APO-AZATHIOPRINE
Azathioprine Tablets USP 50 mg
IMMUNOSUPPRESSIVE AGENT

Product Description
Pale yellow, flat-faced, peanut-shaped, beveled-edge tablets, scored and engraved "AZ 50" on one side, "APO" on the other. Apo-Azathioprine 50mg is packed in HDPE bottles of 100 tablets.

Pharmacokinetics
Azathioprine is well absorbed following oral administration. After oral administration of [35S]-azathioprine, the maximum plasma radioactivity occurs at 1-2 hours and decays with a half-life of 4-6 hours. This is not an estimate of the half-life of azathioprine itself, but reflects the elimination from plasma of azathioprine and the [35S]-containing metabolites of the drug. Studies in which the plasma concentration of azathioprine and 6-MP have been determined following intravenous administration of azathioprine have estimated the mean plasma T1/2 for azathioprine to be in the range of 6-28 minutes and the mean plasma T1/2 for 6-MP to be in the range 38-114 minutes after i.v. administration of the drug.
Azathioprine is principally excreted as 6-thiouric uric acid in the urine. 1-methyl-4-nitro-5-thioimidazole has also been detected in urine as a minor excretory product. A small proportion of the drug may be cleaved between the sulphur-atom and the purine ring. Only a small amount of the dose of azathioprine administered is excreted unmetabolised in the urine.

Pharmacodynamics
Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down *in vivo* into 6-MP and a methylnitroimidazole moiety. The 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid. The rate of conversion varies from one person to another. Nucleotides do not traverse cell membranes and therefore do not circulate in body fluids. Irrespective of whether it is given directly or is derived *in vivo* from azathioprine, 6-MP is eliminated mainly as the inactive oxidised metabolite thiouric acid. This oxidation is brought about by xanthine oxidase, an enzyme that is inhibited by allopurinol. The activity of the methylnitroimidazole moiety has not been defined clearly.
While the precise modes of action remain to be elucidated, some suggested mechanisms include:

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

Because of these mechanisms, the therapeutic effect of Azathioprine may be evident only after several weeks or months of treatment.
Azathioprine appears to be well absorbed from the upper gastro-intestinal tract.
Plasma levels of azathioprine and 6-MP do not correlate well with the therapeutic efficacy or toxicity of Azathioprine.

Indications
Used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and procedures which influence the immune response. Therapeutic effect may be evident only after weeks or months and can include a steroid-sparing effect, thereby reducing the toxicity associated with high dosage and prolonged usage of corticosteroids.
Apo-Azathioprine, in combination with corticosteroids and/or other immunosuppressive agents and procedures, is indicated to enhance the survival of organ transplants, such as renal transplants, cardiac transplants, and hepatic transplants; and to reduce the corticosteroid requirements of renal transplant recipients.
Apo-Azathioprine, either alone or more usually in combination with corticosteroids and/or other drugs and procedures, has been used with clinical benefit (which may include reduction of dosage or discontinuation of corticosteroids) in a proportion of patients suffering from the following:

severe rheumatoid arthritis;
systemic lupus erythematosus;
dermatomyositis and polymyositis;
auto-immune chronic active hepatitis;
pemphigus vulgaris;
polyarteritis nodosa;
auto-immune haemolytic anaemia;
chronic refractory idiopathic thrombocytopenic purpura.

Recommended Dosage & Mode of Administration
<u>Transplantation - adults and children</u>
Depending on the immunosuppressive regimen employed, a dosage of up to 5 mg/kg body weight/day may be given on the first day of therapy, either orally or intravenously.
Maintenance dosage should range from 1 to 4 mg/kg body weight/day and must be adjusted according to clinical requirements and haematological tolerance.
Evidence indicates that Apo-Azathioprine therapy should be maintained indefinitely, even if only low doses are necessary, because of the risk of graft rejection.
<u>Dosage in other conditions - adults and children</u>
In general, starting dosage is from 1 to 3 mg/kg body weight/day, and should be adjusted, within these limits, depending on the clinical response (which may not be evident for weeks or months) and haematological tolerance.

When therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. If no improvement occurs in the patient's condition within 3 months, consideration should be given to withdrawing Apo-Azathioprine.
The maintenance dosage required may range from less than 1 mg/kg body weight/day to 3 mg/kg body weight/day, depending on the clinical condition being treated and the individual patient response, including haematological tolerance.
In patients with renal and/or hepatic insufficiency, dosages should be given at the lower end of the normal range.
Use in the elderly
There is limited experience of the administration of Apo-Azathioprine to elderly patients. Although the available data do not provide evidence that the incidence of side effects among elderly patients is higher than that among other patients treated with Apo-Azathioprine, it is recommended that the dosages used should be at the lower end of the range.
Particular care should be taken to monitor haematological response and to reduce the maintenance dosage to the minimum required for clinical response.

Contraindications
Apo-Azathioprine is contra-indicated in patients known to be hypersensitive to azathioprine. Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to Apo-Azathioprine.
Apo-Azathioprine therapy should not be initiated in patients who may be pregnant, or who are likely to become pregnant without careful assessment of risk versus benefit.

Warnings and Precautions
Monitoring
There are potential hazards in the use of Apo-Azathioprine. It should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of therapy.
It is suggested that during the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than 3 months.
Patients receiving Apo-Azathioprine should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestations of bone marrow depression.
There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with Apo-Azathioprine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine.
Renal and/or hepatic insufficiency
It is recommended that the dosages used should be at the lower end of the normal range and that haematological response should be carefully monitored. Dosage should be further reduced if haematological toxicity occurs.
Caution is necessary during the administration of Apo-Azathioprine to patients with hepatic dysfunction, and regular complete blood counts and liver function tests should be undertaken. In such patients the metabolism of Apo-Azathioprine may be impaired, and the dosage of Apo-Azathioprine should therefore be reduced if hepatic or haematological toxicity occurs.
Limited evidence suggests that Apo-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 Apo-Azathioprine.
Mutagenicity
Chromosomal abnormalities have been demonstrated in both male and female patients treated with Apo-Azathioprine.
Effects on fertility
Relief of chronic renal insufficiency by renal transplantation involving the administration of Apo-Azathioprine has been accompanied by increased fertility in both male and female transplant recipients.
Carcinogenicity
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.
Patients receiving multiple immunosuppressive agents may be at risk of over-immunosuppression, therefore such therapy should be maintained at the lowest effective level.
As is usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor.
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.
Varicella Zoster Virus Infection

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.

Interactions with other Medications
Allopurinol/ oxipurinol/ thiopurinol
Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol which results in reduced conversion of biologically active 6 thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol, 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. There is considerable variation in the potency of this interaction.
Warfarin
Inhibition of the anticoagulant effect of warfarin, when administered with azathioprine, has been reported.
Cytotoxic products/products with a myelosuppresive effect
If possible the concomitant administration of cytostatic agents, or of products with a possible inhibiting effect on bone marrow , such as penicillamine, should be avoided. There has been a casuistical announcement that presume that haematological disorders can occur due to the concomitant administration of azathioprine and captopril. There have been indications of a possible inhibiting effect of cimetidine and indomethacin on the bone marrow which may be potentiated by the concomitant administration of azathioprine.

Pregnancy and Lactation
Teratogenicity
Evidence of the teratogenicity of Apo-Azathioprine in man is equivocal.
Mutagenicity
Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes from the off-spring of patients treated with Azathioprine. 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.
Use in Pregnancy and Lactation
Azathioprine should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit. There have been reports of premature birth and low birth weight following maternal exposure to azathioprine, particularly in combination with corticosteroids. Leucopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took azathioprine throughout their pregnancies. Extra care in haematological monitoring is advised during pregnancy.
Lactation
6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment.

Adverse Effects
Infection and infestations
Transplant patients receiving Azathioprine in combination with other immunosuppressants.
Very common: Viral, fungal, and bacterial infections.
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 warnings and precautions)
Blood and lymphatic system disorders
Very common: Depression of bone marrow function; leucopenia.
Common: Thrombocytopenia.
Gastrointestinal disorders
Uncommon: Pancreatitis.
Rare: Colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population.
Hepato-biliary disorders
Uncommon: Cholestasis and degeneration of liver function tests.
Skin and subcutaneous tissue disorders
Rare: Alopecia
Immune system disorders
Uncommon: Hypersensitivity reactions

Overdose and Treatment
Symptoms and signs
Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with Apo-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. The immediate toxic effects of this overdose were nausea, vomiting and diarrhoea, followed by mild leucopenia and mild abnormalities in liver function. Recovery was uneventful.
Treatment

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

Storage conditions
Store below 30°C

Dosage Forms and Available Packaging
Apo-Azathioprine 50mg is packed in HDPE bottles of 100 tablets.

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