APPROVED PROFESSIONAL INFORMATION

AZAMUN 50 mg

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

AZAMUN 50 mg, tablets

COMPOSITION

Each film-coated tablet contains 50 mg azathioprine.

Excipients: croscarmellose sodium, maize starch, mannitol, microcrystalline cellulose, Opadry Clear OY-7240 (hypromellose, macrogol), povidone K25, sodium stearyl fumarate.

PHARMACOLOGICAL CLASSIFICATION

A 26 Cytostatic agents.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Azathioprine is a purine antimetabolite and possesses immunosuppressive properties. It is a prodrug of 6-mercaptopurine.

Azathioprine is cleaved by nucleophiles such as glutathione, to 6-mercaptopurine, which in turn can be converted into 6-mercaptopurine nucleotides. These nucleotides lead to an inhibition of de novo purine synthesis.

Pharmacokinetic properties

Azathioprine is well absorbed by the gastro-intestinal tract and reaches maximum blood levels within 1 to 2 hours after administration. Mercaptopurine is metabolised either by methylation of the sulfhydryl group and subsequent oxidation of the methylated derivatives or by xanthine oxidase to 6-thiouric acid.

Azathioprine and its metabolites are excreted primarily in the urine.

INDICATIONS

Transplantation

AZAMUN is mainly used as an immunosuppressant in the management of patients receiving organ transplants. It is used in combination with corticosteroids and/or other immunosuppressive agents and procedures.

Auto-Immune Diseases

AZAMUN is used to treat diseases with an auto-immune component. In a proportion of patients suffering from rheumatoid arthritis, systemic lupus erythematosus, auto-immune active chronic hepatitis, pemphigus vulgaris, auto-immune haemolytic anaemia or idiopathic thrombocytopenic purpura, AZAMUN has a therapeutic effect when these conditions are:

(a) refractory to corticosteroids or,

(b) controlled by corticosteroids in dosages which are producing side effects.

The aim of AZAMUN is to reduce the required maintenance dose of steroids and thus reducing adverse events. Therapeutic effect may be evident only after weeks or months.

CONTRAINDICATIONS

- Hypersensitivity to azathioprine or any of the excipients. Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable sensitivity to AZAMUN.
- Pregnancy and breastfeeding (see “Pregnancy and Lactation”).

WARNINGS and SPECIAL PRECAUTIONS

THE RISKS ASSOCIATED WITH AZAMUN THERAPY SHOULD BE CONSIDERED AGAINST THE SEVERITY OF THE PATIENT'S CONDITION AND THE EXPECTED BENEFICIAL CLINICAL EFFECT.

AZAMUN should not be prescribed unless the patient can be adequately monitored for toxic effects throughout the duration of the therapy.

Bone Marrow Depression and Haematopoiesis

DURING THE FIRST EIGHT WEEKS OF AZAMUN THERAPY COMPLETE BLOOD COUNTS, INCLUDING PLATELET COUNTS MUST BE PERFORMED AT LEAST WEEKLY, OR MORE FREQUENTLY IF HIGH DOSAGE IS USED OR IF SEVERE RENAL AND/OR HEPATIC DISORDER IS PRESENT.

During the course of therapy, AZAMUN may have to be discontinued because of haematopoietic toxicity. The maximum effect of AZAMUN on the white cell count usually becomes manifest within the first two weeks of initiating treatment, but thereafter the risk of complications gradually declines as the duration of therapy increases.

The commonest complication is leucopenia which may be accompanied by thrombocytopenia.

Thrombocytopenia alone, anaemia, pancytopenia and bleeding have also been reported.

It is essential that blood counts be taken monthly throughout the period of therapy. If AZAMUN is used in conjunction with or soon after withdrawal of another medicine known to have a depressive effect on the bone marrow, it is particularly important that frequent blood counts be taken.

Since AZAMUN may have a delayed action, it is important to reduce the dosage or withdraw the medication temporarily at the first sign of an abnormally large fall in leucocyte count and/or other evidence of persistent depression of the bone marrow. Such bone marrow depression is usually reversible at the doses recommended for auto-immune disease.

