New Zealand Data Sheet

1. PRODUCT NAME

Azamun® 25 mg, 50 mg, 75 mg, 100mg, Film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azamun 25 mg: each tablet contains 25 mg azathioprine
Azamun 50 mg: each tablet contains 50 mg azathioprine
Azamun 75 mg: each tablet contains 75 mg azathioprine
Azamun 100 mg: each tablet contains 100 mg azathioprine

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Azamun 25 mg: Light yellow, circular, biconvex tablet engraved “AZA” and “25” on one side and plain on the other side.
Azamun 50 mg: Light yellow, circular, biconvex tablet engraved “AZA”’ and “50” separated by a line on one side and plain on the other side.
Azamun 75 mg: Light yellow, circular, biconvex tablet engraved “AZA” and “75” on one side and plain on the other side.
Azamun 100 mg: Light yellow, circular, biconvex tablet engraved “AZA” and “100” on one side and plain on the other side.

The scoreline on Azamun 50 mg is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Dose and method of administration

Azathioprine is a potent immunosuppressive 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.

Children considered to be overweight may require doses at the higher end of the dose range and therefore close monitoring of response to treatment is recommended.

Dose

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, the initial dose should be approximately 1.0 mg/kg/day (50 to 100 mg) gradually increasing in increments of 0.5 mg/kg/day over several weeks, if necessary, up to a maximum dose of 2.5 mg/kg/day.

When a 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 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 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.

Special populations

Elderly population

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 (refer to, renal and/or hepatic impairments).

Renal and/or hepatic impairment

In patients with renal/or hepatic insufficiency, dosages should be given at the lower end of the normal range (refer to section 4.4).

TPMT-deficient patients

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe azathioprine toxicity from conventional doses of azathioprine and generally require substantial dose reduction. The optimal starting dose of heterozygous deficient patients has not been established.

Most patients with heterozygous TPMT deficiency can tolerate recommended azathioprine doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available, refer to section 4.4 for further information.

Interactions requiring specific dose adjustments

When xanthine oxidase inhibitors, such as allopurinol, and azathioprine are administered concomitantly it is essential that only one quarter of the usual dose of azathioprine is given since allopurinol decreases the rate of catabolism of azathioprine e.g., an azathioprine dose of 100 mg should be reduced to 25 mg (refer to section 4.5).

Method of Administration

Azamun tablets should be administered at least 1 hour before or 3 hours after food or milk.

Azamun tablets should be swallowed whole with liquid and must not be divided, chewed or crushed.

4.3. Contraindications

- Hypersensitivity to azathioprine, 6-mercaptopurine or to any of the excipients listed in section 6.1.
- Azamun therapy should not be initiated in patients who may be pregnant, who are likely to become pregnant in the near future, or who are known to be pregnant.
- Patients with rheumatoid arthritis previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan or others) may have a prohibitive risk of neoplasia if treated with azathioprine.

4.4. Special warnings and precautions for use

Co-administration of ribavirin and azathioprine is not advised. Ribavirin may reduce efficacy and increase the toxicity of azathioprine (see section 4.5).

Cytomegalovirus (CMV) disease

Cytomegalovirus (CMV) viraemia resulting in severe pneumonitis and associated haemophagocytic syndrome manifesting in patients with inflammatory bowel disease (IBD) has been reported in literature (see Section 4.8).

Caution should be exercised, and specialist literature consulted when determining the risks of CMV reactivation and IBD deterioration.

Monitoring

There are potential hazards in the use of Azathioprine. It should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of therapy.

Azathioprine is hepatotoxic and liver function tests should be routinely monitored during treatment (see section 4.8). More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. Cases of non-cirrhotic portal hypertension/portosinusoidal vascular disease have been reported. Early clinical signs include liver enzyme abnormalities, mild jaundice, thrombocytopenia, and splenomegaly (see section 4.8). The patient should be informed about the symptoms of liver injury and advised to contact their doctor immediately if these occur.

Particular care should be taken to monitor haematological response and to reduce the maintenance dosage to the minimum required for clinical response.

During the first 8 weeks of therapy, complete blood counts, including platelets, must 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 recommended that complete blood counts are repeated at intervals of no longer than one month

or more frequently if dosage alterations or other changes to therapy are made. Delayed haematological suppression may occur.
Prompt reduction in dosage or temporary withdrawal of the medicine may be necessary if there is a rapid fall in, or persistently low, leucocyte count or other evidence of bone marrow depression.

Patients receiving azathioprine should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding, black tarry stools and blood in urine or stools, or other manifestations of bone marrow depression. Bone marrow suppression is reversible if azathioprine is withdrawn early enough.

