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 with known effect: Each tablet contains 45 mg of lactose (as lactose monohydrate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White to yellowish-white, round, biconvex film-coated tablet of diameter 6.0-6.4mm and height of 3.1-3.7mm, with no score-line.

4.1 Therapeutic indications

Azathioprine is indicated in combination with other immunosuppressive agents for the prophylaxis of transplant rejection in patients receiving allogeneic kidney, liver, heart, lung or pancreas transplants.

Azathioprine is usually indicated in immunosuppressive regimens as an adjunct to immunosuppressive agents that form the mainstay of treatment (basic immunosuppression).

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 is indicated in severe cases of the following diseases in patients who are intolerant to steroids or who are dependent on steroids and in whom the therapeutic response is inadequate despite treatment with high doses of steroids:

- severe active rheumatoid arthritis that cannot be kept under control by less toxic agents (disease-modifying anti-rheumatic drugs (DMARDs));
- Severe or moderately severe inflammatory intestinal diseases (Crohn’s disease or ulcerative colitis);
- Systemic lupus erythematosus;
- Dermatomyositis and polymyositis;
- Auto-immune chronic active hepatitis;
- Polyarteritis nodosa;
- Refractory warm auto-immune haemolytic anaemia;
- Chronic refractory idiopathic thrombocytopenic purpura.
- Pemphigus vulgaris

4.2 Posology and method of administration

Posology

**Transplantation**
Depending on the immunosuppressive regimen selected, a loading dose of up to 5 mg/kg bodyweight/day orally is usually given. The maintenance dose can range from 1-4 mg/kg bodyweight per day, and must be adjusted according to clinical requirements and haematological intolerance.

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**
In general, the starting dosage is 1-3 mg/kg bodyweight/day, and should be adjusted according to the clinical response (which may be evident only after weeks or months) and haematological tolerance. For the treatment of chronic active hepatitis the dosage is usually between 1.0 and 1.5 mg/kg bodyweight/day. When the therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with maintenance of the response. If no improvement occurs in the patient's condition within three to six months, consideration should be given to withdrawing the medicinal product. 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.

**Patients with renal and/or hepatic impairment**
In patients with renal and/or mild to moderate hepatic dysfunction, dosages should be given at the lower end of the normal range. Azathioprine is contraindicated in severe hepatic impairment (see Section 4.3).

**Paediatric population**
There are insufficient data to recommend the use of Azathioprine for the treatment of juvenile chronic arthritis, systemic lupus erythematosus, dermatomyositis, and polyarteritis nodosa (in children and adolescents < 18 years).
Concerning the other indications the given dose recommendations apply for children and adolescents as well as for adults.

**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).

**Elderly**
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 Patients with renal and/or hepatic impairment).

It is recommended that the dosages used should be at the lower end of the normal range (for controls of blood count see section 4.4).

When allopurinol, oxipurinol or thiopurinol is given concomitantly with azathioprine, the dose of azathioprine must be reduced to a quarter of the original dose since allopurinol decreases the rate of catabolism of azathioprine (see section 4.4 and 4.5).

It can take weeks or months before a therapeutic effect is seen.

The medicinal product may be given over the long term unless the patient cannot tolerate the preparation.

In cases, such as rheumatoid arthritis and certain haematological conditions, the treatment can be stopped after a certain period without problems.

**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: Monitoring and section 5.2).

Method of administration
Azathioprine film-coated tablets are supplied for oral administration, and the tablet should be taken with at least a glass of liquid (200 ml). Azathioprine should be taken with or just after food, or a meal.

4.3 Contraindications
a) Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
b) Hypersensitivity to 6-mercaptopurine (6-MP-metabolite of azathioprine) should alert the prescriber to probable hypersensitivity to azathioprine.
c) Severe infections.
d) Severely impaired hepatic or bone-marrow function.
e) Pancreatitis.
f) Any live vaccine especially BCG, smallpox, yellow fever.
g) Azathioprine therapy should not be initiated in patients who may be pregnant, or who are likely to become pregnant without careful assessment of risk versus benefit (see section 4.6).
h) Lactation (see Section 4.6).

