Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imuger 25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg of azathioprine.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Pale-yellow, film-coated, round, biconvex tablet, marked 'AE over 25' on one side and 'G' on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Azathioprine is indicated in combination with other immunosuppressive agents for the prophylaxis of transplant rejection in patients receiving allogenic kidney, liver, heart, lung, orpancreas transplants. Azathioprine is usually indicated in immunosuppressive regimens as anadjunct to immunosuppressive agents that formthe mainstay of treatment(basis immunosuppression).

Azathioprine is indicated in the following diseases, in patients who are intolerant to steroids or 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 disease (Crohn's disease or ulcerative colitis)
- systemic lupus erythematosus
- dermatomyositis
- autoimmune hepatitis
- polyarteritis nodosa
- pemphigus vulgaris
- refractory warm autoimmune haemolytic anaemia
- chronic refractory idiopathic thrombocytopenic purpura

4.2 Posology and method of administration

Posology

Therapy with azathioprine should be initiated by a physician experienced in the administration and monitoring of immunosuppressive medicinal products.

Transplantation
Depending on the immunosuppressive regime selected, a loading dose of up to 5 mg/kg/body weight/day orally is usually given. The maintenance dose can range from 1-4 mg/kg/body weight/day and must be adjusted according to the clinical requirements and haematological tolerance. There is evidence indicating that treatment be continued indefinitely, even if only low doses are necessary, because of risk of rejection.

Chronic active autoimmune hepatitis
The initial dose is usually between 1.0 and 1.5 mg/kg body weight/day and the maintenance dose is up to 2 mg/kg body weight/day.

Other Conditions

In general, the starting dosage is 1-3 mg/kg/body weight/day and should be adjusted according to the clinical response (which may not be evident for weeks or months) and haematological tolerance.
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 four months, consideration should be given to withdrawing the medicinal product.
The maintenance dosage required may range from less than 1 mg/kg body weight/day to 3 mg/kg/body weight/day depending on the clinical condition being treated and the individual patient response including haematological tolerance.

Interactions with xanthine oxidase inhibitors
With concomitant use of xanthine oxidase inhibitors such as allopurinol, oxipurinol or thiopurinol the dose of azathioprine must be reduced to 25% of the original dose, because allopurinol, oxipurinol and thiopurinol reduce the metabolism of azathioprine (see sections 4.4 and 4.5).

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

Special populations

Use in the elderly
There is no specific information on how elderly patients tolerate azathioprine. It is advisable to monitor renal and hepatic functions and consider a dose reduction if there is a functional impact (see section 4.2). It is recommended that the dosages used should be at the lower end of the normal range (for monitoring of blood count see section 4.4).

Renal and hepatic impairment

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

Paediatric population
There are insufficient data to recommend the use of azathioprine for the treatment of juvenile idiopathic 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).

Use in TPMT-deficient patients
Patients with hereditary problems of small or non-existent thiopurine S methyltransferase (TPMT) activity are at increased risk of severe azathioprine toxicity from conventional doses of azathioprine, and usually require a significant dose reduction. The optimal starting dose for homozygous patients with TPMT deficiency has not been established (see sections 4.4 and 5.2).

Most patients with heterozygous TPMT deficiency tolerate the recommended azathioprine doses, but some of them may require dose reduction. Tests of genotype and phenotype of TPMT are available (see sections 4.4 and 5.2).

Patients with NUDT15 variant
Patients with an inherited, mutated NUDT15 gene have an increased risk of serious azathioprine toxicity (see section 4.4). These patients generally require a dose reduction, particularly those patients who are homozygous for the NUDT15 variant (see section 4.4). Genotypical testing of NUDT15 variants may be considered before starting treatment with azathioprine. In every case it is necessary to monitor the blood count carefully.

Method of administration
Imuger film-coated tablets are supplied for oral administration. The tablet should be taken with at least a glass of liquid (200 ml). Imuger film-coated tablets should be taken during meals. Azathioprine should be taken at least 1 hour before or 2 hours after a meal or milk (see section 5.2).

4.3 Contraindications

Hypersensitivity to azathioprine, 6-mercaptopurine (metabolite of azathioprine) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Vaccination

Vaccination with live vaccines can cause infections in immunocompromised patients. Therefore, it is recommended that patients do not receive live vaccine until at least 3 months after the end of treatment with azathioprine (see section 4.5).