The effect on white cell count is not closely correlated with the immunosuppressive effect of AZAMUN; a good immunosuppressive effect can often be obtained without change in the white cell count, but sometimes the count may be greatly reduced without any apparent immunosuppression.

Therapeutic use of AZAMUN is associated with reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content. Megaloblastic bone marrow changes have been observed and severe megaloblastic anaemia and erythroid hypoplasia have occurred occasionally.

Infection

AZAMUN has an immunosuppressant effect involving both antibody and cell mediated immunity. Infection, which is always a hazard of immunosuppressive therapy, particularly when corticosteroids are given, may require the dosage of immunosuppressive agents to be reduced temporarily.

Fungal, protozoal, viral and uncommon bacterial infections in patients on immunosuppressive therapy including AZAMUN have occurred and should be treated vigorously. Some of these have proved fatal.

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

Hypersensitivity Reactions

Reversible alopecia, rashes, muscle and joint pains, fever, rigors, pneumonitis, pancreatitis, meningitis, dysrhythmias, renal dysfunction, and hypotension may occur, some or all of which may represent hypersensitivity reactions.

Pruritus and erythema, often of an area previously irradiated, may occur. Anaphylaxis may occur. Headache, malaise, weakness, dizziness, vomiting, arthralgia, impaired liver functions and cholestatic jaundice have also been reported.

It has been suggested that the imidazole side chain gives rise to sensitivity, whereas the 6-mercaptopurine (6-MP) molecule gives rise to cholestasis.

Hepatic and Renal Impairment

Consideration must be given to withholding AZAMUN if there is evidence of toxic hepatitis or biliary stasis. Elevated serum bilirubin levels have been observed in some patients after initiation of AZAMUN therapy.

The dosage of AZAMUN must be reduced for the treatment of active chronic hepatitis (see “Dosage and Directions for Use”).

AZAMUN should be used with care in patients with renal or hepatic impairment. These patients may eliminate the medicine and its metabolites at a reduced rate with a consequent cumulative effect. The dosage of AZAMUN should therefore be reduced in such cases, particularly in anuric patients.

The effects of AZAMUN are enhanced by allopurinol. The dose of AZAMUN should be reduced to one-quarter of the usual dose when AZAMUN and allopurinol are given concomitantly.

Failure to reduce the dosage of AZAMUN in the presence of allopurinol can result in severe bone marrow depression (see “Interactions”).

Gastrointestinal Intolerance

AZAMUN therapy may have to be adjusted if anorexia, nausea, vomiting or diarrhoea occurs. Stomatitis, mouth ulceration, oesophagitis, abdominal pain, intestinal haemorrhage, ulceration and perforation have been reported.

Other

Persistent negative nitrogen balance has been observed in some patients on continuous AZAMUN and corticosteroid therapy. If this occurs, the dosage should be reduced. Other reported complications include drug fever, serum sickness, pulmonary oedema, reversible pneumonitis, peritoneal haemorrhage, retinopathy, alopecia, arthralgia, and Raynaud's phenomenon.

Hyperuricaemia and acute renal failure due to uric acid nephropathy and hyperphosphataemia may occur. Pigmentation of the skin and nails may also occur.

Mutagenicity

Chromosomal abnormalities, which can occur independently of the influence of AZAMUN, have been demonstrated in both male and female transplant recipients.

Chromosomal abnormalities, which disappear in time, have been demonstrated in offspring of transplant recipients.

AZAMUN has long term effects on the gonads and may suppress ovarian and testicular function with amenorrhoea and inhibition of spermatogenesis.

Immunosuppression and Cancer

Some homograft recipients, whose immune responses have been suppressed, appear to be vulnerable to neoplasia either in the transplanted organ or at some other unrelated site, during the first few weeks or months after transplantation. This is a recognised hazard after transplantation and it could conceivably occur also when AZAMUN therapy is used in the treatment of auto-immune disease.