4.4 Special warnings and precautions for use

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended (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
a) There are potential dangers in the use of azathioprine tablets; they should therefore not be prescribed unless the patient can be adequately monitored for toxic effects throughout the duration of treatment.
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 treatment, a complete blood count, including platelet count, should be performed at least once weekly.
It should be controlled more frequently
- if high dosages are used
- in elderly patients
- if renal function is impaired or if severe renal disorder is present
- if hepatic function is mildly to moderately impaired or if hepatic disorder is present (see sections 4.2 and 5.2)
- if bone marrow function is mildly to moderately impaired (see also section 4.2)
- in patients with hyperplensim.
The frequency of the blood counts control may be reduced after 8 weeks or later in therapy. It is recommended that complete blood counts be 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 must be advised to inform their doctor immediately about ulcerations of the throat, fever, any evidence of infections, unexpected bruising, bleeding or other signs
of myelosuppression. Bone marrow suppression is reversible if azathioprine is withdrawn early enough.

b) Renal and/or hepatic insufficiency
It has been suggested that the toxicity of azathioprine may be enhanced in the presence of renal insufficiency, but controlled studies have not supported this suggestion. Nevertheless, it is recommended that the dosages used should be at the lower end of the normal range and that haematological response should be carefully monitored. Dosage should be further reduced if haematological toxicity occurs. Caution is necessary during the administration of azathioprine especially in patients with hepatic dysfunction, and regular complete blood counts and liver function tests should be undertaken.

More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. In such patients the metabolism of azathioprine may be impaired, and the dosage of azathioprine should therefore be reduced if hepatic or haematological toxicity occurs. The patient should be instructed to discontinue azathioprine immediately if jaundice becomes apparent.

c) Close monitoring of blood counts is required if azathioprine is given together with
- allopurinol, oxipurinol or thiopurinol (see section 4.2 and 4.5)
- derivatives of aminosalicylic acid, such as mesalazin, olsalazin or suphasalazin (see section 4.5)
- ACE inhibitors, trimethoprim/sulphamethoxazole, cimetidine or indomethacin (see section 4.5)
- agents with cytotoxic/myelosuppressive properties (see section 4.5)

d) About 10% of patients have a thiopurine methyltransferase deficiency due to genetic polymorphism. They may therefore be unable to metabolise azathioprine completely. Consequently they may be exposed to an increased myelotoxic effect and prone to developing rapid bone marrow depression following the initiation of treatment with azathioprine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Also it has been reported that decreased TPMT activity increases the risk of secondary leukaemias and myelodysplasia in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (see section 4.8 Undesirable effects). Special care should therefore be taken during co-administration of aminosaliclylate derivatives, including sulphasalazine, which are inhibitors of the TMPT enzyme. Phenotyping or genotyping of the patient is desirable before administration of the medicinal product in order to investigate a possible thiopurine transferase deficiency.

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 drugs whose primary or secondary toxicity is myelosuppression (see section 4.5: Cytostatic/myelosuppressive agents).

e) Limited data indicate that azathioprine is not effective in patients with hereditary hypoxanthine-guanine-phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome). Therefore, given the abnormal metabolism in these patients, azathioprine should not be used in these patients.

f) If allopurinol, oxipurinol and/or thiopurinol are given concomitantly with azathioprine, the dosage of azathioprine must be reduced (see section 4.2 and 4.5).
g) Special care is necessary when azathioprine is given concomitantly with neuromuscular acting agents, like tubocurarine or succinylcholine. 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 surgery. Coagulation should be closely monitored when anticoagulants of the coumarin type are given concomitantly with azathioprine (see section 4.5).

i) Withdrawal of azathioprine can result in a severe worsening of the condition, e.g. in SLE with nephritis, Crohn’s disease, ulcerative colitis or autoimmune hepatitis.

j) Withdrawal of azathioprine should always be a gradual process performed under close monitoring.

k) If inactivated or toxoid vaccines are applied together with azathioprine, immune response should always be controlled by means of titre determination.