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

Ribavirin
Administration of ribavirin concomitantly with azathioprine is not recommended. Ribavirin may reduce the effect and may increase the toxicity of azathioprine (see section 4.5).

Monitoring
The initiation of treatment with azathioprine in presence of pre-existing severe infections, severe disorders of the liver and bone marrow function as well as the presence of pancreatitis should only be carried out with careful consideration of benefit-risk and the precautions described below.

Particular caution should be exercised in patients with untreated acute infections.

There are potential dangers in the use of azathioprine film-coated tablets; they should therefore not be prescribed unless 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 a clinical response.

During the first eight weeks of treatment, a complete blood count, including platelet count must be performed at least once weekly. It should be controlled more frequently:

- if high doses are used
- in elderly patients
- if renal function is impaired; the dose must be reduced if haematologic toxicity develops (see sections 4.2 and 5.2)
- if hepatic function is impaired (see also sections 4.2 and 5.2). Regular liver function tests should be performed, and the dose reduced if hepatic or hematologic toxicity develops.

The frequency of the blood count monitoring may be reduced after 8 weeks. It is recommended that complete blood counts be repeated monthly, or at least at intervals of no longer than 3 months.

At the first sign of an abnormal decrease in blood counts, treatment should be immediately discontinued as leukocytes and platelets may continue to fall after treatment is discontinued.

Patients must be advised to inform their doctor immediately about ulcerations of the throat, fever, infections, bruising, bleeding or other signs of myelosuppression. Bone marrow suppression is reversible if azathioprine is stopped early enough.

Close monitoring of blood counts is required if azathioprine is given together with:

- allopurinol, oxipurinol or thiopurinol (see sections 4.2 and 4.5)
- derivatives of aminosalicylic acid, such as mesalazine, olsalazine or sulfasalazine (see section 4.5)
- ACE inhibitors, trimethoprim/sulfamethoxazole, cimetidine or indomethacin (see section 4.5)
- agents with cytotoxic/myelosuppressive properties (see section 4.5).

In general, special care should be taken when administering azathioprine in patients with hepatic impairment as life-threatening liver damage has been reported (see section 4.8). This is particularly important in patients with severe hepatic

dysfunction and azathioprine should be used in this case only after careful risk-benefit assessment. Azathioprine is hepatotoxic and liver function tests must be performed routinely during treatment; increase in these parameters may require dose reduction or temporary discontinuation. More frequent monitoring is recommended in patients with pre-existing liver disease, or in patients concomitantly receiving other potentially hepatotoxic treatment. Patients should be instructed to immediately discontinue azathioprine, if they develop jaundice.

Thiopurine methyltransferase (TPMT)

About 10% of patients have thiopurine methyltransferase (TPMT) deficiency due to genetic polymorphism. They may therefore be unable to metabolise azathioprine completely. Consequently they may be exposed to an increased myelotoxic effect.

Special care should therefore be taken during co-administration of aminosalicylate derivatives (including olsalazine, mesalazine or sulfasalazine), which are inhibitors of the TPMT enzyme. Phenotyping or genotyping the patient is desirable, before administration of the drug in order to investigate a possible thiopurine transferase deficiency. There have been reports of a possible link between decreased TPMT activity and secondary leukaemia and myelodysplasia in patients receiving 6-mercaptopurine in combination with other cytotoxic drugs (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. Close monitoring of blood counts is therefore still necessary.

Patients with NUDT15 variant
Patients with an inherited mutated NUDT15 gene have an increased risk of serious azathioprine toxicity, such as early leukopenia and alopecia, from conventional doses in thiopurine treatment. A dose reduction is generally required, particularly for those patients who are homozygous for the NUDT15 variant (see section 4.2). The frequency of NUDT15 c.415C>T has an ethnic variability: approx. 10% in Asians, 4% in Latin Americans, 0.2% in Europeans and 0% in Africans. In every case it is necessary to monitor the blood count carefully.

Myelosuppressive agents
It may be necessary to reduce the dose of azathioprine when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression (see section 4.5).

