SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

IMURAN TABLETS 25 MG

IMURAN TABLETS 50 MG

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Azathioprine

Each tablet contains 25 mg or 50 mg of the active substance azathioprine.
Excipient(s) with known effect

Each 25 mg tablet contains 37 mg lactose monohydrate.
Each 50 mg tablet contains 74 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
Imuran 25 mg: Orange, round, biconvex, film-coated tablets, unscored, branded 'IM 2'.

Imuran 50 mg: Yellow, round, biconvex, scored, film-coated tablets, branded 'IM 5'.

The score line is not for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Immunosuppressive agent used in transplantation surgery for suppression of graft rejection.
For special cases of rheumatoid arthritis, not responsive to other agents, and only by rheumatology experts in hospitals or rheumatic clinics.

4.2 Posology and method of administration

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

General
When the oral route is impractical azathioprine injection may be administered by the i.v. route only, however, this route should be discontinued as soon as oral therapy can be tolerated once more.

Imuran tablets should be administered at least 1 hour before or 3 hours after food or milk (see Section 5.2 Pharmacokinetics: Absorption).

Dosage in transplantation – a*dults*
Depending on the immunosuppressive regimen employed, a dosage of up to 5mg/kg bodyweight/day may be given on the first day of therapy, either orally or intravenously.

Maintenance dosage should range from 1-4mg/kg bodyweight/day and must be adjusted according to clinical requirements and haematological tolerance.

Corticosteroid therapy is usually given concomitantly with Imuran.

Evidence indicates that Imuran therapy should be maintained indefinitely, even if only low doses are necessary, because of the risk of graft rejection.

Dosage in other conditions - adults:
In general, starting dosage is from 1-3mg/kg bodyweight/day, and should be adjusted, within these limits, depending on the clinical response (which may not be evident for weeks or months) and haematological tolerance.

In general, starting dosage rarely exceeds 3mg/kg bodyweight/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 the maintenance of that response. If no improvement occurs in the patient's condition within 3 months, consideration should be given to withdrawing Imuran.

The maintenance dosage required may range from less than 1 mg/kg bodyweight/day to 3 mg/kg bodyweight/day, depending on the clinical condition being treated and the individual patient response, including haematological tolerance.

Paediatric population
Transplants
See Dosage in transplantation - adults.

Other Indications:

Overweight children
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 (see Section 5.2 Pharmacokinetics: Special Patient Populations: Overweight children).

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 Imuran in elderly patients. There is limited experience of the administration of Imuran to elderly patients. Although the available data do not provide evidence that the incidence of side effects among elderly patients is higher than that among other patients treated with Imuran, it is advisable to monitor renal and hepatic function, and to consider dosage reduction if there is impairment (see Section 4.2 Posology and method of administration - Renal and/or hepatic impairment).

The dosage is adjusted on the basis of the clinical state and the response of the individual patient. If no improvement has occurred after 3 months, consideration should be given to discontinuing the drug.

Renal and/or hepatic impairment
In patients with renal and/or hepatic insufficiency, consideration should be given to reducing the dosage (see Section 4.4 Special warnings and precautions for use).

Drug interactions
When xanthine oxidase inhibitors, such as allopurinol, and azathioprine are administered concomitantly it is essential that only 25% of the usual dose of azathioprine is given since allopurinol decreases the rate of catabolism of azathioprine (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

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 for homozygous deficient patients has not been established (see Section 4.4 Special warnings

and Precautions for Use: Monitoring and Section 5.2 Pharmacokinetics).

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 (see Section 4.4 Special warnings and precautions for use: Monitoring and Section 5.2 Pharmacokinetics).

4.3 Contraindications

Hypersensitivity to the active ingredient azathioprine or to any of the excipients listed in section 6.1.
Hypersensitivity to 6-mercaptopurine should alert the prescriber to probable hypersensitivity to azathioprine.