l) Mutagenicity and carcinogenicity (see also section 4.8). Patients receiving immunosuppressive therapy, including azathioprine are at an increased risk of developing lymphoproliferative disorders, non-Hodgkin’s lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi’s and non-Kaposi’s) and uterine cervical cancer in situ. The increased risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. It has been reported that reduction or discontinuation of immunosuppression may be associated with partial or complete regression of lymphoproliferative disorder, non-Hodgkin’s lymphomas and Kaposi’s sarcomas. 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 should be warned about undue exposure to the sun or UV rays, and the skin should be examined at regular intervals. Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimize the risk of skin cancer and photosensitivity (see also section 4.8 Undesirable Effects).

m) Particular caution should be exercised in patients with untreated acute infections (see section 4.3).

n) Patients with concomitant cytotoxic therapy may only be given azathioprine under supervision.

o) 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.

Effects on fertility
Relief of chronic renal insufficiency by renal transplantation involving the administration of azathioprine has been accompanied by increased fertility in both male and female transplant recipients (for contraceptive measures see section 4.6).

Note for handling the drug:
Azathioprine is mutagenic and potentially carcinogenic. When handling this substance appropriate precautions must be taken. This should be especially considered in pregnant nurses (see section 6.6).

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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. 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.

Varicella Zoster Virus Infection (see also section 4.8 Undesirable Effects)
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).

4.5 Interaction with other medicinal products and other forms of interaction

a) Allopurinol/ oxipurinol/ thiopurinol: Allopurinol, oxipurinol and thiopurinol have an inhibitory effect on the metabolism of azathioprine by blocking the enzyme xanthine oxidase. (see sections 4.2 and 4.4) 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 original dose.

b) Neuromuscular blocking 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.

c) If azathioprine is combined with other immunosuppressants, such as
cyclosporin or tacrolimus, excessive immunosuppression must be taken
into consideration.

d) There is a risk of an increased myelosuppressive effect of azathioprine, as
a result of inhibition of its hepatic metabolism, if azathioprine is
administered concomitantly with aminosalicylic acid derivatives such as
olsalazine, mesalazine and sulphasalazine (see section 4.4).

e) Warfarin: Inhibition of the anticoagulant effect of warfarin and
acenocoumarol has been reported if administered concomitantly 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.

f) Concomitant therapy with azathioprine and ACE inhibitors,
trimethoprim/sulphamethoxazole, cimetidine or indomethacin increase the
risk of myelosuppression (see section 4.4).

g) Cytostatic/ myelosuppressive drugs: Concomitant therapy with azathioprine
and agents with myelosuppressive/cytotoxic properties effect may enhance
the myelotoxic effect. This applies also to myelosuppressive therapies
completed only shortly before initiation of treatment with azathioprine (see
section 4.4).
Where possible, concomitant administration of cytostatic drugs, or drugs
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 has been a case report suggesting that haematological abnormalities
may develop due to the concomitant administration of azathioprine and
captopril.

h) It has been shown that furosemide reduced the metabolism of azathioprine
by human hepatic tissue in vitro. The clinical relevance of this is not
known.

i) Vaccines: The immunosuppressive activity of azathioprine can lead to an
atypical and possibly harmful response to live vaccines, and therefore, for
theoretical reasons, the administration of live vaccines to patients being
treated with azathioprine is contraindicated on theoretical grounds (see
section 4.3).

j) 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 (see section 4.4).

k) Other interactions: As there is in vitro evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulfasalazine inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent azathioprine therapy (see Special Warnings and Special Precautions for Use). Therefore, lower doses of azathioprine may need to be considered when administered concomitantly with aminosalicylate derivatives.

l) 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 Metabolism).

m) 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.

4.6 Fertility, pregnancy and lactation

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.