Renal and/or hepatic function
Caution is recommended when administering azathioprine in patients with impaired renal and/or hepatic function. Consideration should be given to reducing the dosage of these patients and haematological response should be closely monitored (see section 4.2).

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

Varicella zoster virus infection
Infection with varicella zoster virus (VZV, varicella and herpes zoster) may become severe in case of concomitant administration of immunosuppressants. Caution should be exercised, particularly with regard to the following:

- Before treatment, the physician should be familiar with the patient's VZV history. Serological testing can be useful for questions about previous virus exposure.
- Patients who have not previously been exposed to the virus should avoid contact with individuals with chickenpox or herpes zoster.
- If the patient is exposed to VZV, special care must be taken to avoid the patient developing chicken pox or herpes zoster, and passive immunisation with varicella-zoster immunoglobulin (VZIG) should be considered.
- If the patient is infected with VZV, appropriate measures should be taken, including antiviral and symptomatic treatment.

Mutagenicity

Chromosomal abnormalities have been observed in both women and men treated with azathioprine. However, it is difficult to assess the role of azathioprine in developing the abnormalities.

Chromosomal abnormalities that disappear over time have been seen in lymphocytes from children of patients treated with azathioprine. Except in extremely rare cases, no physical signs of abnormalities have been observed.

Azathioprine and long-wave ultraviolet light had a synergistic clastogenic effect in patients treated with azathioprine for various diseases.

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 sections 4.2 and 4.5).

Anticoagulants
Coagulation should be closely monitored when anticoagulants of the coumarin type are given concomitantly with azathioprine (see section 4.5).

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

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* (see section 4.8). 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.

An increased number of skin tumours have occurred in patients during treatment with azathioprine. They have been mainly on areas of skin exposed to the sun. Patients should be warned about undue exposure to the sun or to UV rays, and wear protective clothing and use a sunscreen with a high protection factor. The skin should be examined at regular intervals (see also section 4.8).

Patients receiving multiple immunosuppressants will have an increased risk of over-immunosuppression, and the dose in these patients should therefore be at the lowest effective dose.

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.

Progressive multifocal leukoencephalopathy (PML)

PML, an opportunistic infection caused by the JC virus, have been reported in patients receiving azathioprine in combination with other immunosuppressive agents. Immunosuppressant therapy should be withheld at the first signs or symptoms suggestive of PML, and appropriate evaluation is required 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 6 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.

Contraceptive measures
Azathioprine has been reported to interfere with the effectiveness of intrauterine contraceptive devices. It is therefore recommended that alternative or additional contraceptive measures be used (see section 4.6).

Withdrawal symptoms seen on discontinuation of Azathioprine treatment
Withdrawal of azathioprine can result in a severe worsening of the condition, e.g. in systemic lupus erythematosus with nephritis, Crohn's disease, ulcerative colitis or autoimmune hepatitis.

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

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).

4.5 Interaction with other medicinal products and other forms of interaction

Vaccines
The immunosuppressive activity of azathioprine can lead to an atypical and possibly harmful 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 inactivated or toxoid vaccines is likely and such a response to hepatitis B vaccine has been observed among patients treated with a combination of azathioprine and corticosteroids. Therefore, the vaccination success should always be checked with a titre determination.

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), which leads to a lower production of the active 6-thioguanine nucleotides, and increases the production of active 6-mercaptopurine ribonucleotide. Severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin, therefore concomitant administration is not advised (see sections 4.4 and. 5.2).

Cytostatic/myelosuppressive agents
Concomitant therapy with azathioprine and agents with myelosuppressive/cytotoxic properties, such as penicillamine, may enhance the myelotoxic effects. This applies also to myelosuppressive therapies completed only shortly before initiation of treatment with azathioprine (see section 4.4).
There are conflicting reports as to whether clinical interaction between azathioprine and trimethoprim/sulfamethoxazole results in severe haematological disorders, such as neutropenia and thrombocytopenia.

If azathioprine is combined with other immunosuppressants, such as ciclosporin or tacrolimus, the greater risk of excessive immunosuppression must be taken into consideration.

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.

Aminosalicylate derivatives
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 aminosalicylate derivatives such as olsalazine, mesalazine and sulfasalazine, (see section 4.4). Therefore, it may be necessary to consider lower doses of azathioprine when administered simultaneously with aminosalicylate derivatives.

