PRODUCT INFORMATION

IMURAN® Tablets and Injection

COMPOSITION:

Film-coated Tablets: 25 mg and 50 mg.

Injection: 50 mg azathioprine, water for injection.

ACTIONS:

Suppression of the immune responses.

PHARMACOLOGY:

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.

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

1. the release of 6-MP which acts as a purine antimetabolite.

2. the possible blockade of -SH groups by alkylation.

3. the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of immune response.

4. 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.

IMURAN appears to be well absorbed from the upper gastrointestinal tract.

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

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 in the management of patients receiving organ transplants.

IMURAN, either alone or more usually in combination with corticosteroids and/or other 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/polymyositis;
autoimmune chronic active hepatitis;
pemphigus vulgaris;
polyarteritis nodosa;
autoimmune haemolytic anaemia;
chronic refractory ideopathic thrombocytopenic purpura.

CONTRAINDICATIONS:

IMURAN is contraindicated in patients known to be hypersensitive to azathioprine or any other component of the preparation. Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to IMURAN.

Patients with rheumatoid arthritis previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan or others) may have a prohibitive risk of neoplasia if treated with IMURAN.

IMURAN therapy should not be initiated in patients who may be pregnant, who are likely to become pregnant in the near future, or who are known to be pregnant (see PRECAUTIONS/WARNINGS).

PRECAUTIONS/WARNINGS:

Monitoring

There are potential hazards to the use of IMURAN. It should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of therapy.

During the first eight weeks of therapy, complete blood counts, including platelets, must 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 recommended that complete blood counts are repeated at intervals of not longer than one month or more frequently if dosage alterations or other changes to therapy are made. Delayed haematological suppression may occur.

Prompt reduction in dosage or temporary withdrawal of the drug may be necessary if there is a rapid fall in, or persistently low, leucocyte count or other evidence of bone marrow depression.

Patients receiving IMURAN should be instructed to report immediately if there is any evidence of infection, unexpected bruising or bleeding, black tarry stools and blood in the urine or stools, 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 myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with IMURAN. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (see 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 is impossible to relate plasma levels of azathioprine or 6-mercaptopurine to therapeutic efficacy or toxicity. Conversion of 6-thioinosinic acid to 6-thiouric acid by xanthine oxidase is not dependent on intact hepatic and/or renal function. Nevertheless, it is recommended that the dosages used are at the lower end of the normal range and that haematological response is 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, which can occur independently of the influence of IMURAN, have been demonstrated in both male and female transplant recipients.

Chromosomal abnormalities which disappear in time have been demonstrated in offspring of transplant recipients. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in these offspring.

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.

Teratogenicity
Studies in pregnant rats, mice and rabbits using azathioprine in dosages from 5-15 mg/kg bodyweight/day over the period of organogenesis have shown varying degrees of foetal abnormalities. Teratogenicity was evident in rabbits at 10 mg/kg bodyweight/day.

Epidemiological evidence in man indicates that the frequency of occurrence of congenital abnormalities in the offspring of maternal transplant recipients is similar to that in the general population.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving IMURAN.

Carcinogenicity (see ADVERSE REACTIONS)
Patients receiving immunosuppressive therapy are at an increased risk of developing lymphomas and other malignancies, notably skin cancers. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

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 by wearing protective clothing and using a sunscreen with a high protection factor.

Renal transplant recipients in some geographical areas are at greater risk of skin cancers than those in other areas.

Other neoplasms reportedly associated with IMURAN include carcinoma of the urinary bladder and adenocarcinoma of the lung.

Varicella Zoster Virus Infection (see ADVERSE REACTIONS)
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.

Use in Pregnancy and Lactation (Pregnancy Category D)
The decision to maintain or discontinue IMURAN during pregnancy, or to terminate the pregnancy, depends on the condition under treatment in which the maternal wellbeing has to be weighed against possible risks to the foetus. As a general rule, IMURAN therapy should not be initiated in patients known to be pregnant.

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.

IMURAN and/or its metabolites have been found in low concentrations in foetal blood and amniotic fluid.

The rare possibility of neonatal leucopenia and/or thrombocytopenia which may not be clinically evident appears to be preventable by reducing maternal dosage of IMURAN if, at 32

weeks' gestation, the maternal leucocyte count is at or below 8.6 x 10^9 per litre. The possibility of neonatal immunosuppression is a serious and potentially fatal complication. Extra care in haematological monitoring is advised during pregnancy.

6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment. Nursing mothers should be advised to consult their physician, since use by nursing mothers is not recommended because of possible adverse effects on the infant.