4.4 Special warnings and precautions for use

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, it is recommended that patients do not receive live organism vaccines until at least 3 months after the end of their treatment with azathioprine (see Section 4.5).
Co-administration of ribavirin and azathioprine is not advised. Ribavirin may reduce efficacy and increase toxicity of azathioprine (see Section 4.5).

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.

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

It is suggested that during the first eight weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than three months.

At the first signs of an abnormal fall in blood counts, treatment should be interrupted immediately as leucocytes and platelets may continue to fall after treatment is stopped.

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

Azathioprine is hepatotoxic and liver function tests should be routinely monitored during treatment. 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.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine therapy (see section 4.6). If cholestasis of pregnancy occurs, case by case assessment is necessary considering the risk-benefit profile of the product (potential withdrawal/dose reduction).

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. This problem could be exacerbated by co-administration with medicinal products that inhibit 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 (see Section 4.8). Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is still necessary. The dosage of azathioprine may need to be reduced when this agent is combined with other medicinal products whose primary or secondary toxicity is myelosuppression (see Section 4.5).

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 allergological tests, and tested negative for the other.

Renal and/or hepatic impairment

Caution is advised during the administration of azathioprine in patients with renal impairment and/or hepatic impairment. Consideration should be given to reducing the starting dosage in these patients and haematological response should be carefully monitored (see Section 4.2 and Section 5.2).

Lesch-Nyhan syndrome
Limited evidence suggests that azathioprine is not beneficial to patients with hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). Therefore, given the abnormal metabolism in these patients, it is not prudent to recommend that these patients should receive azathioprine.

Neuromuscular blocking agents
Special care is necessary when azathioprine is given concomitantly with neuromuscular blocking agents such as atracurium, rocuronium, cisatracurium or suxamethonium (also known as succinylcholine) (see section 4.5). Anesthesiologists should check whether their patients are administered azathioprine prior to surgery.

Mutagenicity
Chromosomal abnormalities have been demonstrated in both male and female patients treated with azathioprine. 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 off-spring of patients treated with azathioprine. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the off-spring of 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 (see Section 4.8):
Patients receiving immunosuppressive therapy, including azathioprine, are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

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

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.

Reports of hepatosplenic T-cell lymphoma have been received when azathioprine is used alone or in combination with anti-TNF agents or other immunosuppressants. Although most reported cases occurred in the IBD population, there have also been cases reported outside of this population (see section 4.8).

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD), and there could potentially be an

increased susceptibility for developing the condition with the use of azathioprine. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with azathioprine should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Metabolism and nutrition disorders

Administration of purine analogues, azathioprine and mercaptopurine, may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency (pellagra). Few cases have been reported with the use of azathioprine, especially in patients with IBD (Crohn's disease, colitis ulcerative). Diagnosis of pellagra should be considered in a patient presenting with localised pigmented rash (dermatitis); gastroenteritis (diarrhoea); or neurologic deficits, including cognitive decline (dementia). Appropriate medical care with niacin/nicotinamide supplementation must be initiated, and dose reduction or discontinuation of azathioprine must be considered.

Varicella Zoster Virus Infection (see 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, 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 (see Section 4.8).

Hepatitis B (see Section 4.8)
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 immunosuppressants are at risk of reactivation of HBV replication, with asymptomatic increases in serum HBV DNA and ALT levels. Local guidelines may be considered including prophylactic therapy with oral anti-HBV agents.

Xanthine oxidase inhibitors
If allopurinol, oxipurinol and/or thiopurinol are given concomitantly with azathioprine, the dosage of azathioprine must be reduced to a quarter of the original dose (see section 4.2).