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

Infliximab
Interaction is observed when treating Crohn's disease in patients in sustained azathioprine therapy. Patients experienced transient increases in 6-TGN levels (6-thioguanine nucleotide, an active metabolite of azathioprine) and decrease of the average leukocyte count in the first weeks after infliximab infusion, which returned to previous levels after 3 months.

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors:
Allopurinol, oxipurinol and thiopurinol have an inhibitory effect on the metabolism of azathioprine by blocking the enzyme xanthinoxidase resulting in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive thiouric acid. If allopurinol, oxipurinol and/or thiopurinol are administered concomitantly with azathioprine, the dose of azathioprine must be reduced to a quarter of the original dose (see sections 4.2 and 4.4).

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.

Effect of azathioprine on other medicinal products

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 non depolarising agents and show that azathioprine potentiates the neuromuscular blockade produced by depolarising agents (see section 4.4).

Anticoagulants
Inhibition of the anticoagulant effect of warfarin and acenocoumarol, has been reported if administered concomitantly with azathioprine and therefore higher doses of anticoagulants may be necessary (see section 4.4). It is therefore recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with azathioprine.

4.6 Fertility, pregnancy and lactation

Pregnancy

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. In animal studies azathioprine was teratogenic and embryotoxic (see section 5.3). There is conflicting information about teratogenicity in humans.
Significant transfer of azathioprine and its metabolites into foetal blood and amniotic fluid after administration to the mother has been shown.
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.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving azathioprine. This also applies to patients with reduced fertility due to chronic uraemia, as fertility generally returns to normal after a transplant.

Azathioprine has been reported to interfere with the effectiveness of intrauterine contraceptive devices. It is therefore recommended that alternative or additional contraceptive measures be used.

After in utero exposure to azathioprine in combination with prednisone, a temporary reduction of immune function is observed. Intra-uterine growth retardation and premature birth have been reported in cases of treatment with azathioprine together with prednisolone. 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.

There have also been reports of spontaneous abortions after either maternal or paternal exposure. Chromosomal abnormalities which disappeared over time have been seen in the lymphocytes of children whose parents were treated with azathioprine. Except in extremely rare cases, no physical evidence of anomaly was observed in children of azathioprine-treated patients.

Breastfeeding

6-mercaptopurine, the active metabolite of azathioprine, 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 human fertility is unknown.

4.7 Effects on ability to drive and use machines

Azathioprine has no or negligible influence on the ability to drive and use machines.

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

Tabulated list of adverse reactions

The adverse reactions are listed below according to system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as: very common (³ 1/10), common (³ 1/100 to <1/10), uncommon (³ 1/1,000 to <1/100), rare (³ 1/10,000 to <1/1,000), very rare (<1/10,000) (including isolated cases), not known (cannot be estimated from the available data).

	Very common (>1/10)	**Common (>1/100 to <1/10)**	**Uncommon (>1/1000 to <1/100)**	**Rare (>1/10000 to <1/1000)**	**Very rare (<1/10000)**	**Not known (cannot be estimated from the available**

						data)
Infections and infestations	Viral, fungal and bacterial infections in transplant patients receiving azathioprine in combination with other immunosuppressants		Viral, fungal and bacterial infections in other patient populations.		Cases of PML associated with JC virus has been reported following use of azathioprine in combination with other immunosuppressive agents (see section 4.4)	
Neoplasms benign, malignant and unspecified (including cysts and polyps)				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 myelo-dysplastic syndromes (see section 4.4)	Hepatosplenic T-cell lymphoma (in IBD patients using other anti-TNF drugs concomitantly)	
Blood and lymphatic system disorders	Leukopenia	Thrombocytopenia	Anaemia	Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia and bone marrow failure	Haemolytic anaemia	
Immune system disorders			Hypersensitivity reactions		Stevens Johnson syndrome and toxic epidermal necrolysis	
Respiratory, thoracic and mediastinal disorders					Pneumonitis (reversible)	
Gastrointestinal disorders		Nausea with occasional vomiting	Pancreatitis		Colitis, diverticulitis and intestinal perforation in transplant recipients. Severe diarrhoea in the population with inflammatory bowel disease	

