabolites have not been demonstrated in the breast milk of patients receiving Azathioprine. However, nursing mothers should be advised to contact their physician, since use by nursing mothers is not recommended because of possible adverse effects on the infant.
Use in Pregnancy:
The decision to maintain or discontinue Azathioprine 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, Azathioprine therapy should not be initiated in patients known to be pregnant.
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.
Studies in pregnant rats, mice and rabbits using azathioprine in dosages from 5 - 15mg/kg bodyweight/ day over the period of organogenesis have shown varying degrees of foetal abnormalities. Teratogenicity was evident in rabbits at 10mg/kg bodyweight/day.
Epidemiological evidence in man indicates that the frequency of occurrance of congenital abnormalities in the offspring of maternal transplant recipients is similar to that in the general population.
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.
Mutagenicity Studies:
Mutagenic effects have been reported in animals, and chromosomal abnormalities (reversible when azathioprine is discontinued) have been noted in humans.
Carcinogenicity Studies:
Patients receiving immunosuppressive therapy, including azathioprine are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and nonmelanoma), 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 EpsteinBarr virus (EBV)-associated lymphoproliferative disorders.
Macrophage activation syndrome
Macrophage activation syndrome (MAS) is a known, lifethreatening 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,

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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.

Adverse effects

Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following administration of azathioprine. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhea, fever, rigors, exanthema, rash, erythema nodosum, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis.
In many cases, rechallenge has confirmed an association with azathioprine.
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, the necessity for continued administration of azathioprine should be carefully considered on an individual basis.
The frequency and severity of adverse effects depends on the dose and duration of administration and on any underlying disease or concomitant therapy. The incidence of adverse reactions is less when azathioprine is given for rheumatoid arthritis than when it is used as an immunosuppressant in renal homotransplantation.
Toxic effects on the gastrointestinal tract and hematologic systems are most common. In addition, the risk of secondary infection and neoplasia is increased.
Rheumatoid Arthritis
Hematologic reactions (leukopenia, thrombocytopenia, anemia) occur most frequently (incidence 28%). These are dose related and usually are mild, but leukopenia is occasionally pronounced and severe. Severe bone marrow depression occurs infrequently. Therefore, complete blood counts, including platelets, should be performed periodically during therapy (eg. weekly during the first month, twice monthly during the second and third months, and monthly thereafter). If there is a rapid fall, a persistent low leukocyte count, or other evidence of bone marrow depression, the dose should be reduced or the drug discontinued.
Although serious infections are a potential hazard of immunosuppressant therapy, the incidence of infections has not increased in patients receiving azathioprine for rheumatoid arthritis.
Gastrointestinal disturbances usually are mild and occur soon after treatment is begun; nausea and vomiting have been reported in about 12% of patients with rheumatoid arthritis.
Hepatoxicity is uncommon (incidence, less than 1%), but it may be severe; the effects generally are reversible after discontinuation of the drug.
An increase in lymphoma, reticulum cell sarcoma, and other neoplasms has been noted in renal transplant patients receiving azathioprine. Although the risk of malignancies is less in patients with rheumatoid arthritis, acute myelogenous leukemia, non-Hodgkin's lymphoma, and solid tumors have been reported in these patients. There may be a prohibitive risk of neoplasia in patients with rheumatoid arthritis who have been treated with alkylating agents.
Immunosuppression
The incidence of hematologic toxicity, neoplasia, and infection is significantly higher in renal homotransplantation than in rheumatoid arthritis (eg. infection rate is 50 to 60 times higher in renal transplant patients). The high incidence of toxicity following renal transplantation may be due to the accumulation of metabolites normally eliminated by the kidney.
Bone marrow depression is uncommon with conventional doses of azathioprine, but is a possibility with larger doses. Hematologic toxicity is usually limited to mild leukopenia and thrombocytopenia.
A limited number of cases of acute idiosyncratic aplastic anaemia has occurred shortly after initiation of therapy or suddenly during a previously stable course.
Nausea, vomiting, and gastrointestinal discomfort are common during the first few months of azathioprine therapy and usually respond to dosage adjustment.
Enzyme changes characteristic of hepatocellular necrosis and cholestasis may occur relatively early (one to two weeks) but also extremely late (years) during treatment and usually require discontinuing the drug. If administration must be continued, close observation is essential, since deaths from hepatic decompensation have occurred.
Pancreatitis and hypersensitivity-type interstitial pneumonitis have been reported occasionally.
Other uncommon adverse effects are skin rash, alopecia, fever, arthralgic, steatorrhea, and negative nitrogen balance.
Since severe leukopenia and/or thrombocytopenia may develop in patients receiving azathioprine, complete blood and platelet counts should be performed at regular intervals. Prompt reduction in dosage or withdrawal of the drug may be necessary if there is evidence of serious bone marrow depression.
Azathioprine is carcinogenic in animals and is associated with increased risk of neoplasia in transplant patients.
Neoplasms benign and malignant (including cysts and polyps)
Rare: neoplasms including lymphoproliferative disorders, skin cancers (melanomas and nonmelanomas), Sarcomas (Kaposi's and nonKaposi's) and uterine cervical cancer in situ, acute myloid leukaemia and myelodysplasia (see Special warnings and precautions for use).