Neuromuscular agents
Special care is necessary when azathioprine is given concomitantly with neuromuscular acting agents like tubocurarine or succinylcholine (see section 4.5). It can also potentiate the neuromuscular block that is produced by depolarising agents such as succinylcholine (see section 4.5). Patients should be advised to inform their anaesthesiologist of their treatment with azathioprine prior to surgery.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccines
The immunosuppressive activity of azathioprine could result in an atypical and potentially deleterious response to live vaccines. It is therefore recommended that patients do not receive live vaccines until at least 3 months after the end of their treatment with azathioprine (see Section 4.4.).

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 polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration.

Effect of concomitant medicinal products on azathioprine

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. and Section 5.2).

Cytostatic/myelosuppressive agents (see Section 4.4)
Where possible, concomitant administration of cytostatic agents, or medicinal products 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 trimethoprim/sulfamethoxazole.

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.

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 25 % of the original dose (see Section 4.2).

Based on non-clinical data, other xanthine oxidase inhibitors, such as febuxostat may prolong the activity of azathioprine possibly resulting in enhanced bone marrow suppression. Concomitant administration is not recommended as data are insufficient to determine an adequate dose reduction of azathioprine.

Aminosalicylate
There is *in vitro* and *in vivo* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulfasalazine) inhibit the TPMT enzyme. Therefore, lower doses of azathioprine may need to be considered when administered concomitantly with aminosalicylate derivatives, (see Section 4.4).

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.

Infliximab
An interaction has been observed between azathioprine and infliximab. Patients receiving ongoing azathioprine experienced transient increases in 6-TGN (6-thioguanine nucleotide, an active metabolite of azathioprine) levels and a decrease in the mean leukocyte count in the initial weeks following infliximab infusion, which returned to previous levels after 3 months.

Neuromuscular agents
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 produced by d-tubocurarine, and show that azathioprine potentiates the neuromuscular blockade produced by succinylcholine (see section 4.4). There is considerable variation in the potency of this interaction.

Effect of azathioprine on other medicinal products

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.

4.6 Fertility, pregnancy and lactation

Fertility
The specific effect of azathioprine therapy on human fertility is unknown.

Pregnancy
Substantial transplacental and transamniotic transmission of azathioprine and its metabolites from the mother to the foetus have been shown to occur.

Azathioprine should not be given to patients who are pregnant or likely to become pregnant in the near future without careful assessment of risk versus benefit.

Evidence of the teratogenicity of azathioprine in man is equivocal. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving azathioprine.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine therapy. Early diagnosis and discontinuation of azathioprine may minimise impact on the foetus. However, a careful assessment of benefit to the mother and impact on the foetus should be performed, if cholestasis of pregnancy is confirmed (see section 4.4).

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

There have been reports of intra-uterine growth retardation, 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.

Leukopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took azathioprine throughout their pregnancies. Extra care in haematological monitoring is advised during pregnancy.

Breast-feeding
6-mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment. Available data has shown that the excreted levels in breast-milk are low. From the limited available data, the risk to newborns/infants is considered to be unlikely but cannot be excluded.

It is recommended that women receiving azathioprine should avoid breastfeeding unless the benefits outweighs the potential risks.

If a decision is made to breastfeed, because 6-mercaptopurine is a strong immunosuppressant, the breastfed infant should be closely monitored for signs of immunosuppression, leukopenia, thrombocytopenia, hepatotoxicity, pancreatitis or other symptoms of 6-mercaptopurine exposure.

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 azathioprine.

4.8 Undesirable effects

Summary of the safety profile

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 most important adverse reactions include bone marrow depression, most frequently expressed as leukopenia, thrombocytopenia or anaemia; viral, fungal and bacterial infections; life-threatening liver injury; hypersensitivity, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Tabulated list of adverse reactions

The following convention has been utilised for the classification of frequency:

Very common ≥ 1/10
Common ≥1/100 and <1/10
Uncommon ≥ 1/1000 and <1/100
Rare ≥1/10,000 and <1/1000
Very rare <1/10,000
Not known (cannot be estimated from the available data)