Relief of chronic progressive renal failure by renal transplantation involving the use of IMURAN has been accompanied by increased fertility in both male and female transplant recipients.

Other Precautions
IMURAN should be used with caution in hypersplenism.

Withdrawal of IMURAN should be gradual and performed under close supervision.

Dental work, whenever possible should be completed prior to initiation of IMURAN therapy or deferred until blood counts are normal.

ADVERSE REACTIONS:

Hypersensitivity Reactions
Several different clinical syndromes, which appear to be of an idiosyncratic hypersensitivity nature, have been described occasionally. They include general malaise, headache, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, vasculitis, myalgia, muscular pains, arthralgia, hypotension, disturbed liver function, cholestatic jaundice, pancreatitis, cardiac dysrhythmia, and renal dysfunction. In many cases, rechallenge has confirmed an association with IMURAN.

Additional adverse reactions of low frequency have been reported. These include skin rashes (approximately 2%), steatorrhoea, negative nitrogen balance, Stevens-Johnson syndrome and toxic epidermal necrolysis (all less than 1%).

It has been suggested that the imidazole side chain gives rise to hypersensitivity, whereas the 6-mercaptopurine (6-MP) molecule gives rise to cholestasis. Immediate withdrawal of azathioprine and supportive circulatory measures have led to recovery in the majority of cases. Other marked underlying pathology has contributed to the very rare deaths reported.

IMURAN should be PERMANENTLY withdrawn after any such clinical syndrome.

Neoplasms benign and malignant (including cysts and polyps)
The risk of developing lymphomas and other malignancies, notably skin cancers 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 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).

Haematopoiesis
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.

Therapeutic use of IMURAN is associated with a reversible, dose-related reduction in numbers of circulating total white cells, granulocytes and lymphocytes together with increases in mean corpuscular volume and red cell haemoglobin content. Megaloblastic bone marrow changes have been observed, but severe megaloblastic anaemia and erythroid hypoplasia are rare.

IMURAN may produce thrombocytopenia which is dose-related and may be delayed.

Alopecia
Hair loss has been described in 50% of renal transplant recipients receiving IMURAN and corticosteroids, but does not appear to be a major problem when IMURAN is used for other indications. It is reversible in over 80% of cases despite continuing immunosuppression.

Susceptibility to infection
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 **PRECAUTIONS/WARNINGS**). Viral, fungal and bacterial infections are very common in transplant patients receiving azathioprine in combination with other immunosuppressants.

Gastrointestinal reactions
Nausea, vomiting and gastrointestinal discomfort may occur during the first few months of IMURAN therapy. These effects are usually reduced by dosage adjustment and by administering the tablets in divided doses and/or after meals.

Serious complications, including colitis, diverticulitis and bowel perforation, have been described in transplant recipients and appear to relate to high dosage of corticosteroids rather than to IMURAN *per se*.

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.

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 Hypersensitivity Reactions).

Pulmonary reactions
Reversible pneumonitis has been described very rarely.

Hepatotoxicity
Hepatotoxicity may manifest by elevation of serum alkaline phosphatase, bilirubin and/or serum transaminases and is generally reversible after interruption of IMURAN. Periodic measurement of serum transaminases, alkaline phosphatase and bilirubin is indicated for early detection of hepatotoxicity. Hepatotoxicity has been uncommon (less than 1%) in rheumatoid arthritis patients.

Rare, but life threatening hepatic damage associated with chronic administration of azathioprine has been described, primarily in transplant patients. Histological findings include sinusoidal dilation, 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. IMURAN should be permanently withdrawn in patients with hepatic veno-occlusive disease.

Other Adverse Reactions
Other adverse reactions include sores in the mouth and on the lips, meningitis, formication, exacerbation of myasthenia gravis and dermatomyositis and alterations in the senses of smell or taste.

DRUG INTERACTIONS:

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 (6-MP) or azathioprine, the dose of 6-MP and azathioprine should be reduced to one quarter of the original dose.

Neuromuscular blocking agents
IMURAN can potentiate the neuromuscular blockade produced by depolarising agents such as succinylcholine and reduce the blockade produced by non-depolarising agents such as tubocurarine.

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

Cytostatic/myelosuppressive agents
IMURAN should be used with caution in patients receiving, or who have recently received, other bone marrow suppressive 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.

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

Aminosalicylates
As there is *in vitro* evidence that aminosalicylate derivatives (eg. olsalazine, mesalazine or sulfasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent IMURAN therapy (see PRECAUTIONS/WARNINGS).