TPMT testing

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 azathioprine. There have been fatal cases of myelosuppression in patients with low or absent TPMT activity treated with thiopurines. This problem could be exacerbated by co-administered with a medicine that inhibits TPMT, such as olsalazine, mesalazine or sulphasalazine. Also, a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (refer to section 4.8).

Patients should be tested for TPMT activity before starting azathioprine. TPMT testing cannot substitute for complete blood count monitoring in patients receiving azathioprine. TPMT genotyping can be used to identify patients with absent or reduced TPMT activity. Patients with low or absent TPMT activity (homozygous for non-functional alleles) are at an increased risk of developing severe, life-threatening myelotoxicity from azathioprine if conventional doses are given. Alternative therapies may be considered for patients who have low or absent TPMT activity. Azathioprine should be administered with caution to patients having one non-functional allele (heterozygous) who are at risk for reduced TPMT activity that may lead to toxicity if conventional doses are given. Dosage reduction is recommended in patients with reduced TPMT activity. The dosage of azathioprine may need to be reduced when this agent is combined with other medicines whose primary or secondary toxicity is myelosuppression.

TPMT testing is widely available through pathology laboratories and genetic testing services.

NUDT15 testing

Patients with inherited mutated NUDT15 gene are at increased risk for severe thiopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy and generally require substantial dose reduction. The precise mechanism of NUDT 15-associated thiopurine-related toxicity is not understood. Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population. The optimal starting dose for heterozygous or homozygous deficient patients has not been established. Close monitoring of blood count is necessary.

Genotypic and phenotypic testing of NUDT15 variants should be considered before initiating thiopurine therapy in all patients (including paediatric patients) to reduce the risk of thiopurine-related severe leukocytopenia and alopecia, especially in Asian populations.

Renal and/or hepatic impairment

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. Dosage should be further reduced if haematological toxicity occurs.

Caution is necessary during the administration of azathioprine to patients with renal and/or hepatic impairment, and regular complete blood counts and liver function tests should be undertaken. In such patients the metabolism of azathioprine may be impaired, and the dosage of azathioprine further reduced if hepatic or haematological toxicity occurs.

Lesch-Nyhan syndrome

Limited evidence suggests that azathioprine is not beneficial to patients with a 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 azathioprine.

Genotoxicity

Chromosomal abnormalities, which can occur independently of the influence of azathioprine, have been demonstrated in both male and female patients treated with azathioprine (see section 4.8**).** It is difficult to assess the role of azathioprine in the development of these abnormalities.

Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes from the offspring of patients treated with azathioprine. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of the patients treated with azathioprine (see section 4.6).

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

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), uterine cancer and cervical cancer *in-situ* (See Section 4.8). The increased risk appears to be related to the degree and duration of immunosuppression rather than to the use of any specific agent. 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.

Reports of hepatosplenic T-cell lymphoma in the inflammatory bowel disease population have been received when azathioprine is used in combination with anti-TNF agents.

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.

Renal transplant recipients in some geographical areas are at greater risk of skin cancers than those in other areas.

Other neoplasms reportedly associated with azathioprine include carcinoma of the urinary bladder and adenocarcinoma of the lung.

Varicella Zoster Virus infection

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended (refer to 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.

Progressive Multifocal Leukoencephalopathy (PML)

PML, an opportunistic infection caused by the JC virus (a type of human polyomavirus) has been reported in patients receiving azathioprine with other immunosuppressive agents. Immunosuppressive therapy should be withheld at the first sign or symptoms suggestive of PML and appropriate evaluation undertaken to establish a diagnosis (refer to section 4.8).

Hepatitis B

Hepatitis B carriers (defined as patients positive for hepatitis B surface antigen [HBsAg] for more than six months), or patients with documented past HBV infection, who receive immunosuppressive medicines are at risk of reactivation of HBV replication, with an asymptomatic increase in serum HBV DNA and ALT levels. Specialist medical literature should be consulted for guidance including prophylactic therapy with oral anti-HBV agents.

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.

Metabolism and nutrition disorders

Administration of purine analogues (azathioprine, mercaptopurine and thioguanine) may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency/pellagra. A few cases have been reported with the use of azathioprine, especially in patients with IBD (Crohn's disease, colitis ulcerative). The diagnosis of pellagra should be considered in patients with a localised pigmented rash, gastroenteritis, and extensive neurological deficits including cognitive deterioration. Therefore, health care professionals should be aware of this condition and initiate appropriate medical care with niacin/nicotinamide supplementation. Dose reduction or discontinuation of azathioprine must also be considered.