Effects on ability to drive and use machines

There are no data on the effect of AZAMUN on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the medicine.

INTERACTIONS

- Allopurinol, oxipurinol and 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. The dose of AZAMUN should be reduced to one-quarter of the usual dose when allopurinol, oxipurinol and/or thiopurinol are given concomitantly (see “Warnings and Special Precautions”).

- Other Immunosuppressants: Such as, adrenocorticoids, glucocorticoid, chlorambucil, cyclophosphamide, ciclosporin, mercaptopurine. Concurrent use with AZAMUN may increase the risk of infection and development of neoplasms.

- Aminosalicylates: As there is in vitro evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the thiopurine methyltransferase (TPMT) enzyme, they should be administered with caution to patients receiving concurrent AZAMUN therapy.

- Neuromuscular blockade: AZAMUN can potentiate the neuromuscular blockade produced by depolarising agents such as succinylcholine and reduce the blockade produced by non-depolarising.

- Cytostatic medicine/medicines with myelosuppressive effects: Where possible, concomitant or recent administration of cytostatic medicine, or medicines which may have a myelosuppressive effect, such as penicillamine, should be avoided.

- Furosemide: Furosemide has been shown to impair the metabolism of azathioprine by human hepatic tissue in vitro. The clinical significance is unknown.

- Cimetidine: It has been suggested that cimetidine may have myelosuppresive effects, which may be enhanced by the concomitant administration of AZAMUN.

- Leucocyte production: Medicines which may affect leucocyte production, including co-trimoxazole, may lead to exaggerated leucopenia, especially in renal transplant recipients.

- Angiotensin converting enzyme inhibitors: The use of angiotensin converting enzyme inhibitors to control hypertension in patients on AZAMUN has been reported to induce severe leucopenia.

Captopril: Neutropenia has occurred in some patients receiving both captopril and AZAMUN. 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.

- Warfarin: AZAMUN decreases warfarin activity and severe bleeding has been reported in patients on long-term warfarin treatment after discontinuation of AZAMUN.

- Vaccines, Killed Virus: The patient's anti-body response to the vaccine may be decreased because normal defence mechanisms may be suppressed.

- Vaccines, Live Virus: Concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus, may increase the side 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 AZAMUN therapy.

- IUD Contraceptives: There have been several reports of women becoming pregnant during AZAMUN /prednisone treatment whilst IUD devices were in place. Because of these failures it is recommended that additional or other methods of contraception should be employed for sexually active women during AZAMUN /prednisone therapy.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established (see “Contraindications”).

Pregnancy:

AZAMUN can cause foetal harm when administered to pregnant women. AZAMUN therapy should not be used in patients known to be pregnant. Adequate and well-controlled studies in humans have not been conducted.

The fact that AZAMUN is potentially teratogenic must be considered when it is to be administered to males or females who may procreate while receiving therapy. There have been a few reports of congenital deformity when the father was receiving AZAMUN at the time of conception.

There have been reports of premature birth and low birth weight following maternal exposure to AZAMUN, particularly in combination with corticosteroids. There have also been reports of spontaneous abortion following either maternal or paternal exposure. AZAMUN and/or its metabolites have been found in low concentrations in foetal blood and amniotic fluid.

Women of Childbearing Potential:

Women of childbearing potential are advised to ensure adequate contraception as AZAMUN is contraindicated for use during pregnancy.

Lactation:

Safety in lactation has not been established.

AZAMUN is distributed, at low concentrations into breast milk of patients receiving AZAMUN (see “Contraindications”).

DOSAGE AND DIRECTIONS FOR USE

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

Film-coated tablets should not be divided. Provided that the film-coat is intact, there is no risk in handling film-coated AZAMUN tablets.

Transplantation

- Loading dose: Depending on the immunosuppressive regimen adopted, a loading dose of 1,0 to 5,0 mg/kg body-weight per day is usually given.