Pregnancy
Substantial transplacental and transamniotic transmission of azathioprine and its metabolites from the mother to the foetus have been shown to occur. Azathioprine must not be used during pregnancy or in patients likely to become pregnant without careful assessment of risks and benefits. In animal studies Azathioprine was teratogenic and embryotoxic (see section 5.3). Azathioprine and its metabolites have been found in low concentrations in foetal blood and amniotic fluid after administration to the mother. Leukopenia and/or thrombocytopenia have been reported in a number of neonates whose mothers received azathioprine during pregnancy. Extra care in haematological monitoring is advised during pregnancy. Evidence of the teratogenicity of azathioprine in man is equivocal. As with all cytotoxic chemotherapy,
contraceptive measures should be taken by both male and female patients of reproductive age during, and for at least 3 months after the end of, azathioprine therapy. This applies also to patients with impaired fertility due to chronic uraemia, since that usually returns to normal after transplantation.

Azathioprine has been reported to interfere with effectiveness of intrauterine contraceptive devices. Therefore, it is recommended to use other or additional contraceptive measures.

After in utero exposure to azathioprine in combination with prednisone, a temporary reduction of immune function is observed. Intra-uterine growth retardation, low birth weight and premature birth have been reported in cases of treatment with azathioprine together with corticosteroids (prednisolone). There have also been reports of spontaneous abortion following either maternal or paternal exposure. The long-term consequences of these properties of azathioprine are not known, but many children exposed to the substance in utero have now reached the age of ten years without any problems being reported.

Breast-feeding

6-Mercaptopurine, the active metabolite of azathioprine, has been identified in the colostrum and breast-milk of women receiving azathioprine treatment. Breast-feeding and concomitant use of azathioprine are contraindicated (see section 4.3).

4.7 Effects on ability to drive and use machines

Studies of the effects of azathioprine on the ability to drive and use machines have not been performed. A detrimental effect on these activities cannot be predicted from the pharmacology of the drug.

4.8 Undesirable effects

For this product there is no modern clinical documentation that can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication. Frequencies are defined using the following convention as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Approximately 15 % of patients can be expected to experience adverse effects. The type, frequency and severity of adverse reactions may depend on the dose of
azathioprine and duration of therapy as well as on the patient’s underlying disease or concomitant therapies.

The principal undesirable effect of azathioprine is a dose-related, generally reversible, depression of bone marrow function expressed mainly as leukopenia (50% in transplant patients).

Although adverse effects on haematopoiesis occur most commonly at the beginning of the treatment with azathioprine, late occurrence has been reported. Therefore, careful monitoring of the blood cell counts is recommended even in patients on stable long-term therapy (see section 4.4).

Type and frequency of undesirable effects of azathioprine are listed under the system organ classes.

Infections and infestations
Transplant patients receiving azathioprine in combination with other immunosuppressants.

Very common
Infections in 20% of renal homographs (RH) patients. Viral, fungal, and bacterial infections in transplant patients receiving azathioprine in combination with other immunosuppressants.

Common
Susceptibility to infection in patients with inflammatory bowel disease.

Other indications.

Uncommon
Infections in rheumatoid patients (<1%). Viral, fungal, and bacterial infections in other patient populations.

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 with varicella, herpes zoster and other infectious agents (see also section 4.4 Special Warnings and Precautions for Use).

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)

Common
In up to 2.8% of renal homograft patients (in decreasing frequency): squamous cell carcinoma at the skin, non-Hodgkin’s lymphoma, cervical cancer, Kaposi’s sarcoma, vulval cancer.

Uncommon
Lymphoproliferative diseases after transplantation

Rare: Neoplasms including lymphoproliferative disorders, non-Hodgkin's lymphomas, skin cancers (melanomas and nonmelanomas), sarcomas non-sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myloid
leukaemia and myelodysplasia (see also section 4.4 Special Warnings and Special Precautions for Use).

There have been rare reports of acute myeloid leukaemia and myelodysplasia (some in association with chromosomal abnormalities).

The risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas, (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, is increased in patients who receive immunosuppressive drugs, particularly in transplant recipients receiving aggressive treatment and such therapy should be maintained at the lowest effective levels. The increased risk of developing non-Hodgkin's lymphomas in immunosuppressed rheumatoid arthritis patients compared with the general population appears to be related at least in part to the disease itself.