Other precautions

Azathioprine should be used with caution in hypersplenism.

Withdrawal of azathioprine should be gradual and performed under close supervision.

Dental work, whenever possible should be completed prior to initiation of azathioprine therapy or deferred until blood counts are normal.

Hypersensitivity

Patients suspected to have previously presented a hypersensitivity reaction to 6- mercaptopurine should not be recommended to use its pro-drug azathioprine, and vice versa, unless the patient has been confirmed as hypersensitive to the culprit drug with allergology tests and tested negative for the other (refer to Section 4.8).

Posterior reversible encephalopathy syndrome (PRES)

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients using azathioprine. If patients using azathioprine present with symptoms indicating PRES such as headache, altered mental status, seizures, hypertension, and visual disturbances, a diagnostic imaging should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of azathioprine is advised. Most cases reported resolved following discontinuation of azathioprine and appropriate treatment.

Use in the elderly

See Section 4.2.

Paediatric Use

See Section 4.2**.**

Effects on laboratory tests

No data available

4.5. Interaction with other medicines and other forms of interaction

Allopurinol/ oxipurinol/ thiopurinol and other xanthine oxidase inhibitors

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, oxipurinol 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 usual dose, refer to section 4.2. For example, an azathioprine dose of 100 mg should be reduced to 25 mg when used concomitantly with allopurinol. Fatal cases have been reported in patients treated concomitantly with azathioprine and allopurinol.

Other xanthine oxidase inhibitors, such as febuxostat, may decrease the metabolism of azathioprine. Concomitant administration is not recommended as data are insufficient to determine an adequate dose reduction of azathioprine.

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.

Anticoagulants

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with azathioprine. Therefore, higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with azathioprine.

Cytostatic/ myelosuppressive agents

Azathioprine should be used with caution in patients receiving, or who have recently received, other bone marrow suppressive agents.

Where possible, concomitant administration of cytostatic medicines, or medicines which may have a myelosuppressive effect, such as penicillamine, should be avoided. There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between azathioprine and co-trimoxazole.

There have been case reports suggesting that haematological abnormalities may develop due to the concomitant administration of azathioprine and ACE inhibitors.

It has been suggested that cimetidine and indomethacin may have myelosuppressive effects which may be enhanced by concomitant administration of azathioprine.

Aminosalicylates

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

Methotrexate

Methotrexate (20 mg/m^2 orally) increased 6-mercaptopurine AUC by approximately 31% and methotrexate (2 or 5 g/m^2 intravenously) increased 6-mercaptopurine AUC by 69% and 93% respectively. Therefore, when azathioprine is administered concomitantly with high dose methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.

Other interactions

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

Medicines known to induce (phenytoin, phenobarbital, rifampicin) or inhibit (ketoconazole, erythromycin) hepatic microsomal enzymes may alter the clearance of azathioprine.

Co-administration of azathioprine and captopril may result in increased susceptibility to leucopenia.

Vaccines

The immunosuppressive activity of azathioprine could result in an atypical and potentially deleterious response to live vaccines and so the administration of live vaccines to patients receiving azathioprine therapy is contraindicated on theoretical grounds.

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 azathioprine do not deleteriously affect the response to a polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration.

Ribavirin

Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin; therefore, co-administration is not advised (See section 4.4).

Infliximab

An interaction has been observed between azathioprine and infliximab. Patients receiving ongoing azathioprine experienced increase in 6-TGN (6-thioguanine nucleotide, an active metabolite of azathioprine) levels and a decrease in the mean leukocyte count following infliximab infusion.

4.6. Fertility, pregnancy and lactation

Pregnancy

Pregnancy category D

The decision to maintain or discontinue Azamun 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, Azamun therapy should not be initiated in patients known to be pregnant.

Women taking Azamun or the female partners of men taking Azamun must not become pregnant during treatment and for 6 months afterwards. Both men and women taking Azamun must use effective contraception during treatment with and for 6 months afterwards. Intrauterine devices are not suitable for contraception in women taking Azamun (or in women whose male partners are taking Azamun).

Cholestasis of pregnancy has occasionally been reported in association with azathioprine therapy. If cholestasis of pregnancy occurs, case by case assessment is necessary considering the risk-benefit profile of the medicine.

Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes from the offspring of patients treated with azathioprine. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of the patients treated with azathioprine (see section 4.4).

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. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving azathioprine.

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 after maternal administration of azathioprine.

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 if, at 32 weeks' gestation, the maternal leucocyte count is at or below 8.6 x 10^9 per litre. The possibility of neonatal immunosuppression is a serious and potentially fatal complication. Extra care in haematological monitoring is advised during pregnancy.