- Maintenance dosage after transplantation: Usually 1,0 to 4,0 mg/kg body-weight per day after transplantation.

Corticosteroids are usually given concomitantly with AZAMUN in order to facilitate survival and function of the transplanted organ. It may be possible to slowly withdraw the steroids completely in some cases. Cessation of AZAMUN therapy, even after a period of years, carries a risk of rejection within a few weeks.

Auto-Immune Diseases

- Dosage for the treatment of severe rheumatoid arthritis, systemic lupus erythematosus, auto-immune active chronic hepatitis, pemphigus vulgaris, auto-immune haemolytic anaemia, idiopathic thrombocytopenic purpura is usually 1,0 to 2,5 mg/kg body-weight per day, depending on patient response.

- Dosage for the treatment of active chronic hepatitis is usually 1,0 to 2,0 mg/kg body-weight per day.

Directions

The dosage of AZAMUN and the duration of treatment may vary according to the condition, its severity and the clinical response obtained. A therapeutic response in auto-immune disease may not be evident for a few days or even weeks after initiation of AZAMUN therapy.

If no discernible improvement occurs in the patient's condition within three months, consideration should be given to the withdrawal of AZAMUN.

Treatment is otherwise undertaken on a long-term basis unless the patient exhibits evidence of intolerance to AZAMUN.

Use in the elderly

The dosage of AZAMUN in the elderly has not been established. It is recommended that the dosage used is at the lower end of the range given.

The maintenance dosage should be reduced to the minimum required for clinical response. Care should be taken to monitor haematological responses.

SIDE EFFECTS

Infections and infestations:

Frequent: Viral, fungal and bacterial infections in transplant patients receiving AZAMUN in combination with other immunosuppressants.

Less frequent: Viral, fungal and bacterial infections in other patient populations. (See also “Warnings and Special Precautions”).

Neoplasms benign and malignant (including cysts and polyps):

Less Frequent: Neoplasms including non-Hodgkin's lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non- Kaposi's) and uterine cervical cancer in situ, acute myeloid leukaemia and myelodysplasia. (See “Warnings and Special Precautions”).

Blood and lymphatic system disorders:

Frequent: Depression of bone marrow function; leucopenia, thrombocytopenia.

Less Frequent: Anaemia, agranulocytosis, pancytopenia and bleeding, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia.

Immune system disorders:

Less Frequent: Hypersensitivity reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Respiratory, thoracic and mediastinal disorders:

Less Frequent: Interstitial pneumonitis.

Gastrointestinal disorders:

Frequent: Nausea and/or vomiting, loss of appetite.

Less Frequent: Pancreatitis, colitis, diverticulitis and bowel perforation reported in the transplant population, severe diarrhoea in inflammatory bowel disease population, sores in mouth and on lips.

Hepato-biliary disorders:

Less frequent: Cholestasis and deterioration of liver function tests, life-threatening hepatic damage, hepatic veno-occlusive disease.

Skin and subcutaneous tissue disorders:

Less Frequent: Alopecia, skin rash.

Renal and urinary disorders:

Frequency unknown: Renal dysfunction.

Cardiac disorders:

Frequency unknown: Tachycardia, hypotension.

General disorders and administrative site conditions:

Frequency unknown: Fever, rigors, muscle pains and weakness.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdose with AZAMUN 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.

Treatment is symptomatic and supportive.

IDENTIFICATION

A light yellow, film-coated, circular, biconvex tablet. Engraved “AZA” breakline “50” on one side and plain on the other side.

PRESENTATION

AZAMUN 50 mg tablets are provided in clear transparent PVC/PVDC/Aluminium blister packs containing 100 tablets.

STORAGE INSTRUCTIONS

Store below or at 30 °C. Protect from light and moisture. Keep blisters in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

36/26/0006

NAME AND BUSINESS ADDRESS OF APPLICANT

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DATE OF PUBLICATION OF THIS PACKAGE INSERT

Date of registration: 24 January 2003

Revision date: 27 November 2015