

NEW ZEALAND DATA SHEET

IMURAN[®] Tablets **(azathioprine 50 mg)**

PRESENTATION

Yellow tablet, film coated, round biconvex, scored, branded GX CH1. Each tablet contains 50 mg azathioprine BP.

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 is indicated for the treatment of moderate to severe Crohn's disease in patients in whom corticosteroid therapy is required, in patients who cannot tolerate corticosteroid therapy, or in patients whose disease is refractory to other standard first line therapy.

IMURAN, either alone or more usually in combination with corticosteroids and/or other medicines 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;
- ulcerative colitis.

DOSAGE AND ADMINISTRATION

IMURAN tablets should be administered at least 1 hour before or 3 hours after food or milk.

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

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

Use in Adults

Adult dose in transplants

Depending on the immunosuppressive regimen employed, a dosage of up to 5 mg/kg bodyweight/day may be given orally on the first day of therapy.

Maintenance dosage should range from 1-4 mg/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.

Adult dose for other indications

In general, starting dosage is from 1-3 mg/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. However, for patients with Crohn's disease, treatment duration of at least 12 months should be considered and a response to treatment may not be clinically apparent until after 3-4 months of treatment.

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 Use in patients with 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 Use in Adults).

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

Use in children

Dose in transplants: (See Adult dose in transplants)

Dose for other indications: (See Adult dose for other indications)

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.

Use in patients with renal and/or hepatic insufficiency

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

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 of heterozygous deficient patients has not been established.

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.

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.

WARNINGS AND PRECAUTIONS

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.

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.

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 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) in combination with other cytotoxics (see Adverse Effects). 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.

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.

The patient should be instructed to discontinue azathioprine immediately if jaundice becomes apparent.

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 Use in Pregnancy and Lactation).

Carcinogenicity:-

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.

Reports of hepatosplenic T-cell lymphoma in the inflammatory bowel disease population have been received when azathioprine is used in combination with anti-TNF agents.

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 Adverse Effects):-

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

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.

Co-administration of ribavirin and azathioprine is not advised. Ribavirin may reduce efficacy and increase toxicity of azathioprine.

Progressive Multifocal Leukoencephalopathy (PML)

PML, an opportunistic infection caused by the JC virus (a type of human polyomavirus) 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 Adverse Effects).

Hepatitis B (see ADVERSE EFFECTS)

Hepatitis B carriers (defined as patients positive for hepatitis B surface antigen [HBsAg] for more than six months), or patients with documented past HBV infection, who receive immunosuppressive drugs are at risk of reactivation of HBV replication, with asymptomatic increases in serum HBV DNA and ALT levels. Specialist medical

literature should be consulted for guidance including prophylactic therapy with oral anti-HBV agents.

Use in Pregnancy - Pregnancy Category D

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. Extra care in haematological monitoring is advised during pregnancy.

Use in Lactation

6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment.

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.

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 or azathioprine, the dose of 6-mercaptopurine 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 can reduce the blockade produced by non-depolarising agents such as tubocurarine.

There is considerable variation in the potency of this interaction.

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.

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 captopril.

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* and *in vivo* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent IMURAN therapy (see Warnings and Precautions).

Methotrexate:-

Methotrexate (20mg/m² orally) increased 6-mercaptopurine AUC by approximately 31% and methotrexate (2 or 5g/m² intravenously) increased 6-mercaptopurine AUC by 69 and 93%, respectively. Therefore, when azathioprine is administered concomitantly with high dose methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.

Other interactions:-

Furosemide 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.

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.

ADVERSE EFFECTS

For this product there is no modern clinical documentation which can be used as support for determining the frequency of adverse effects. Adverse effects may vary in their incidence depending on the indication. The following convention has been utilised for the classification of frequency: Very common $\geq 1/10$, common $\geq 1/100$, $< 1/10$, uncommon $\geq 1/1000$ and $< 1/100$, rare $\geq 1/10,000$ 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.
- Very rare: cases of JC virus associated PML have been reported following the use of azathioprine in combination with other immunosuppressants (see Warnings and Precautions).

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 and reactivation with vzv, hepatitis B and other infectious agents.

Neoplasms benign and malignant (including cysts and polyps)

- Rare: Neoplasms including non-Hodgkin's lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*, acute myeloid leukaemia and myelodysplasia. (see Warnings and Precautions).
- Very rare: Hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease when used in combination with anti-TNF agents.

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

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.

OVERDOSE

Symptoms and signs

Unexplained infections, 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 7.5 g of azathioprine. The immediate toxic effects of this overdose were nausea, vomiting and diarrhoea, followed by mild leucopenia and mild abnormalities in liver function. Recovery was uneventful.

Treatment

There is no specific antidote. Further management should be as clinically indicated or as recommended by the National Poisons Centre (ph: 0800 POISON or 0800 764 766).

The value of dialysis in patients who have taken an overdose of IMURAN is not known, though azathioprine is partially dialysable.

FURTHER INFORMATION

Pharmacodynamic Properties

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:-

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 the 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.

Pharmacokinetics

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-mercaptopurine do not correlate well with the therapeutic efficacy or toxicity of IMURAN.

Preclinical Safety Data

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.

Excipients

Hypromellose, lactose, macrogol 400, magnesium stearate, starch-maize, starch-pregelatinised maize and stearic acid.

PHARMACEUTICAL PRECAUTIONS

Incompatibilities:

None reported.

Shelf Life:

5 years

Special Precautions for Storage:

Store below 30°C.

Instructions for Handling

Safe handling:-

Health professionals who handle IMURAN uncoated tablets should follow guidelines for the handling of cytotoxic drugs according to prevailing local recommendations and/or regulations.

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.

PACKAGE QUANTITIES

50 mg tablets: Blister pack of 100.

MEDICINES SCHEDULE

Prescription Only Medicine

SPONSOR DETAILS

Pharmacy Retailing (NZ) Limited
Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

DATE OF PREPARATION

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