SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Azathioprine 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg azathioprine.

Excipient(s) with known effect:
Each film-coated tablet contains 42.75 mg lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White to yellowish-white film-coated tablet, biconvex, no score-line.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Azathioprine is used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and procedures which influence the immune response. Therapeutic effect may be evident only after weeks or months and can include a steroid-sparing effect, thereby reducing the toxicity associated with high dosage and prolonged usage of corticosteroids.

Azathioprine in combination with corticosteroids and/or other immunosuppressive agents and procedures, is indicated to enhance the survival of organ transplants, such as renal transplants, cardiac transplants, and hepatic transplants. It also reduces the corticosteroid requirements of renal transplant recipients.

Azathioprine is indicated for the treatment of moderate to severe inflammatory bowel disease (IBD) (Crohn’s disease or ulcerative colitis) in patients in whom corticosteroid therapy is required, in patients who cannot tolerate corticosteroid therapy, or in patients whose disease is refractory to other standard first line therapy.

Azathioprine either alone or more usually in combination with corticosteroids and/or other medicinal products and procedures has been used with clinical benefit (which may include reduction of dosage or discontinuation of corticosteroids) in a proportion of patients suffering from the following:

- 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

4.2 Posology and method of administration

Posology

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.

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

Populations

Adults

Transplants

Depending on the immunosuppressive regime employed, a dosage of up to 5 mg/kg bodyweight/day may be given on the first day of therapy, either orally or intravenously.

Maintenance dosage should range from 1-4 mg/kg/bodyweight/day 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 indications

In general, starting dosage is from 1-3 mg/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.

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 the medicinal product.

However, for patients with IBD, a treatment duration of at least twelve months should be considered and a response to treatment may not be clinically apparent until after three to four months of treatment.

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: The posology in children is the same as in adults (see Section 4.2 Adults – Transplants).

Other indications:
The posology in children is the same as in adults (see Section 4.2 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).

Elderly population
There is limited experience of the administration of azathioprine 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 azathioprine, it is advisable to monitor renal and hepatic function, and to consider dosage reduction if there is impairment (see section 4.2).

Renal impairment
Since azathioprine pharmacokinetics has not been formally studied in renal impairment, no specific dose recommendations can be given. Since impaired renal function may result in slower elimination of azathioprine and its metabolites, consideration should be given to reducing the starting doses in patients with impaired renal function. Patients should be monitored for dose related adverse effects (see section 4.4 and section 5.2).

Hepatic impairment
Since azathioprine pharmacokinetics has not been formally studied in hepatic impairment, no specific dose recommendations can be given. Since impaired hepatic function may result in reduced elimination of azathioprine and its metabolites, consideration should be given to reducing the starting doses in patients with impaired hepatic function. Patients should be monitored for dose related adverse effects (see section 4.4 and section 5.2)

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: Monitoring and Section 5.2).

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 and section 5.2).

Interactions with other medicinal products
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).

Patients with NUDT15 variant
Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-mercaptopurine toxicity (see 4.4). These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes (see 4.4). Genotypic testing of NUDT15 variants may be considered before initiating 6-mercaptopurine therapy. In any case, close monitoring of blood counts is necessary.

Method of administration

For oral use.
Azathioprine may be taken with food or on an empty stomach, but patients should standardise the method of administration. 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 4.8).
The dose should not be taken with milk or dairy products (see Section 4.5).
Azathioprine should be taken at least 1 hour before or 2 hours after milk or dairy products (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance 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 3 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).

Patients with TPMT deficiency
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, Cytostatic/myelosuppressive agents).

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.

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 offspring 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
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.

Infections

Patients treated with 6-mercaptopurine alone or in combination with other immunosuppressive agents, including corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection, and viral reactivation. The infectious disease and complications may be more severe in these patients than in non-treated patients.
Prior exposure to or infection with varicella zoster virus should be taken into consideration prior to starting treatment. Local guidelines may be considered, including prophylactic therapy if necessary.
Serologic testing prior to starting treatment should be considered with respect to hepatitis B. Local guidelines may be considered, including prophylactic therapy for cases which have been confirmed positive by serologic testing. Cases of neutropenic sepsis have been reported in patients receiving 6- mercaptopurine for ALL.

Patients with NUDT15 variant
Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-mercaptopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy. They generally require dose reduction, particularly those being NUDT15 variant homozygotes (see 4.2).
The frequency of NUDT15 c.415C>T has an ethnic variability of approximately 10 % in East Asians, 4 % in Hispanics, 0.2 % in Europeans and 0 % in Africans. In any case, close monitoring of blood counts is necessary.

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.

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.

Excipients(s) with known effect
Lactose:
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

4.5 Interaction with other medicinal products and other forms of interaction

Food, milk and dairy products
The administration of azathioprine with food may decrease systemic exposure slightly but this is unlikely to be of clinical significance (see Section 4.8). Therefore, azathioprine may be taken with food or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken with milk or dairy products since they contain xanthine oxidase, an enzyme which metabolises 6–mercaptopurine and might therefore lead to reduced plasma concentrations of 6–mercaptopurine (see Section 4.2 and 5.2).

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.

<u>Effect of concomitant medicinal products on azathioprine</u>

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 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.

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors
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 (eg. 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/m2 orally) increased 6-mercaptopurine AUC by approximately 31% and methotrexate (2 or 5 g/m2 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.

