

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1473/007/001

Case No: 2050893

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDowell Pharmaceuticals

4 Altona Road, Lisburn, N. Ireland, BT27 5QB

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Imuran 25mg Film-Coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **13/02/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imuran 25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25mg azathioprine.

Excipients: contains lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from the UK:

Orange, round, biconvex tablets with “GX EL5” on one side and plain on the other.

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.

Dosage in transplantation - adults and children:

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 and children:

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.

In patients with renal and/or hepatic insufficiency, dosages should be given at the lower end of the normal range (see 4.4 Special Warnings and Special Precautions for Use for further details).

Use in the elderly: (see Renal and/or hepatic insufficiency)

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 recommended that the dosages used should be at the lower end of the range (see Dosage in other conditions, above)

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

4.3 Contraindications

Imuran is contraindicated in patients with known hypersensitivity to azathioprine or with a known hypersensitivity to 6-mercaptopurine.

4.4 Special warnings and precautions for use**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.

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.

Patients receiving Imuran should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestations of bone marrow depression.

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.

Renal and/or hepatic insufficiency:

It has been suggested that the toxicity of Imuran 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 Imuran to patients with hepatic dysfunction, and regular complete blood counts and liver function tests should be undertaken. In such patients the metabolism of Imuran may be impaired, and the dosage of Imuran should therefore be reduced to the lower end of the recommended range. Dosage should be further reduced if hepatic or haematological toxicity occurs.

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 varicellazoster 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.

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin: Inhibition of the anticoagulant effect of warfarin, when administered with azathioprine, has been reported.

Cytostatic/myelosuppressive agents: 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 Imuran and co-trimoxazole. There has been a case report suggesting that haematological abnormalities may develop due to the concomitant administration of Imuran and cimetidine.

It has been suggested that cimetidine and indomethacin may have myelosuppressive effects which may be enhanced by concomitant administration of Imuran.

Aminosalicylate: As there is in vitro evidence that aminosalicylate derivatives (e.g. olsalazine, meslazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent Imuran therapy (see 4.4 Special Warnings and Special Precautions for Use).

Other interactions: Frusemide has been shown to impair the metabolism of azathioprine by human hepatic tissue in vitro. The clinical significance is unknown.

Vaccines: The immunosuppressive activity of Imuran could result in an atypical and potentially deleterious response to live vaccines and so the administration of live vaccines to patients receiving Imuran therapy is contra-indicated on theoretical grounds.

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 Imuran do not deleteriously affect the response to polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration.

4.6 Pregnancy and lactation

Pregnancy: 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.

Azathioprine and/or its metabolites have been found in low concentrations in foetal blood and amniotic fluid after maternal administration of azathioprine.

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).

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).

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

Uncommon: pancreatitis

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

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

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: There is no specific antidote. Gastric lavage has been used. Subsequent monitoring, including haematological monitoring, is necessary to allow prompt treatment of any adverse effects which may develop. 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

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down in vivo into 6-MP and a methylnitroimidazole moiety. The 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid. The rate of conversion varies from one person to another. Nucleotides do not traverse cell membranes and therefore do not circulate in body fluids.

Irrespective of whether it is given directly or is derived in vivo from azathioprine, 6-MP is eliminated mainly as the inactive oxidised metabolite thiouric acid.

This oxidation is brought about by xanthine oxidase, an enzyme which is inhibited by allopurinol. The activity of the methylnitroimidazole moiety has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP. Determinations of plasma concentrations of azathioprine or 6-MP have no prognostic value as regards effectiveness or toxicity of these compounds.

Mode of action

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

- *the release of 6-MP which acts as a purine antimetabolite.
- *the possible blockade of -SH groups by alkylation.
- *the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response.
- *damage to deoxyribonucleic acid (DNA) through incorporation of purine thio-analogues.

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

5.2 Pharmacokinetic properties

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

Studies in mice with 35S-azathioprine showed no unusually large concentration in any particular tissue, but there was very little 35S found in brain.

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

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

Titanium dioxide (E171)
Iron oxide, yellow (E172)
Iron oxide, red (E172)
Lactose
Maize starch
Pregelatinised starch
Stearic acid
Magnesium stearate
Hypromellose
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date for this product shall be the date shown on the container and outer package 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

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

McDowell Pharmaceuticals
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Northern Ireland

8 Parallel Product Authorisation Number

PPA 1473/7/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 13th February 2009

10 DATE OF REVISION OF THE TEXT