Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imuran 50mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg of azathioprine.

Also contains lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from the UK:
Yellow, round, biconvex tablets with “GX CH1” and a scoreline on one side and plain on the other.
The scoreline should not be used to break the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Imuran 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.

Imuran, 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; and to reduce the corticosteroid requirements of renal transplant recipients.

Imuran, either alone or more usually in combination with corticosteroids and/or other drugs 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

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

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

Imuran tablets should be administered at least 1 hour before or 3 hours after food or milk (see Section 5.2 Pharmacokinetics: Absorption).
Dosage in transplantation - adults:
Depending on the immunosuppressive regimen employed, a dosage of up to 5mg/kg bodyweight/day may be given on the first day of therapy, either orally or intravenously.

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

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

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

When therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. If no improvement occurs in the patient's condition within 3 months, consideration should be given to withdrawing Imuran.

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

Paediatric population

Transplants

See Dosage in transplantation - adults.

Other Indications:

Overweight children
Children considered to be overweight may require doses at the higher end of the dose range and therefore close monitoring of response to treatment is recommended (see Section 5.2 Pharmacokinetics; Special Patient Populations; Overweight children).

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

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

Drug interactions

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

TPMT-deficient patients

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe azathioprine toxicity from conventional doses of azathioprine and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established (see Section 4.4 Special warnings and Precautions for Use: Monitoring and Section 5.2 Pharmacokinetics).

Most patients with heterozygous TPMT deficiency can tolerate recommended azathioprine doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see Section 4.4 Special warnings and precautions for use: Monitoring and Section 5.2 Pharmacokinetics).

4.3 Contraindications

Imuran is contraindicated in patients with known hypersensitivity to azathioprine or any other component of the preparation. If patients also have a known hypersensitivity to 6-mercaptopurine, the consulting doctor must be informed of 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, immunisations with live organism vaccines are not recommended (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Co-administration of ribavirin and azathioprine is not advised. Ribavirin may reduce efficacy and increase toxicity of azathioprine (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Monitoring:
There are potential hazards in the use of Imuran. 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 8 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 Imuran 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. The patient should be instructed to discontinue azathioprine immediately if jaundice becomes apparent.

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppression effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with Imuran. This problem could be exacerbated by co-administration with drugs 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 (Imuran)) in combination with other cytotoxics (see Adverse Reactions).

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 Interaction with other medicinal products and other forms of interaction: Cytostatic/myelosuppressive agents).
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 dosage in these patients and haematological response should be carefully monitored (see Section 4.2 Posology and method of administration).

Lesch-Nyhan syndrome
Limited evidence suggests that Imuran 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 Imuran.

Mutagenicity:
Chromosomal abnormalities have been demonstrated in both male and female patients treated with Imuran. It is difficult to assess the role of Imuran 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 Imuran. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of patients treated with Imuran. Azathioprine and long-wave ultraviolet light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine for a range of disorders.

Effects on Fertility:
Relief of chronic renal insufficiency by renal transplantation involving the administration of Imuran has been accompanied by increased fertility in both male and female transplant recipients (see section 4.6 Pregnancy and Lactation).

Carcinogenicity (see also section 4.8 Undesirable Effects):
Patients receiving immunosuppressive therapy are at an increased 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. The 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 non-Hodgkin's lymphomas and Kaposi's sarcomas.

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.

Varicella Zoster Virus Infection (see also 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.

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

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 Undesirable effects).

4.5 Interaction with other medicinal products and other forms of interaction

Vaccines

The immunosuppressive activity of azathioprine could result in an atypical and potentially deleterious response to live vaccines and so the administration of live vaccines to patients receiving azathioprine therapy is not recommended (see Section 4.4. Special warnings and Precautions for Use).

A diminished response to killed vaccines is likely and such a response to hepatitis B vaccine has been observed among patients treated with a combination of azathioprine and corticosteroids.

A small clinical study has indicated that standard therapeutic doses of azathioprine do not deleteriously affect the response to polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration.

Effect of concomitant drugs on azathioprine

Ribavirin

Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin; therefore co-administration is not advised (see Section 4.4. Special warnings and Precautions for Use and Section 5.2 Pharmacokinetics: Metabolism).

Cytostatic/myelosuppressive agents (see Section 4.4 Special warnings and Precautions for Use)

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 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: Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol, oxipurinol and/or thiopurinol are given concomitantly with 6-mercaptopurine or azathioprine, the dose of 6-mercaptopurine and azathioprine should be reduced to 25 % of the original dose (See Section Section 4.2 Posology and Method of Administration: Drug Interactions).

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 also Section 4.4 Special warnings and Precautions for Use).

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

Effect of azathioprine on other drugs

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

4.6 Fertility, pregnancy and lactation

Fertility

See Section 4.4 Special warnings and precautions for use: Effects on fertility.

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

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

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

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.

Leucopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took azathioprine throughout their pregnancies.

Lactation:
6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment. (See 5.3 Preclinical Safety Data). It is recommended that mothers receiving azathioprine should not breastfeed.

4.7 Effects on ability to drive and use machines

There are no data on the effect of azathioprine on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the drug.

4.8 Undesirable effects

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication. The following convention has been utilised for the classification of frequency:- Very common ≥1/10, common ≥1/100 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

Infections and Infestations

Very common:	viral, fungal and bacterial infections in transplant patients receiving azathioprine in combination with other immunosuppressants
Uncommon:	viral, fungal and bacterial infections in other patient populations.

Patients receiving Imuran 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 4.4 Special Warnings and Special 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 Special Warnings and Precautions for use).

Neoplasms Benign and Malignant (including cysts and polyps)
Rare: neoplasms including non-Hodgkin's lymphomas, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myeloid leukaemia and myelodysplasia. (See also section 4.4 Special Warnings and Special Precautions for Use).

The risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanomas and non-melanomas), 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.

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

Blood and Lymphatic System Disorders
Very common: depression of bone marrow function; leucopenia
Common: thrombocytopenia,
Uncommon: anaemia
Rare: agranulocytosis, pancytopenia, aplastic anemia, megaloblastic anaemia, erythroid hypoplasia

Imuran 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 Imuran when receiving concurrent allopurinol therapy.

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

Immune System Disorders
Uncommon: hypersensitivity reactions

Very rare: 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 Imuran. 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 Imuran.

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 Imuran, the necessity for continued administration of Imuran should be carefully considered on an individual basis.

Respiratory, Thoracic and Mediastinal Disorders
Very rare: reversible pneumonitis

Gastrointestinal Disorders
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
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 Imuran for inflammatory bowel disease. The possibility that exacerbation of symptoms might be drug-related should be borne in mind when treating such patients.

Pancreatitis has been reported in a small percentage of patients on Imuran 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 Imuran on occasions.

Hepato-biliary Disorders
Uncommon: cholestasis and deterioration of liver function tests
Rare: life-threatening hepatic damage

Cholestasis and deterioration of liver function have occasionally been reported in association with Imuran 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 primarily in transplant patients. 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
Rare: alopecia

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. The relationship between alopecia and azathioprine treatment is uncertain.

4.9 Overdose

Symptoms and signs: Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with Imuran and result from bone marrow depression which may be maximal after 9-14 days. These signs are more likely to be manifest following chronic overdosage, rather than after a single acute overdose. There has been a report of a patient who ingested a single overdose of 7.5g 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: 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 Imuran 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

Mode 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 Imuran 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

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

Absorption

The absorption of azathioprine is incomplete and variable. The median (range) absolute bioavailability of 6- MP after administration of azathioprine 50 mg is 47% (27 – 80%). The extent of absorption of azathioprine is similar across the gastrointestinal tract, including the stomach, jejunum, and cecum. However, the extent of 6-MP absorption, after azathioprine administration is variable and differs between the sites of absorption, with the highest extent of absorption in the jejunum, followed by the stomach and then the cecum.

Although there are no food effect studies with azathioprine, pharmacokinetic studies with 6-MP have been conducted that are relevant to azathioprine. The mean relative bioavailability of 6−MP was approximately 26% lower following administration with food and milk compared to an overnight fast. 6-MP is not stable in milk due to the presence of xanthine oxidase (30% degradation within 30 minutes) (see Pharmacokinetics: Metabolism). Azathioprine should be administered at least 1 hour before or 3 hours after food or milk (see Section 4.2 Posology and method of administration).

Distribution

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

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

Metabolism

Azathioprine is rapidly broken down *in vivo* by glutathione-S-transferase into 6-MP and a methylnitroimidazole moiety. The 6-MP readily crosses cell membranes and is extensively metabolized by many multi-step pathways to active and inactive metabolites, with no one enzyme predominating. Because of the complex metabolism, inhibition of one enzyme does not explain all cases of lack of efficacy and/or pronounced myelosuppression. The predominant enzymes responsible for the metabolism of 6-MP or its downstream metabolites are: the polymorphic enzyme thiopurine S-methyltransferase (TPMT) (see Special Warnings and Precautionsfor Use: Monitoring and Interactions: Aminosalicylates), xanthine oxidase (see Interactions: Allopurinol/oxipurinol/thiopurinol and Pharmacokinetics: Absorption), inosine monophosphate dehydrogenase (IMPDH) (see Interactions: Ribavirin), and hypoxanthine guanine phosphribosyltransferase (HPRT). Additional enzymes involved in the formation of active and inactive metabolites are: guanosine monophosphate synthetase (GMPS, which form TGNs) and inosine triphosphate pyrophosphatase(ITPase). Azathioprine itself is also metabolized by aldehyde oxidase to form 8-hydroxy azathioprine, which may be active. There are also multiple inactive metabolites formed via other pathways.

There is evidence that polymorphisms in the genes encoding the different enzyme systems involved with metabolism of azathioprine may predict adverse drug reactions to azathioprine therapy.

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 Special Warnings and Precautions for Use).
Elimination:

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

Special Patient Populations

Elderly

No specific studies have been carried out in the elderly (see Dosage and Administration).

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-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 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 Dosage and Administration).

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 Dosage and Administration).

Azathioprine and/or its metabolites are eliminated by haemodialysis, with approximately 45% of radioactive metabolites eliminated during dialysis of 8 hours.

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 Posology and Method of Administration).

5.3 Preclinical safety data

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

Tablet core:
Lactose
Maize starch
Pregelatinised starch
Stearic acid
Magnesium stearate

Film-coat:
Hypromellose
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer packaging of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Blister strips in an overlabelled carton. Pack size: 100 tablets.

6.6 Special precautions for disposal and other handling

Safe handling of Imuran: Health professionals who handle uncoated tablets should follow guidelines for the handling of cytotoxic drugs according to prevailing local recommendations and/or regulations (for example, the Royal Pharmaceutical Society of Great Britain Working Party Report on the Handling of Cytotoxic Drugs, 1983).
Provided that the film-coating is intact, there is no risk in handling film-coated Imuran Tablets. Film-coated Imuran Tablets should not be divided and, provided the coating is intact, no additional precautions are required when handling them.
Disposal: Imuran Tablets should be disposed of in a manner appropriate to the prevailing local regulatory requirements for the destruction of dangerous substances.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Clear Pharma Limited
157-173 Roden Street
Belfast BT12 5QA
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1823/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th October 2013

10 DATE OF REVISION OF THE TEXT