Use in indications other than prevention of transplant rejection increases the risk of the development of tumours. This risk is lower than when used for the indication organ transplantation because, in this indication, weaker immune suppression is used than in the indication organ transplantation. However, the type of tumours is not different from the above-mentioned, which typically occur under conditions of immunosuppression (induced by oncivirus or natural radiation).

**Blood and the lymphatic system disorders**

*Very common*

Leukopenia in transplant recipients (50 %) and patients with rheumatoid arthritis (28 %), depression of bone marrow function.

*Common*

Leukopenia in patients with inflammatory bowel disease (5-10 %), thrombocytopenia

*Uncommon: anaemia*

*Rare*

Granulocytopenia, pancytopenia and aplastic anaemia
Megaloblastic anaemia, erythroid hypoplasia
TPMT deficiency, hepatic and renal impairment predispose for myelosuppression, agranulocytosis.

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.

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**

*Uncommon: hypersensitivity reactions*
After a hypersensitivity reaction to azathioprine therapy with azathioprine should not be reinstated.

**Very rare**
Hypersensitivity reactions with lethal outcome. Stevens-Johnson syndrome and toxic epidermal necrolysis

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

In many cases, rechallenge has confirmed an association with 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.

**Respiratory, thoracic and mediastinal disorders**

**Rare**

**Very rare**: reversible pneumonitis

**Gastrointestinal disorders**

**Very common**
Anorexia with occasional vomiting (10% in patients with rheumatoid arthritis)

**Common**
Nausea
A minority of patients experience nausea when first given azathioprine. This appears to be relieved by administering the tablets after meals.

**Uncommon**
Pancreatitis
Steatorrhoea

**Rare**
Gastrointestinal ulcers, intestinal haemorrhage, necrosis

**Very rare**: colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population

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 drugrelated 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 drug, although rechallenge has confirmed an association with azathioprine on occasions.

Gastrointestinal disturbance may be reduced by administering azathioprine in divided doses and/or during meals.

**Hepatobiliary disorders**

**Common**
hepatic dysfunction
Different pathologies including, destructive cholangitis, bacillary angiomatosis (peliosis hepatitis), disse space fibrosis and nodular regenerative hyperplasia in 3-10 % in patients after organ transplantation

**Uncommon**
Hepatotoxicity occur in < 1 % of patients with rheumatoid arthritis, and degeneration of liver function tests.

cholestasis and deterioration of liver function tests

**Rare**
Veno-occlusive hepatic disease
A rare, but life-threatening veno-occlusive hepatic damage during chronic administration of azathioprine has been described, mainly in transplant patients. Histological findings include sinusoidal dilatation, peliosis hepatis, veno-occlusive disease and nodular regenerative hyperplasia. In occasional cases discontinuation of azathioprine led to either a temporary or permanent recovery from the liver histology and the symptoms.

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

**Skin and subcutaneous tissue disorders**

**Rare:**
Alopecia
Hair loss has been described a number of times in patients receiving azathioprine alone or in combination with other immunosuppressive agents. In many cases this symptom disappeared/resolved spontaneously despite continuing therapy. The relationship between alopecia and azathioprine treatment is uncertain photosensitivity.

**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 at www.mhra.gov.uk/yellowcard

4.9 **Overdose**
Symptoms and signs
In the event of overdose the most likely effect is bone marrow suppression, reaching its maximum mostly 9-14 days after dosing. The principal signs of bone marrow suppression are ulcerations in the throat, fever and unexplained infections. Furthermore, bruising, bleeding and fatigue may occur. These signs are more likely to be manifest following chronic overdosage, rather than after a single acute overdose. Although improvement may be delayed, it usually occurs from the twelfth day after overdose, provided that the patient has not taken a high dose in the meantime. 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 leucopenia and mild abnormalities in liver function. Recovery was uneventful.

