AZATHIOPRINE TABLETS USP 25MG / 50MG TAJ PHARMA

1. NAME OF THE MEDICINAL PRODUCT

Azathioprine Tablets USP 25mg Taj Pharma
Azathioprine Tablets USP 50mg Taj Pharma

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

a) Each tablet contains:
Azathioprine USP…….25mg
Excipeints……q.s.

b) Each tablet contains:
Azathioprine USP…….50mg
Excipeints……q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azathioprine is an antimetabolite which is used as an immunosuppressant, either as monotherapy or more often in combination with other drugs (mainly corticosteroids) and procedures which modulate the immune response. Therapeutic effect may be apparent only after weeks or months. Combination therapy with Azathioprine and corticosteroids may allow the dosage of corticosteroids to be reduced, resulting in a reduction of the toxicity associated with chronic use of corticosteroids at high doses.

Azathioprine, in combination with corticosteroids and/or other immunosuppressive drugs and procedures, is indicated to improve the survival of organ transplants, including renal, cardiac and hepatic transplants and to reduce the requirement for corticosteroids in renal transplant recipients.

Azathioprine tablets, either as a monotherapy or more usually in combination with corticosteroids and/or other drugs and procedures, may have a significant therapeutic effect in a proportion of patients suffering from auto-immune chronic active hepatitis, severe rheumatoid arthritis, systemic lupus erythematosus (SLE), chronic refractory idiopathic thrombocytopenic purpura, auto-immune haemolytic anaemia, pemphigus vulgaris, polyarteritis nodosa, dermatomyositis and polymyositis.

Clinical benefit may include a reduction in the dosage of corticosteroids or discontinuation of corticosteroid therapy.

4.2 Posology and method of administration

Posology

Adults: Azathioprine tablets are given by mouth.

Transplantation: a dose of up to 5 mg/kg body weight per day should be given on the first day of treatment, depending on the immunosuppressive regimen selected. The maintenance dosage is usually 1.0-4.0 mg/kg body weight per day and must be adjusted in accordance with clinical requirements and haematological tolerance. Treatment should be maintained indefinitely, even if only low doses are necessary, as cessation of Azathioprine therapy carries a risk of graft rejection.

Other Conditions: for the treatment of the conditions listed under "Therapeutic Indications". Generally, the starting dose should be 1 to 3 mg/kg body weight per day and should be adjusted, within these limits,

in accordance with the clinical response and haematological tolerance. A therapeutic response may not be evident for weeks or months after initiation of Azathioprine therapy. If no improvement in the patient's condition is evident within three months, consideration should be given to withdrawal of Azathioprine.

When a therapeutic response has been achieved, consideration should be given to reducing the dose to the minimum level necessary to maintain the response.

The maintenance dosage of Azathioprine may range from <1 mg/kg body weight per day to 3 mg/kg body weight per day, depending on the condition, its severity, the clinical response obtained and haematological tolerance.

In patients with impaired renal and/or hepatic function the dosage administered should be at the lower end of the normal range (see precautions).

Paediatric population: As for adults.

Elderly: see renal and hepatic impairment. Although experience with Azathioprine in elderly patients is limited, there is no evidence that the incidence of adverse events in elderly patients is higher than among the general patient population. However, it is recommended that the doses administered to elderly patients should be at the lower end of the normal range. The haematological response should be monitored carefully and the dose should be reduced to the minimum required for therapeutic response.

Method of administration

For oral use. Swallow the tablets whole. Do not break, chew or crush the tablets.

4.3 Contraindications

Azathioprine is contraindicated in patients known to be hypersensitive to azathioprine. Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to azathioprine. Azathioprine therapy should not be initiated in patients known to be pregnant or in those who are likely to become pregnant in the near future without careful assessment of risk versus benefit (see sections 4.4 and 4.6).

4.4 Special Warnings and precautions for use

There are potential hazards in the use of this preparation. Therefore, it should not be prescribed unless the patient can be adequately monitored for toxic effects throughout the duration of the therapy.

During the first eight weeks of therapy with azathioprine complete blood counts, including platelet counts, must be performed at least weekly (and more frequently when higher dosages are used or in the presence of disturbed renal or hepatic function). The blood count frequency may be reduced later in therapy, but it is recommended that complete blood counts are repeated monthly or at least at intervals of not longer than three months.

Patients receiving azathioprine should be instructed to report immediately any evidence of infections, unexpected bruising or bleeding or other manifestations of bone marrow depression.

Rare individuals with an inherited thiopurine methyltransferase (TPMT) deficiency may be unusually sensitive to azathioprine-induced myelosuppression and can be susceptible to rapid bone marrow depression following initiation of azathioprine therapy. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Also it has been reported that

decreased TPMT activity increases the risk of secondary leukaemias and myelodysplasia in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (see section 4.8).