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 blocking agents
There is clinical evidence that azathioprine antagonises the effect of non-depolarising muscle relaxants. Experimental data confirm that azathioprine reverses the neuromuscular blockade produced by non-depolarising agents, and show that azathioprine potentiates the neuromuscular blockade produced by depolarising agents (see section 4.4).

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

Pregnancy:

There are limited amount of data from the use of azathioprine in pregnant women
Substantial transplacental and transamniotic transmission of azathioprine and its metabolites from the mother to the foetus have been shown to occur.

Animal studies have shown reproductive toxicity (see section 5.3)
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. 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).

Women of childbearing potential/contraception in men and women
Due to the genotoxic potential of azathioprine (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with azathioprine and for 6 months following completion of treatment.
Men are recommended to use effective contraceptive measures and to not father a child while receiving azathioprine and for 3 months following completion of treatment.

Mutagenicity
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 offspring of patients treated with azathioprine. 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 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.

Breastfeeding
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.

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

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 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
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
	Uncommen	viral, fungal and bacterial infections in other patient populations, bacterial and viral infections, infections associated with neutropenia
	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, myelodysplasia (see also 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
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
Metabolism and nutrition disorders	Not known	Pellagra (refer to section 4.4)
Hepatobiliary disorders	Uncommon	Cholestasis and cholestasis of pregnancy
	Rare	Life-threatening hepatic damage, non-cirrhotic portal hypertension, portosinusoidal vascular disease
Investigations	Uncommon	Liver function test abnormal
Skin and subcutaneous tissue disorders	Rare	Alopecia
	Not known	Acute febrile neutrophilic dermatosis (Sweet's syndrome), photosensitivity

Description of selected adverse reactions

<u>Infections and infestations</u>
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)

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 . 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 Hepato-biliary 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, the necessity for continued administration of azathioprine should be carefully considered on an individual basis.

Gastrointestinal disorders
Some patients experience nausea when first given azathioprine. This 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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in Google play or Apple App store.

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 to 14 days. These signs are more likely to be manifest following chronic overdosage, rather than after a single acute overdose. There has been a report of a patient who ingested a single overdose of 7.5 g 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

Therapeutic Group and ATC code: Antineoplastic and Immunosuppressive agents: L04AX01

Mechanism of action
Azathioprine is a pro-drug of 6-mercaptopurine (6-MP). 6-MP is inactive but acts as a purine antagonist and requires cellular uptake and intracellular anabolism to thioguanine nucleotides (TGNs) for immunosuppression. The TGNs and other metabolites (e.g. 6-methyl-mecaptopurine ribonucleotides) inhibit de novo purine synthesis and purine nucleotide interconversions. The TGNs are also incorporated into nucleic acids and this contributes to the immunosuppressive effects of the drug. Other potential mechanisms of azathioprine include the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response.
Because of these mechanisms, the therapeutic effect of azathioprine may be evident only after several weeks or months of treatment.

The activity of the methylnitroimidazole moiety, a metabolite of azathioprine but not 6-MP, has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP.

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 may be taken with food or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken with milk or dairy products (see Section 4.2).

After oral administration of [^{35}S]-azathioprine, the maximum plasma radioactivity occurs at 1-2 hours and decays with a half-life of 4-6 hours. This is not an estimate of the half-life of azathioprine itself, but reflects the elimination from plasma of azathioprine and the [35S]-containing metabolites of the drug. As a consequence of the rapid and extensive metabolism of azathioprine, only a fraction of theradioactivity measured in plasma is comprised of unmetabolised drug. Studies in which the plasma concentration of azathioprine and 6-mercaptopurine have been determined following intravenous administration of azathioprine have estimated the mean plasma T1/2 for azathioprine to be in the range of 6-28 minutes and the mean plasma T1/2 for 6-mercaptopurine to be in the range 38-114 minutes after i.v. administration of the drug.

Azathioprine is principally excreted as 6-thiouric uric acid in the urine. 1-methyl-4-nitro-5-thioimidazole has also been detected in urine as a minor excretory product. This would indicate that, rather than azathioprine being exclusive cleaved by nucleophilic attack at the 5-position of the nitroimidazole ring to generate 6-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.

Thiopurine S-Methyl Transferase (TPMT)
TPMT activity is inversely related to red blood cell 6-MP 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).

<u>Special Patient Populations</u>
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-MP 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

Teratogenicity
Studies in pregnant rats, mice and rabbits using azathioprine in dosages from 5-15 mg/kg bodyweight/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

Core:
Lactose monohydrate
Maize starch
Povidone K25
Colloidal silicon dioxide
Magnesium stearate

Coating:
Hypromellose
Microcrystalline cellulose
Macrogol stearate 400
Talc

Colouring agent:
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The film-coated tablets are packed in polypropylene-aluminium blister or PVC/PVDC-aluminium blister in a carton box.

Pack sizes: 20, 28, 30, 50, 90 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

There are no risks associated with handling tablets with intact coating. In that case no special safety precautions are necessary.

However, cytotoxic agents should be handled in strict accordance with the instructions when nursing staff have divided or crushed the tablets (see sections 4.2 and 4.4).

Surplus medical products as well as contaminated appliances should be temporarily stored in clearly labelled containers. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Maxis 1
Western Road
Bracknell
United Kingdom

RG12 1RF

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1247

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/10/2002

10 DATE OF REVISION OF THE TEXT

12/07/2025