Hepatobiliary disorders			Cholestasis	Liver injury		
Skin and subcutaneous tissue disorders				Alopecia		Acute febrile neutrophilic dermatosis (Sweet's syndrome) Photosensitivity reaction
Investigations			Liver function test abnormal			

Description of selected adverse reactions

Infections and infestations
Patients treated with azathioprine alone or in combination with other immunosuppressants, primarily corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infections with varicella, herpes zoster 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, including skin cancer (melanoma and non-melanoma), sarcomas (Kaposi and non-Kaposi) and cervical carcinoma in situ, is increased in patients receiving immunosuppressive therapy. Particularly at risk are transplant patients receiving aggressive treatment, and the dose in these patients should therefore be at the lowest effective dose. The increased risk of developing non-Hodgkin's lymphoma in patients with rheumatoid arthritis compared with the general population appears partly to be due to the illness itself.

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

Blood and lymphatic system disorders
Use of azathioprine can lead to dose-dependent, usually reversible suppression of bone marrow function, usually in the form of leukopenia, but also sometimes in the form of anaemia and thrombocytopenia. In rare cases, agranulocytosis, pancytopenia and aplastic anaemia. These side effects occur predominantly in patients who are predisposed to myelotoxicity, for example patients with TPMT deficiency, renal or hepatic impairment, and the dose of azathioprine is not reduced when administered in combination with allopurinol.

Reversible dose-dependent increases in mean cell volume and erythrocytes haemoglobin concentration may occur. Megaloblastic bone marrow changes have also been observed, but severe megaloblastic anaemia and erythroid hypoplasia are rare.

Although adverse effects on haematopoiesis occur most commonly at the beginning of 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).

Immune system disorders
Different clinical symptoms, which are apparently idiosyncratic signs of hypersensitivity have been reported following administration of azathioprine. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, chills, exanthema, erythema nodosum, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis. In several cases, the connection with azathioprine has been confirmed by resumed treatment.
Other significant underlying pathology has contributed to very rare reports of deaths. In case of a hypersensitivity reaction immediate withdrawal of azathioprine and institution of circulatory support where appropriate have led to recovery in the majority of cases. Following a hypersensitivity reaction to the product, azathioprine should not be re-administered.

Gastrointestinal disorders
Some patients experience nausea when first taking azathioprine. To reduce nausea, the dose should be taken after a meal.

Pancreatitis has been reported in a small number of patients, particularly in kidney transplant recipients and patients with inflammatory bowel diseases. It's difficult to relate pancreatitis to a particular drug, but resumed treatment has occasionally confirmed an association with azathioprine.

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 re-exposure, has been reported in patients with inflammatory bowel disease treated with azathioprine. If there is any exacerbation of symptoms in these patients, a possible causal relationship with the azathioprine treatment should be taken into consideration.

Hepatobiliary disorders

A rare, but life-threatening veno-occlusive hepatic disease during chronic administration of azathioprine has been described, mainly in transplant patients. Histologic 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 in liver histology and the symptoms.

Usually reversible cholestasis and liver function abnormalities are occasionally reported in association with azathioprine. This may be associated with features of hypersensitivity reaction (see Immune system disorders).

Skin and subcutaneous tissue disorders

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 spontaneously despite continuing therapy. The relationship between alopecia and azathioprine remains uncertain.

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Symptoms

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 ulceration of the throat, fever and infections. Furthermore, bruising, bleeding and fatigue may occur. A single large dose of azathioprine is less likely to have a toxic effect than a chronic minor overdosage (e.g. on prescription).

In a case of ingestion of a single overdose of 7.5 g azathioprine the immediate toxic effects were nausea, vomiting and diarrhoea followed by leukopenia and minor changes in liver function. Recovery was without additional symptoms.

Management

There is no specific antidote for azathioprine. Treatment is symptomatic. In the event of overdose, blood count and hepatic function in particular should be monitored in case blood transfusions and other appropriate supportive treatment are needed. It is possible that active treatment (such as the use of activated charcoal) is not effective in case of an overdose of azathioprine unless the treatment is performed within 60 minutes after ingestion.
The benefit of dialysis in patients who have taken an overdose of azathioprine is unknown, though azathioprine is partially dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents. Immunosuppressants. Other immunosuppressants, ATC code: L04 AX 01

Azathioprine is an inactive pro-drug of 6-mercaptopurine (6-MP), which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to thioguanine nucleotides (TGNs) for immunosuppression. TGNs and other metabolites (e.g. 6-methylmercaptopurine 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 medicinal product. Other potential mechanisms of azathioprine include:

- The inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation and activity of cells involved in the immune response (B and T lymphocytes).