Treatment

There is no specific antidote for azathioprine. Gastric lavage has been used. Subsequent monitoring, including haematological monitoring, is necessary to allow prompt treatment of any adverse effects which may develop. In the event of overdose, blood count and hepatic function in particular should be monitored. 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 known to be partially dialysable, and in severe cases dialysis may be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressive agents, azathioprine ATC code: L04AX01

Azathioprine is used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) which influence the immune response.

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down in vivo into 6-MP and 1-methyl-4-nitro-5-thiomidazole. 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 activity of the methylnitroimidazole moiety has not been defined clearly. However, in various systems it appears to modify the activity of azathioprine, compared with that of 6-MP.

Azathioprine has an effect on both immunological reaction and tumour growth. Its major role has been as an agent for suppressing the immune response, and although the precise mechanism by which this effect is achieved is not known, the following mechanisms of action have been suggested:

i. The action of the released 6-MP as a purine antimetabolite.
ii. The possible blockade of -SH groups by alkylation.
iii. The inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation and activity of immunocompetent cells (B- and T-lymphocytes).
Damage to deoxyribonucleic acid (DNA) through incorporation of purine thioanalogues.

5.2 Pharmacokinetic properties

Azathioprine is readily absorbed following oral administration. Peak plasma concentrations are reached 1-2 hours after taking a dose. Azathioprine is distributed rapidly through the body. The plasma half-life is 3-5 hours. Only small amounts of the medicinal product bind to plasma proteins, a maximum of 30%. 12.5% enter the cerebrospinal fluid.

Azathioprine is extensively metabolised to 6-thioinosinic acid and methylmercaptopurine-ribonucleotide, which, in part, are responsible for the effect of the medicinal product.

The effect in vivo is made more difficult by the action of methylnitroimidazole, which is also found.

Up to 50% of a dose are excreted in urine during the first 24 hours after administration, with approximately 10% as unchanged substance. Only 12.6% of the dose appearing in the stool after 48 hours. There is no evidence of enterohepatic circulation. A lowered dosage for patients with reduced renal function may be necessary, probably as a result of reduced elimination of the active metabolites of azathioprine.

Also in patients with hepatic impairment the metabolism of azathioprine is altered. Conversion into the active form is reduced and especially the breakdown to eliminable metabolites is diminished.

Mercaptopurin, an active metabolite of azathioprine, has been identified in the colostrum and breast-milk of women receiving azathioprine treatment.
5.3 Preclinical safety data

Teratogenicity or embryolethality has been seen in a number of animal species, with a varying degree of susceptibility. In rabbits, a dose of 5-15mg/kg body weight daily on days 6-14 of pregnancy produced skeletal abnormalities; in mice and rats, doses of 1-2mg/kg body weight daily on days 3-12 were lethal to the embryos.

Teratogenicity was evident in rabbits at 10 mg/kg bodyweight/day.

Azathioprine was mutagenic in a number of in-vitro and in-vivo genotoxicity assays.

In long-term carcinogenicity studies of azathioprine in mice and rats, an increased incidence of lymphosarcomas (mice) and epithelial tumours and carcinomas (rats) were observed at dosages that were up to 2-fold the human therapeutic dosage.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
maize starch
povidone
colloidal silicon dioxide
magnesium stearate

Coating:
hypromellose
microcrystalline cellulose
polyoxyl 8 stearate
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 either polypropylene-aluminium blister or PVC/PVDC-aluminium blister in a carton box.

The pack contains 20, 28, 30, 50 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Provided that the film-coating is intact, there is no risk in handling film-coated azathioprine tablets and no additional precautions are required.

However, azathioprine tablets should be handled in strict accordance with guidance for handling cytotoxic agents when people have crushed the tablets (see section 4.4).

Surplus medical products as well as contaminated appliances should be temporarily stored in markedly labelled containers and then discarded safely. High-temperature incineration is recommended.
7 MARKETING AUTHORISATION HOLDER

TILLOMED LABORATORIES LIMITED
3 HOWARD ROAD
EATON SOCON
ST. NEOTS
CAMBRIDGESHIRE
PE19 8ET
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 11311/0475

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/12/2008

10 DATE OF REVISION OF THE TEXT

11/11/2016