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 contraindicated 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.

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

Drugs known to induce (phenytoin, phenobarbital, rifampicin) or inhibit (ketoconazole, erythromycin) hepatic microsomal enzymes may alter the clearance of IMURAN.

Coadministration of IMURAN and Captopril may result in increased susceptibility to leucopenia.

OVERDOSAGE:

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. Occasional reports describe ingestion of from 0.5 - 7.5 g IMURAN on a single occasion with apparent uneventful recovery.

Treatment
Treatment is symptomatic and has included gastric lavage. If overdosage occurs the blood picture and hepatic function in particular should be monitored. Azathioprine is dialysable but the procedure is of doubtful value since azathioprine is rapidly metabolised with entry of metabolites into tissue cells.

DOSAGE, RECONSTITUTION & ADMINISTRATION:

IMURAN Injection should be used ONLY when the oral route is impractical and should be discontinued as soon as oral therapy is tolerated.

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 adopted, a loading dose of up to 5 mg/kg bodyweight/day either orally or intravenously is usually given.

Maintenance dosage may range from 1 to 4 mg/kg bodyweight/day orally (or intravenously ONLY if oral therapy is not tolerated) 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 risk of graft rejection.

Dosage in other conditions - Adults and Children
In general, the initial dose should be approximately 1.0 mg/kg/day (50 to 100mg) gradually increasing in increments of 0.5mg/kg/day over several weeks, if necessary up to a maximum dose of 2.5mg/kg/day.

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

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

Use in the Elderly (see Renal and/or hepatic insufficiency)
The rapid *in vivo* cleavage of the azathioprine molecule followed by tissue fixation makes it impossible to relate plasma drug levels to toxicity. There are no specific data as to the tolerance of IMURAN in elderly patients. It is recommended that the dosages used are at the lower end of the range given for adults and children.

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

Reconstitution and dilution of IMURAN Injection
The contents of each vial should be reconstituted by the addition of 5 mL to 15 mL of Water for Injections, B.P. The reconstituted solution is chemically and physically stable for up to 5 days when stored between 5°C and 25°C (see below).

No antimicrobial preservative is included, therefore reconstitution and dilution must be carried out under full aseptic conditions, preferably immediately before use, and any unused solution discarded after 24 hours.

When diluted on the basis of 5 mL of reconstituted solution added to a volume of between 20 mL and 200 mL of one of the following infusion solutions, IMURAN is stable for up to 24 hours at room temperature (15°C to 25°C) (see below):-

Sodium Chloride Intravenous Infusion, B.P. (0.45% w/v and 0.95% w/v).

Sodium Chloride (0.18% w/v) and Glucose (4.0% w/v) Intravenous Infusion B.P.

Should any visible turbidity or crystallisation appear in the reconstituted or diluted solution the preparation must be discarded.

Addition of reconstituted IMURAN Injection to any other infusion solution or an intravenous admixture is not recommended.

Administration
IMURAN Injection, when reconstituted as directed, results in a very irritant solution with a pH of 10 to 12.

When the reconstituted solution is diluted as directed above, the pH of the resulting solution may be expected to be within the range pH 8.0 to 9.5 (the greater the dilution the lower the pH).

Where dilution is not practicable, the reconstituted solution should be injected slowly over a period of not less than one minute and followed immediately by not less than 50 mL of one of the recommended infusion solutions.

Care must be taken to avoid perivenous injection which may produce tissue damage. Should this occur accidentally, the injection/infusion should be stopped immediately and appropriate local therapy instituted.

Safe handling of IMURAN

IMURAN Injection
It is recommended that the handling of IMURAN follows the 'SHPA Guidelines for the Handling of Cytotoxic Drugs in Pharmacy Departments' as listed in the 'Practice Guidelines of the Society of Hospital Pharmacists of Australia 1991'.

IMURAN Tablets
Film-coated IMURAN Tablets should not be divided.

Provided that the film coating is intact, there is no risk in handling film-coated IMURAN Tablets.

PRESENTATION:

Injection: 50 mg preservative free (as sodium salt).

Tablets: 25 mg (Orange film coated tablets, round, biconvex, unscored, debossed GX EL5 on one face and plain on the other) 100's.

50 mg (Yellow film coated tablets, round, biconvex, scored, debossed GX above the score and CH1 below the score on one face and plain on the other) 100's.

STORAGE:

Injection Store below 25°C.
Protect from light. Keep dry.

Tablets Store below 30°C.
Protect from light.

POISON SCHEDULES: S4

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