Breast-feeding

6-Mercaptopurine has been identified in the colostrum and breastmilk of women receiving azathioprine treatment. Nursing mothers should be advised to consult their physician, since use by nursing mothers is not recommended because of possible adverse effects on the infant.

Effects on 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

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 medicine. However, adverse effects of azathioprine include dizziness which could affect the ability to drive and use machines.

4.8. Undesirable effects

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 ≥1/10, common ≥1/100, <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

System organ class	Frequency	Adverse reactions
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.
	Very rare	Cases of JC virus-associated PML have been reported following the use of azathioprine in combination with other immunosuppressants (refer to section 4.4)
Patients receiving azathioprine alone or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection and reactivation with VZV, hepatitis B, Cytomegalovirus (CMV) and other infectious agents (refer to section 4.4**)**		
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Rare	Neoplasms including lymphoproliferative disorders, skin cancers (malignant melanoma and non-melanoma), sarcomas (Kaposi's and non- Kaposi's), uterine cancer, cervical cancer *in situ*, acute myeloid leukaemia and myelodysplasia (refer to section 4.4)
	Very rare	Hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease when used in combination with anti-TNF agents.
The risk of developing lymphomas and other malignancies, notably skin cancers (malignant melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's), uterine cancer and cervical cancer *in situ*, is increased in patients who receive immunosuppressive medicines, particularly in transplant recipients receiving aggressive treatment and such therapy should be maintained at the lowest effective levels. The increased risk of developing 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

System organ class	Frequency	Adverse reactions
	Rare	Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia
	Very rare	Haemolytic anaemia
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. Therapeutic use of azathioprine is associated with a reversible, dose-related reduction in numbers of circulating total white cells, granulocytes and lymphocytes together with increases in mean corpuscular volume and red cell haemoglobin content. Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and erythroid hypoplasia are rare. Azathioprine may produce thrombocytopenia which is dose-related and may be delayed.		
Immune system disorders	Common	Skin rashes
	Uncommon	Hypersensitivity
	Very rare	Stevens-Johnson syndrome and toxic epidermal necrolysis
Several different clinical syndromes, which appear to be of an idiosyncratic hypersensitivity nature, have been described occasionally. They include general malaise, headache, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, erythema nodosum, vasculitis, myalgia, muscular pains, arthralgia, hypotension, disturbed liver function, cholestatic jaundice, pancreatitis, cardiac dysrhythmia, and renal dysfunction. In many cases, rechallenge has confirmed an association with azathioprine. Additional adverse reactions of low frequency have been reported. These include steatorrhoea and negative nitrogen balance (both less than 1%). It has been suggested that the imidazole side chain gives rise to hypersensitivity, whereas the 6-mercaptopurine (6-MP) molecule gives rise to cholestasis. Immediate withdrawal of azathioprine and supportive circulatory measures has led to recovery in the majority of cases. Other marked underlying pathology has contributed to the very rare deaths reported. Azamun should be PERMANENTLY withdrawn after any such clinical syndrome.		
Nervous system disorders	Unknown	Posterior reversible encephalopathy syndrome (PRES), tremor
Metabolism and nutrition disorders	Unknown	Pellagra (see Section 4.4)
Respiratory, thoracic and mediastinal disorders	Very rare	Pneumonitis (reversible)
Gastrointestinal disorders	Common	Nausea, vomiting
	Uncommon	Pancreatitis
	Very rare	Colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population.
	Unknown	Sialadenitis
Nausea, vomiting and gastrointestinal discomfort may occur during the first few months of azathioprine therapy. These effects are usually reduced by dosage adjustment and by administering the tablets in divided doses and/or after meals. Serious complications, including		