Body System	Frequency	Side effects
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 (see Section 4.4).
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Rare	Neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*, acute myeloid leukaemia and myelodysplastic syndrome (see Section 4.4).
	Not known	Hepatosplenic T-cell lymphoma (see Section 4.4).
Blood and lymphatic system disorders	Very common	Bone marrow depression, leukopenia
	Common	Thrombocytopenia
	Uncommon	Anaemia
	Rare	Agranulocytosis, pancytopenia, aplastic anemia, megaloblastic anaemia, erythroid hypoplasia
Immune system disorders	Uncommon	Hypersensitivity
	Very rare	Stevens-Johnson syndrome and toxic epidermal necrolysis
Metabolism and nutrition Disorders	Not known	Pellagra (Refer to section 4.4)
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
Hepatobiliary disorders	Uncommon	Cholestasis and cholestasis of pregnancy
	Rare	Life-threatening liver injury
	Not known	Non-cirrhotic portal hypertension, portosinusoidal vascular disease
Investigations	Uncommon	Liver function test abnormal

Body System	Frequency	Side effects
Skin and subcutaneous tissue disorders	Rare	Alopecia
	Not known	Acute febrile neutrophilic dermatosis (Sweet's syndrome), photosensitivity

Description of selected adverse reactions

Infections and infestations

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 and other infectious agents. (see Section 4.4).

Neoplasms benign, malignant and unspecified (including cysts and polyps)

The risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*, is increased in patients who receive immunosuppressants, 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

Azathioprine may be associated with a dose-related, generally reversible, depression of bone marrow function, most frequently expressed as leukopenia, but also sometimes as anaemia and thrombocytopenia and rarely as agranulocytosis, pancytopenia and aplastic anaemia. These occur particularly in patients predisposed to myelotoxicity, such as those with TPMT deficiency and renal or hepatic insufficiency and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol therapy.

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

Immune system disorders

Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following administration of azathioprine tablets. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, erythema nodosum, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis. (see Hepatobiliary disorders).

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

Immediate withdrawal of azathioprine and institution of circulatory support where appropriate have led to recovery in the majority of cases.

Other marked underlying pathology has contributed to the very rare deaths reported.
Following a hypersensitivity reaction to azathioprine tablets, the necessity for continued administration should be carefully considered on an individual basis.

Gastrointestinal disorders

Some patients experience nausea when first given azathioprine. With oral administration, nausea appears to be relieved by administering the tablets after meals. However, administration of azathioprine tablets after meals may reduce oral absorption, therefore monitoring for therapeutic efficacy should be considered after administration in this way (see Section 4.2, 4.5 and 5.2).

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 azathioprine for inflammatory bowel disease. The possibility that exacerbation of symptoms might be related to the medicinal product 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.

Hepatobiliary disorders
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).

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.

Skin and subcutaneous tissue disorders

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.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

In addition, you can report via the following address: Padagis.co.il

4.9 Overdose

Symptoms and signs

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 to14 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 7.5g of azathioprine.
The immediate toxic effects of this overdose were nausea, vomiting and diarrhoea, followed by mild leukopenia and mild abnormalities in liver function. Recovery was uneventful.

Treatment

As there is no specific antidote, blood counts should be closely monitored and general supportive measures, together with appropriate blood transfusion, instituted if necessary. Active measures (such as the use of activated charcoal) may not be effective in the event of azathioprine overdose unless the procedure can be undertaken within 60 minutes of ingestion.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

The value of dialysis in patients who have taken an overdose of azathioprine is not known, though azathioprine is

partially dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS,

IMMUNOSUPPRESSANTS, Other immunosuppressants, ATC code: L04AX01

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down *in vivo* into 6-MP and a methylnitroimidazole moiety. The 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid. The rate of conversion varies from one person to another. Nucleotides do not traverse cell membranes and therefore do not circulate in body fluids. Irrespective of whether it is given directly or is derived in vivo from azathioprine, 6-MP is eliminated mainly as the inactive oxidised metabolite thiouric acid. This oxidation is brought about by xanthine oxidase, an enzyme that is inhibited by allopurinol. The activity of the methylnitroimidazole moiety has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP. Determination of plasma concentrations of azathioprine or 6-MP have no prognostic values as regards effectiveness or toxicity of these compounds.