Interactions

Allopurinol:
Allopurinol-induced inhibition of xanthine oxidase-mediated metabolism may result in greatly increased azathioprine activity and toxicity. Concurrent use should be avoided if possible, especially in renal transplant patients because of the high risk of oxipurinol (an active allopurinol metabolite) accumulation and consequent azathioprine toxicity if the transplanted kidney is rejected.
If concurrent use is essential, it is recommended that azathioprine dosage be reduced to 25-33% of the usual dosage, the patient be carefully monitored and subsequent dosage adjustments be based on patient response and evidence of toxicity.
Blood Dyscrasia-Causing Medications:
Leukopenic and/or thrombocytopenic effects of azathioprine may be increased with concurrent or recent therapy if these medications cause the same effects.
Dosage adjustment of azathioprine, if necessary, should be based on blood counts.
Other Bone Marrow Depressants or Radiation Therapy:
Concurrent use with azathioprine may increase the bone marrow depressant effects of these medications and radiation therapy; dosage reduction may be required. Use prior to azathioprine therapy may be associated with an increased risk of development of neoplasms.
Other Immunosuppressants:
Such as, adrenocorticoids, glucocorticoid, chlorambucil, cyclophosphamide, cyclosporine, mercaptopurine.
Concurrent use with azathioprine may increase the risk of infection and development of neoplasms.
Vaccines, Killed Virus:
The patient's anti-body response to the vaccine may be decreased because normal defense mechanisms may be suppressed. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medication used, the underlying disease, and other factors; estimates vary from 3 months to 1 year.
Trimethoprim:
Inhibits creatinine excretion in the urine in azathioprine treated patients.
Concomitant Use of Muscle Relaxants:
There is clinical evidence that azathioprine antagonises the effect of non-depolarising muscle relaxants such as curare, d-tubocurarine and pancuronium. Experimental data confirm that azathioprine reverses the neuromuscular blockade caused by d-tubocurarine, and show that azathioprine potentiates the neuromuscular blockade caused by suxamethionium.
Captopril:
Neutropenia has occurred in some patients receiving both captopril and azathioprine. Serious infections resulting from the neutropenia and which proved fatal in a few cases occurred only in patients with impaired renal function. Captopril should only be concurrently prescribed when benefit outweighs risk.
Neutropenia was noted 2.5 to 13 weeks after captopril was initiated. Thus white blood cell and differential counts should be performed throughout therapy with captopril.
Vaccines, Live Virus:
Concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, may increase the sideadverse effects of the vaccine virus, and/or may decrease the patient's antibody response to the vaccine, because normal defence mechanisms may be suppressed by azathioprine therapy. Immunisation of these patients should be undertaken only with extreme caution after careful review of the patient's haematologic status and only with the knowledge and consent of the physician managing the azathioprine therapy. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppressioncausing medication used, the underlying disease, and other factors; estimates vary from 3 months to 1 year.
Patients with leukaemia in remission should not receive live virus vaccine until at least 3 months after their last chemotherapy. In addition, immunisation with oral polio-virus vaccine should be postponed in persons in close contact with the patient, especially family members.
IUD Contraceptives:
There have been several reports of women becoming pregnant during azathioprine/prednisone treatment whilst IUD devices were in place. Because of these failures it is recommended that additional of other methods of contraception should be employed for sexually active women during azathioprine/prednisone therapy.

Overdosage

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 - 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 from 0.5 - 7.5g azathioprine on a single occasion with apparently uneventful recovery. Treatment is symptomatic and has included gastric lavage. Azathioprine is dialysable but the procedure is of doubtful value since azathioprine is rapidly metabolised with entry of metabolites into tissue cells.

Pharmaceutical Precautions

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

Medicine classifications

Controlled Medicine as per Malaysia guideline.

Package quantities

Blister pack, 100 tablets.

Further Information

Azathioprine is 6-1(1-methyl-4-nitro-imida-zol-5-ylthio) purine. It has a molecular formula and weight of C9H7N7O2S and 277.3 respectively.
Other ingredients of the tablets are: mannitol, maize cornflour, opadry clear OY-7240, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and polyvinylpyrrolidinone.

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