Renal and/or hepatic insufficiency: Controlled studies have not supported the suggestion that the toxicity of azathioprine is augmented by renal insufficiency. Despite this, it is recommended that the initial doses used should be at the low end of the recommended range and haematological parameters should be closely monitored. Dosage should be reduced further if haematological toxicity becomes evident.

Azathioprine should be administered with caution in patients with hepatic dysfunction and complete blood counts and liver function tests should be undertaken regularly. The biotransformation of azathioprine may be impaired in such patients and therefore the doses used should be at the low end of the recommended range. Dosage should be reduced further if haematological or hepatic toxicity becomes evident.

There is limited evidence to suggest that azathioprine is not of benefit to patients with Lesch- Nyhan syndrome (hypoxanthine-guanine phosphoribosyltransferase deficiency). Azathioprine is not recommended in patients with this metabolic abnormality.

Genotoxicity: Chromosomal abnormalities have been demonstrated in both male and female patients receiving azathioprine. It is difficult to assess the role of azathioprine in the development of such abnormalities.

Carcinogenicity (see also section 4.8):

Patients receiving immunosuppressive therapy, including azathioprine are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non- Kaposi's) and uterine cervical cancer *in situ*. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given concomitantly, increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

In patients with rheumatoid arthritis the increased risk of lymphoma appears to be related at least partially to the disease itself.

Patients receiving multiple immunosuppressive agents may be at risk of over- immunosuppression, therefore such therapy should be maintained at the lowest effective level.

Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimize the risk of skin cancer and photosensitivity (see section 4.8).

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 (see also section 4.8): 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.

4.5 Interaction with other medicinal products and other forms of interaction

Allopurinol/Oxipurinol/Thiopurinol: Xanthi ne 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, 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, although there is considerable inter-individual variability in this interaction.

Warfarin: Concomitant administration with azathioprine has been reported to result in inhibition of the anticoagulant effect of warfarin.

Cytostatic/myelosuppressive agents: Concomitant use of azathioprine and cytostatic drugs, or other drugs which may have myelosuppressive effects (such as penicillamine), should be avoided. There are conflicting reports of interactions between azathioprine and co-trimoxazole, involving serious haematological abnormalities.

There has been a case report of haematological abnormalities following concomitant administration of azathioprine and captopril.

A suggestion has been made that indomethacin and cimetidine could have myelosuppressive effects, which may be potentiated by concomitant administration of azathioprine.

Other interactions:

As there is *in vitro* evidence that aminosalicylate derivatives (eg. olsalazine, mesalazine or sulfasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent Azathioprine therapy (section 4.4).

Furosemide has been demonstrated to impair the biotransformation of azathioprine by human liver tissue *in vitro*. The clinical

significance of this observation is not known.

The immunosuppressive activity of azathioprine could theoretically result in an abnormal and possibly harmful reaction to live vaccines, and therefore the administration of live vaccines to patients receiving azathioprine is contraindicated.

A reduced immune response to killed vaccines is likely, and such an effect has been reported with hepatitis B vaccine in patients treated with azathioprine and corticosteroid combination therapy.

A small clinical study has demonstrated that azathioprine, when used at therapeutic doses, does not diminish the response to polyvalent pneumococcal vaccine, as determined on the basis of mean anti-capsular specific antibody concentration.

4.6 Fertility, pregnancy and lactation

Pregnancy: Azathioprine therapy should not be initiated in patients known to be pregnant unless the potential benefits to the mother are considered to outweigh the potential risks to the foetus and the mother.

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 following administration of azathioprine to the mother.

Leucopenia and/or thrombocytopenia have been reported in a proportion of new-born babies whose mothers were receiving azathioprine throughout pregnancy. Extra care in the monitoring of haematological parameters is recommended during pregnancy.

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

Epidemiological evidence of teratogenicity in man is inconclusive. As with all cytotoxic drugs, adequate contraceptive measures are recommended when either partner is receiving azathioprine therapy.

Chromosomal abnormalities which disappear in time have been demonstrated in lymphocytes from 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 receiving azathioprine for a number of conditions.

Breast-feeding: 6-Mercaptopurine has been detected in the colostrum and breast milk of patients receiving azathioprine.

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.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable Effects

For this product there is no modern clinical documentation that can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication.

The following convention has been utilised for the classification of frequency: very common (≥1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1,000, <1/100), rare (≥ 1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and infestations

Transplant patients receiving azathioprine in combination with other immunosuppressants.

Very common: Viral, fungal and bacterial infections.

Other indications.

Uncommon: Viral, fungal and bacterial infections.

Patients receiving azathioprine alone, or in combination with other immunosupressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection with varicella, herpes zoster and other infectious agents (see section 4.4).