While the precise modes of action remain to be elucidated, some suggested mechanisms include:

1. the release of 6-MP which acts as a purine antimetabolite.

2. the possible blockade of-SH groups by alkylation.

3. the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response.

4. damage to deoxyribonucleic acid (DNA) through incorporation of purine thio-analogues.

Because of these mechanisms, the therapeutic effect of Imuran may be evident only after several weeks or months of treatment.

Imuran appears to be well absorbed from the upper gastro-intestinal tract.

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

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

5.2 Pharmacokinetic properties

Absorption

Azathioprine is well absorbed following oral administration. Although there are no food effect studies with azathioprine, pharmacokinetic studies with 6-mercaptopurine have been conducted that are relevant to azathioprine. The mean relative bioavailability of 6-mercaptopurine was approximately 27% lower following administration with food and milk compared to an overnight fast. 6-mercaptopurine is not stable in milk due to the presence of xanthine oxidase (30% degradation within 30 minutes) (see Section 4.2). Azathioprine should be administered at least 1 hour before or 3 hours after food or milk (see Section 4.2 Posology and method of administration).
Azathioprine is principally excreted as 6-thiouric uric acid in the urine. 1-methyl-4-nitro-5-thioimidazole has also been detected in urine as a minor excretory product. This would indicate that, rather than azathioprine being exclusive cleaved by nucleophilic attack at the 5-position of the nitroimidazole ring to generate 6-mercaptopurine and 1-methyl-4-nitro-5-(S-glutathionyl)imidazole. A small proportion of the drug may be cleaved between the S

atom and the purine ring. Only a small amount of the dose of azathioprine administered is excreted unmetabolised in the urine.

Distribution

The volume of distribution at steady state (Vdss) of azathioprine is unknown. The mean (± SD) apparent Vdss of 6-MP is 0.9 (±0.8) L/kg, although this may be an underestimate because 6-MP is cleared throughout the body (and not just in the liver).

Approximately 30% of azathioprine is protein bound.

Concentrations of 6-MP in cerebrospinal fluid (CSF) are low or negligible after i.v. or oral administration of 6-MP.

Biotransformation

Thiopurine S-Methyl Transferase (TPMT)

TPMT activity is inversely related to red blood cell 6-mercaptopurine derived thioguanine nucleotide concentration, with higher thioguanine nucleotide concentrations resulting in greater reductions in white blood cell and neutrophil counts. Individuals with TPMT deficiency develop very high cytotoxic thioguanine nucleotide concentrations.

Genotypic testing can determine the allelic pattern of a patient. Currently, 3 alleles—TPMT*2, TPMT*3A and TPMT*3C—account for about 95% of individuals with reduced levels of TPMT activity. Approximately 0.3% (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90% of individuals have normal TPMT activity with two functional alleles. There may also be a group of approximately 2% who have very high TPMT activity. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in red blood cells and can also be informative (see section 4.4).

Elimination

After oral administration of 100mg 35S-azathioprine, 50% of the radioactivity was excreted in the urine over 24 hours and 12% in the faeces after 24 hours. In the urine, the major compound was the inactive oxidised metabolite thiouric acid. Less than 2% was excreted in the urine as azathioprine or 6-MP. Azathioprine has a high extraction ratio with a total clearance greater than 3L/min in normal volunteers. There are no data on the renal clearance or half-life of azathioprine. The renal clearance of 6-MP and the half-life of 6-MP are 191 mL/min/m2 and 0.9 hr respectively.