Because of these mechanisms, the therapeutic effect of azathioprine may be evident only after several weeks or months of treatment (see section 4.2).

Unlike 6-MP, the activity of the azathioprine metabolite 1-methyl-4-nitro-5-thioimidazole has not been clearly determined. However, compared with 6-MP it appears to modify the activity of azathioprine in several systems.

5.2 Pharmacokinetic properties

Absorption
Azathioprine is incompletely and variably absorbed. The mean absolute bioavailability of 6-MP after administration of azathioprine 50 mg is 47% (range: 27-80%). The extent of absorption of azathioprine is similar throughout the gastrointestinal tract, including the stomach, jejunum and caecum. The extent of 6-MP absorption after application of azathioprine however, varies depending on where the absorption occurs, with the highest level in the jejunum, followed by the stomach and caecum.Although there are no food effect studies with azathioprine, pharmacokinetic studies with 6 MP, which are also relevant to azathioprine, have been performed. The mean relative bioavailability of 6-MP was approximately 26% lower following administration with food and milk, compared to after fasting. 6-MP is not stable in milk due to the presence of xanthine oxidase (30% degradation within 30 minutes) (see "Biotransformation"). Azathioprine should be taken at least 1 hour before or 2 hours after a meal or milk (see section 4.2).
Peak plasma concentrations are reached 1-2 hours after taking a dose. Azathioprine is distributed rapidly throughout the body.

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, since 6-MP is metabolised throughout the body (and not only in the liver). Only 30% of the medicinal product binds to plasma proteins. 12.5% enters the cerebrospinal fluid.

6-MP concentration in the cerebrospinal fluid are low or negligible after intravenous or oral use.
Biotransformation:
Azathioprine is rapidly degraded *in vivo* by glutathione-S-transferase to 6-MP and1-methyl-4-nitro-5-thioimidazole. 6-MP readily crosses the cell membrane and is extensively metabolized through multiple pathways with many steps to active and inactive metabolites, with no one enzyme predominating. Because of the complexity of metabolism, inhibition of a single enzyme does not explain all cases of non-efficacy and / or pronounced myelosuppression. The enzymes that are mainly responsible for the metabolism of 6-MP or further metabolites are: the polymorphic enzyme thiopurine S-methyltransferase (TPMT) (see sections 4.4 and 4.5), xanthine oxidase (see section 4.5), inosine monophosphate dehydrogenase (IMPDH) (see section 4.5) and hypoxanthine guanine phosphoribosyltransferase (HPRT). Additional enzymes that are involved in the formation of the active and inactive metabolites are: guanosine monophosphate synthetase (GMPS, which forms TGNs) and inosine triphosphate pyrophosphatase (ITPase). Azathioprine itself is also metabolised by aldehyde oxidase to the probably active 8-hydroxy-azathioprine. There are also formed several inactive metabolites via other pathways.

There are indications that polymorphisms in the genes encoding the various enzyme systems involved in the metabolism of azathioprine may predict side effects of treatment with azathioprine.

Thiopurine S-methyltransferase (TPMT)
TPMT activity is inversely related to the red blood cell concentration of 6-MP-derived thioguanine nucleotide, with higher concentrations of thioguanine nucleotide resulting in greater reductions in leukocyte and neutrophil counts. People with TPMT deficiency develop very high concentrations of cytotoxic thioguanine nucleotide.

Studies of genotype can determine the allelic pattern of a patient. Currently, 3 alleles (TPMT * 2, TPMT * 3A and TPMT * 3C) are responsible for approximately 95% of persons 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 undetectable enzyme activity. Approximately 10% of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT

activity and 90% of patients have normal TPMT activity with two functional alleles. There may also be a group of approximately 2%, who have a very high TPMT activity. Phenotype testing determines the level of thiopurine nucleotides or TPMT activity in red blood cells, and can also provide information (see section 4.4.). Determination of genotype does not guarantee against adverse events such that monitoring should be unchanged.