Neoplasms benign, and malignant (including cysts and polyps)

Rare: Neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*, acute myloid leukaemia and myelodysplasia (see section 4.4.)

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 increased 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 chromasomal abnormalities)

Blood and lymphatic system disorders

Very common: Depression of bone marrow function; leucopenia.

Common: Thrombocytopenia.

Uncommon: Anaemia.

Rare: Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia.

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 TPMT deficiency and renal or hepatic insufficiency and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol therapy.

Reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content have occurred in association with azathioprine therapy. Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and erythroid hypoplasia is rare.

Immune system disorders

Uncommon: Hypersensitivity reactions

Very rare: Stevens-Johnson syndrome and toxic epidermal necrolysis.

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, diarrhoea, fever, rigors, exanthema, rash, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis (see Hepatobiliary disorders).

In many cases, re-challenge 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.

Respiratory, thoracic and mediastinal disorders

Very rare: Reversible pneumonitis
Reversible pneumonitis has been described very rarely.

Gastrointestinal disorders

Ucommn Pancreatitis.

Rare: Colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population.

A minority of patients experience nausea when first given azathioprine. This appears to be relieved by administering the tablets 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 re-challenge, 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 re-challenge has confirmed an association with azathioprine on occasions.

Hepatobiliary disorders

Uncommon: Cholestasis and degeneration of liver function tests.

Rare: Life-threatening hepatic damage.

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 a hypersensitivity reaction (see Hypersensitivity reactions).

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 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.

Skin and subcutaneous tissue disorders

Rare: Alopecia, photosensitivity.

Hair loss has been described on a number of occasions in patients receiving azathioprine and other immunosuppressive agents. In many instances the condition resolved spontaneously despite continuing therapy. The relationship between alopecia and azathioprine treatment is uncertain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9Overdose

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. There has been a case report of a single overdose of 7.5 g azathioprine. The acute toxic effects suffered by the patient in this case 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 employed. Subsequent monitoring (including monitoring of haematological and biochemical parameters) is recommended to ensure prompt treatment of any adverse effects which may emerge. The value of dialysis in overdosage is not known, although azathioprine is partially dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP. Determination of plasma concentrations of azathioprine or 6-MP have no prognostic values as regards effectiveness or 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 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.

Studies in mice with [^{35}S]-azathioprine showed no unusually large concentration in any particular tissue, and there was very little [^{35}S]-label found in brain.

Plasma levels of azathioprine and 6-MP do not correlate well with the therapeutic efficacy or toxicity of azathioprine.

5.2 Pharmacokinetic properties

Azathioprine is well absorbed following oral administration. After oral administration of [^{35}S]-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 [^{35}S]-containing metabolites of the drug. As a consequence of the rapid and extensive metabolism of azathioprine, only a fraction of the radioactivity measured in plasma is comprised of unmetabolised 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 $t_{1/2}$ for azathioprine to be in the range of 6-28 minutes and the mean plasma $t_{1/2}$ 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.

This would indicate that, rather than azathioprine being exclusive cleaved by nucleophilic attack at the 5-position of the nitroimidazole ring to generate 6-MP and 1-methyl-4-nitro-5- (S-glutathionyl)imidazole. A small proportion of the drug may be cleaved between the S atom and the purine ring. Only a small amount of the dose of azathioprine administered is excreted unmetabolised in the urine.

5.3 Preclinical safety data

There are no preclinical findings of relevance to the prescriber, which are additional to the information presented elsewhere in this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Maize starch, microcrystalline cellulose, Mannitol, Povidone, Croscarmellose sodium, Sodium stearyl fumarate.

Film coating: Hypromellose, Macrogol.

6.2 Incompatibilities

none known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

this medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polypropylene containers with polyethylene caps (with optional polyethylene ullage filler), blister packs or HDPE containers with PE snap-on caps, containing 28, 30, 50,

56, 60, 84, 90, 100, 112, 168, 500 or 1000 tablets.

6.6 Special precautions for disposal and other handling

Provided that the film-coating is intact, there is no risk in handling film-coated tablets. Azathioprine Tablets should not be divided and, provided the coating is intact, no additional precautions are required when handling them.

7. MANUFACTURED IN INDIA BY:

TAJ PHARMACEUTICALS LTD.
Mumbai, India
Unit No. 214.Old Bake House,
Maharashtra chambers of Commerce Lane,
Fort, Mumbai - 400001
at:Gujarat, INDIA.
Customer Service and Product Inquiries:
1-800-TRY-FIRST (1-800-222-434 & 1-800-222-825)
Monday through Saturday 9:00 a.m. to 7:00 p.m. EST
E-mail: tajgroup@tajpharma.com