Mercaptopurine, a metabolite of azathioprine, has been identified in the colostrum and breast-milk of women receiving azathioprine treatment.

Special Patient Populations

Paediatric population -Overweight children

In a US clinical study, 18 children (aged 3 to 14 years) were evenly divided into two groups; either a weight to height ratio above or below the 75th percentile. Each child was on maintenance treatment of 6-mercaptopurine and the dosage was calculated based on their body surface area. The mean AUC (0- ∞) of 6-mercaptopurine in the group above the 75th percentile was 2.4 times lower than that for the group below the 75th percentile. Therefore, children considered to be overweight may require azathioprine doses at the higher end of the dose range and close monitoring of response to treatment is recommended (see section 4.2).

Patients with renal impairment

Studies with azathioprine have shown no difference in 6-mercaptopurine pharmacokinetics in uremic patients compared to renal transplant patients. Since little is known about the active metabolites of azathioprine in renal impairment, consideration should be given to reducing the dosage in patients with impaired renal function (see section 4.2).

Azathioprine and/or its metabolites are eliminated by haemodialysis, with approximately 45% of radioactive

metabolites eliminated during dialysis of 8 hours.

Patients with hepatic impairment
A study with azathioprine was performed in three groups of renal transplant patients: those without liver disease, those with hepatic impairment (but no cirrhosis) and those with hepatic impairment and cirrhosis. The study demonstrated that 6-mercaptopurine exposure was 1.6 times higher in patients with hepatic impairment (but no cirrhosis) and 6 times higher in patients with hepatic impairment and cirrhosis, compared to patients without liver disease. Therefore, consideration should be given to reducing the dosage in patients with impaired hepatic function (see section 4.2).

5.3 Preclinical safety data

Mutagenicity
Azathioprine was found to be mutagenic in a number of *in vitro* and *in vivo* genotoxicity assays

Carcinogenicity
Long-term carcinogenicity studies of azathioprine showed an increased incidence of lymphosarcomas, as well as epithelial tumours and carcinomas in mice and rats, respectively, at dosages of up to 2-fold the human therapeutic dose and at lower dosages in immunocompromised mice.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive Ingredients core:
Lactose Monohydrate, Maize starch, Pregelatinised starch, Magnesium stearate, Stearic acid,

Inactive Ingredients coating:
Imuran 50 mg tablets
Hypromellose
Macrogol 400
Imuran 25 mg tablets
Opadry Orange 06B230003 (Hypromellose, Titanium Dioxide, Macrogol 400, Iron Oxide Yellow, Iron Oxide Red).

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date is indicated on the packaging materials

6.4 Special precautions for storage

Store at or below 25°C.

Protect from light.

6.5 Nature and contents of container

For 50 mg tablets: PVC/aluminium foil blister packs containing 100 tablets.

For 25 mg tablets: Clear, amber or white opaque PVC/aluminium foil blister pack, containing 100 tablets.

6.6 Special precautions for disposal and other handling

Safe handling

Health professionals who handle uncoated azathioprine tablets should follow guidelines for the handling of cytotoxic medicinal products according to prevailing local recommendations and/or regulations.

Provided that the film-coating is intact, there is no risk in handling film-coated azathioprine tablets.

Film-coated azathioprine tablets should not be divided and, provided the coating is intact, no additional precautions are required when handling them.

Disposal:

Azathioprine tablets should be disposed of in a manner appropriate to the prevailing local regulatory requirements for the destruction of dangerous substances.

7 MANUFACTURER

ASPEN PHARMA TRADING LTD, DUBLIN, IRELAND

8 REGISTRATION No.

IMURAN 50MG TABLETS 042-65-22964-00
IMURAN 25MG TABLETS 034-79-25384-00

9 REGISTRATION HOLDER

Padagis Israel Agencies Ltd.,
1 Rakefet St., Shoham, Israel.

10 DATE OF REVISION OF THE TEXT

Revised in May 2025.

05.2025