Elimination
The plasma half-life is 3-5 hours. After oral administration of 100 mg 35S-azathioprine, 50 % of the radioactivity is excreted in the urine within 24 hours and 12 % in the faeces within 48 hours. The main component in the urine was the inactive oxidized metabolite thiourea. Less than 2% was excreted in the urine as azathioprine or 6-MP. Azathioprine has a high hepatic extraction ratio with a total clearance greater than 3 l/min in normal volunteers. There are no data on renal clearance or half-life of azathioprine. The renal clearance of 6-MP and half-life of 6-MP are 191 ml/min/m^2, and 0.9 hours, respectively.
6-MP has been detected in the colostrum and breast milk of women who were treated with azathioprine (6-MP is excreted in breast milk at concentrations of 3.4 ng/ml to 18 ng/ml).

Special populations

Elderly patients
No specific studies have been conducted in the elderly (see section 4.2).

Paediatric population – Overweight children
In a clinical trial in the United States, 18 children (aged 3 to 14 years) were evenly divided into two groups; the crucial factor was whether the ratio of weight to height was above or below the 75th percentile. Each child was on maintenance treatment with 6-MP and the dosage was calculated based on their body surface area. The mean AUC (0-∞) of 6-MP in the group above the 75th percentile was 2.4 times lower than for the group below the 75th percentile. Therefore, under certain circumstances, overweight children need azathioprine doses in the upper range of the dose spectrum, and close monitoring of response to treatment (see section 4.2).

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

Azathioprine and/or its metabolites are eliminated by haemodialysis. Approximately 45% of the radioactive metabolites are eliminated during dialysis of 8 hours.

Hepatic impairment
In case of hepatic impairment, the metabolism of azathioprine is altered. Conversion into the active metabolites is restricted. Most important, the elimination of metabolites is reduced (see sections 4.2 and 4.4).

A study with azathioprine was conducted in three groups of renal transplant patients: patients without liver disease, patients with hepatic impairment (but not cirrhosis) and in patients with hepatic impairment and cirrhosis. The study showed that exposure to 6-MP was 1.6 times higher in patients with hepatic impairment (but not cirrhosis), and 6 times higher in patients with hepatic impairment and cirrhosis compared with patients without liver disease. Therefore, consideration should be given to reducing the dosage in patients with hepatic impairment (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship(s)

There is no correlation between the plasma levels of azathioprine and 6-mercaptopurineMP and the therapeutic efficacy or toxicity of azathioprine.

5.3 Preclinical safety data

Reproductive toxicology

In embryo toxicity studies, azathioprine showed a teratogenicity or embryo-lethal effect in various animal species.
In rabbits, doses of 5 mg/kg to 15 mg/kg bodyweight/day caused skeletal malformations. In mice and rats, doses between 1 mg/kg and 2 mg/kg bodyweight/day resulted in embryo death.

Mutagenicity

Azathioprine has been shown to be mutagenic in a number of *in vitro* and *in vivo* tests.

Carcinogenicity

Long-term studies of the carcinogenicity of azathioprine in mice and rats, during which azathioprine was administered at up to two time the equivalent human therapeutic dose and at lower doses in immunocompromised mice, have shown an increase in lymphosarcomas (mice) and squamous cell tumours (rats).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablet core contains:
Cellulose, microcrystalline
Mannitol
Maize starch
Povidone K25
Croscarmellose sodium
Sodium stearyl fumarate

The film-coat contains:
Hypromellose
Macrogol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package.
Do not store above 25°C.

6.5 Nature and contents of container

Azathioprine film-coated tablets are available in the following pack sizes:

Polypropylene pots with polyethylene cap with a tamper evident seal (Securitainers^{Ò}) - 20, 30, 50, 100, 500 or 1,000.

High density polyethylene snap closure containers - 20, 30, 50, 100, 500 or 1,000.

PVC/Aluminium foil blister packs – 20, 30, 50, 90, or 100.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 halved 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 and then discarded safely. High-temperature incineration is recommended.

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

7 MARKETING AUTHORISATION HOLDER

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