

## Data Sheet

# AZAMUN

***Azathioprine 50mg tablets***

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## Name of the Medicine

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AZAMUN

Azathioprine 50mg tablets (Ph.Eur)

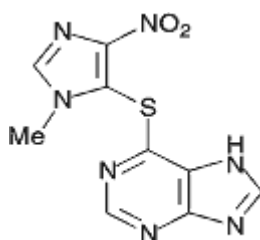
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## Description

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Azathioprine is an imidazolyl derivative of mercaptopurine. It acts as an immunosuppressant and anti-neoplastic agent. Azathioprine is 6-1(1-methyl-4-nitro-imidazol-5-ylthio)purine. It has a molecular formula and weight of  $C_9H_7N_7O_2S$  and 277.3 respectively. The CAS number is 446-86-6.

The structural formula is:



The tablets also contain as excipients: mannitol, maize starch, Opadry Clear OY-7240, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and povidone.

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## Pharmacology

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### ***Mechanism of Action***

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 blood stream.

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 similarity 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 mercaptopurine 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.

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## Indications

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AZAMUN is used as an immunosuppressant anti-metabolite 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 immunosuppressive agents and procedures is indicated to enhance the survival of organ transplants, such as renal, cardiac and hepatic transplants; and to reduce the corticosteroid requirements of renal transplant recipients.

AZAMUN is indicated for the treatment of moderate to severe Crohn's disease in patients in whom corticosteroid therapy is required, in patients who cannot tolerate corticosteroid therapy, or patients whose disease is refractory to other standard first line therapy.

AZAMUN, either alone or in combination with corticosteroids 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
- chronic refractory idiopathic thrombocytopenic purpura.
- ulcerative colitis

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## Contraindications

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

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## Precautions

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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***

Pregnancy category D

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.

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.

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 - 15 mg/kg/day over the period of organogenesis have shown varying degrees of foetal abnormalities. Teratogenicity was evident in rabbits at 10 mg/kg/day.

Epidemiological evidence in man indicates that the frequency of occurrence 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. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of patients treated with AZAMUN. 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.

## ***Carcinogenicity Studies***

Azathioprine has been shown to be carcinogenic in animals, and may be associated with an increased risk of development of carcinomas in humans, especially skin cancer and reticulum cell tumours or lymphomas in renal transplant patients and acute leukaemia and some solid tumours in

rheumatoid arthritis patients. The risk of neoplastic toxicity appears to be lower in rheumatoid arthritis patients, however, there is evidence that the risk is increased with prior use of alkylating agents.

Haematological status must be monitored regularly during treatment (at least weekly during the first 2 months of therapy), as should liver and renal function. If infection develops, the dose of azathioprine should be reduced and appropriate therapy instituted.

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. It has been reported that reduction or discontinuation of immunosuppression may be associated with partial or complete regression of non-Hodgkin's lymphomas and Kaposi's sarcomas.

Patients receiving multiple immunosuppressive agents may be at risk of overimmunosuppression, 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.

### ***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.

### ***Effects on Ability to Drive or Operate Machinery***

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

### ***Interactions with other Medicines***

## **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.

### **Neuromuscular blocking agents:**

AZAMUN 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.

### **Aminosalicylates**

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

### **Other interactions**

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

### **Vaccines, Killed Virus**

The patient's anti-body response to the vaccine may be decreased because normal defence 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.

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.

A small clinical study has indicated that standard therapeutic doses of AZAMUN do not deleteriously affect the response to polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration

### **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 suxamethonium.

### **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 side-adverse 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 immunosuppression-causing 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.

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## **Adverse effects**

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For this product there is no modern clinical documentation which 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  $\geq 1/10$ , common  $\geq 1/100$ ,  $< 1/10$ , uncommon  $\geq 1/1000$  and  $< 1/100$ , rare  $\geq 1/10,000$  and  $< 1/1000$ , very rare  $< 1/10,000$ .

### **Infections and infestations**

Very common: viral, fungal and bacterial infections in transplant patients receiving azathioprine in combination with other immunosuppressants

Uncommon: viral, fungal and bacterial infections in other patient populations.

Patients receiving AZAMUN 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 and other infectious agents (see also Special Warnings and Special Precautions for Use).

### **Neoplasms benign and malignant (including cysts and polyps)**

Rare: 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 Special Warnings and Special Precautions for Use).

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 chromosomal abnormalities).

### **Blood and lymphatic system disorders**

Very common: depression of bone marrow function; leucopenia

Common: thrombocytopenia

Uncommon: anaemia

Rare: agranulocytosis, pancytopenia, aplastic anemia, megaloblastic anaemia, erythroid hypoplasia

AZAMUN 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 AZAMUN when receiving concurrent allopurinol therapy.

Reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content have occurred in association with AZAMUN therapy.

Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and erythroid hypoplasia are 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 AZAMUN. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis. (see Hepato-biliary disorders).

In many cases, rechallenge has confirmed an association with AZAMUN.

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 AZAMUN, the necessity for continued administration of AZAMUN should be carefully considered on an individual basis.

### **Respiratory, thoracic and mediastinal disorders**

Very rare: reversible pneumonitis

### **Gastrointestinal disorders**

Common: nausea

Uncommon: pancreatitis

Very 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 AZAMUN. 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 rechallenge, has been reported in patients treated with AZAMUN 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 AZAMUN 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 rechallenge has confirmed an association with AZAMUN on occasions.

### **Hepato-biliary disorders**

Uncommon: cholestasis and deterioration of liver function tests

Rare: life-threatening hepatic damage

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

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

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.

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## **Dosage and Administration**

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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 5 mg/kg/day is usually given.

Maintenance dosage may range from 1-4 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, starting dosage rarely exceeds 3 mg/kg/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. However, for patients with Crohn's disease, a treatment duration of at least 12 months should be considered and a response to treatment may not be clinically apparent until after 3-4 months of treatment.

The maintenance dosage required may range from less than 1 mg/kg/day to 3 mg/kg/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 haematological response is carefully monitored.

The maintenance dosage used for the treatment of liver disorders is at the low end of the recommended range.

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.

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## **Overdosage**

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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.

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## **Presentation and Storage conditions**

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**AZAMUN 50 mg Tablets:** Pale yellow, film coated biconvex tablet; one side is marked "AZA" and a score over "50".

### ***Storage***

Shelf life is 3 years. Store below 30 °C and protect from light and moisture.

### ***Pack quantities***

Blister pack of 100 tablets.

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## **Medicine Classification**

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Prescription Medicine.

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## **Name and Address of Sponsor**

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## **Date of Preparation**

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May 2009.