<table>
<tr><th>System organ class</th><th>Frequency</th><th>Adverse reactions</th></tr>
<tr><td colspan="3">colitis, diverticulitis and bowel perforation, have been described in transplant recipients receiving immunosuppressive therapy, and appear to relate to high dosage of corticosteroids rather than to azathioprine per se. Severe diarrhoea, recurring on rechallenge, has been reported in patients treated with azathioprine for inflammatory bowel disease. The possibility that exacerbation of symptoms might be medicine-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 medicine, although rechallenge has confirmed an association with azathioprine on occasions.</td></tr>
<tr><td rowspan="3">Hepatobiliary disorders</td><td>Uncommon</td><td>Cholestasis and deterioration of liver function tests</td></tr>
<tr><td>Rare</td><td>Life-threatening hepatic damage</td></tr>
<tr><td>Unknown</td><td>Non-cirrhotic portal hypertension, portosinusoidal vascular disease</td></tr>
<tr><td colspan="3">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 Immune system disorders). Hepatotoxicity may manifest by elevation of serum alkaline phosphatase, bilirubin and/or serum transaminases and is generally reversible after interruption of azathioprine. Periodic measurement of serum transaminases, alkaline phosphatase and bilirubin is indicated for early detection of hepatotoxicity. Hepatotoxicity has been uncommon (less than 1%) in rheumatoid arthritis patients. Rare, but life-threatening hepatic damage associated with chronic administration of azathioprine has been described. 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. Azathioprine should be permanently withdrawn in patients with hepatic veno-occlusive disease. Also, in patients using azathioprine for long term especially for IBD, treating physicians should consider nodular regenerative hyperplasia in their differential diagnosis when patients develop clinical manifestations of non-cirrhotic portal hypertension like gastric-oesophageal varices, splenomegaly, ascites and thrombocytopenia. Hence, it is advised that such patients should be monitored for these signs to avoid further complications.</td></tr>
<tr><td rowspan="2">Skin and subcutaneous tissue disorders</td><td>Rare</td><td>Alopecia</td></tr>
<tr><td>Unknown</td><td>Acute febrile neutrophilic dermatosis (Sweet’s Syndrome), photosensitivity reaction</td></tr>
<tr><td colspan="3">Hair loss has been described in 50% of renal transplant recipients receiving azathioprine and corticosteroids but does not appear to be a major problem when azathioprine is used for other indications. It is reversible in over 80% of cases despite continuing immunosuppression.</td></tr>
</table>

Other Adverse Effects

Other adverse reactions include sores in the mouth and on the lips, meningitis, formication exacerbation of myasthenia gravis and dermatomyositis and alterations in the senses of smell or taste.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions https://pophealth.my.site.com/carmreportnz/s/

4.9. Overdose

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 - 14 days. These signs are more likely to be manifest following chronic overdosage, rather than after a single acute overdose. There has been a report of a patient who ingested a single overdose of 7.5 g of azathioprine. The immediate toxic effects of the 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. The value of dialysis in patients who have taken an overdose of azathioprine is not known, though azathioprine is partially dialysable.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressant; ATC code: L04AX01

Azathioprine is an imidazolyl 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 the cell membrane 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 which 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. Determinations of plasma concentrations of azathioprine or 6-MP have no prognostic value as regard effectiveness or toxicity of these compounds.

Mechanism of action

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.

5.2. Pharmacokinetic properties

Azathioprine appears to be well absorbed from the upper gastrointestinal tract.

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

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

5.3. Preclinical safety data

Teratogenicity

Studies in pregnant rats, mice and rabbits using azathioprine in dosages from 5-15 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 bodyweight/day.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Azamun contains cellulose microcrystalline, mannitol, povidone, maize starch, croscarmellose sodium, sodium stearyl fumarate in the tablet core. The tablet coating contains Opadry clear OY-7240 (macrogol 400 and hypromellose).

6.2. Incompatibilities

Not known.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Azamun 25 mg and 50 mg: Store at or below 30°C and protect from light and moisture.
Azamun 75 mg and 100 mg: Store at or below 25°C and protect from light and moisture.

6.5. Nature and contents of container

Azamun 25 mg: 30, 60 and 100 tablets in PVC/PVDC-Aluminium foil blister strips.
Azamun 50 mg, 75 mg, 100 mg: 100 tablets in PVC/PVDC-Aluminium foil blister strips.

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

Azamun 50 mg: 13 August 1998

Azamun 25 mg, 75 mg, 100 mg: 26 June 2014

10. DATE OF REVISION OF THE TEXT

17 November 2025

Summary table of changes

Section Changed	Summary of new information

4.2, 4.4, 4.5, 4.6, 4.7, 4.8	Editorial updates
4.4	To align with overseas reference medicine, updated information on metabolism and nutrition disorders and added information on posterior reversible encephalopathy syndrome (PRES)
4.5	To align with overseas reference medicine, added further information on interaction of azathioprine and allopurinol
4.8	Converted text to table format and to align with overseas reference medicine. Added haemolytic anaemia to Blood and lymphatic system disorders with frequency very rare; Posterior reversible encephalopathy syndrome (PRES) and tremor to Nervous system disorders with frequency unknown; Pellagra to Metabolism and nutrition disorders with frequency unknown; vomiting to Gastrointestinal disorders with frequency common; sialadenitis to Gastrointestinal disorders with frequency unknown; photosensitivity reaction to Skin and subcutaneous tissue disorders with frequency unknown
4.9	Addition of 'risk assessment' wording into overdose statement
8	Deleted New Zealand