NEW ZEALAND DATA SHEET

1. IMURAN

Imuran Injection (azathioprine 50 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of the active ingredient azathioprine as the sodium salt.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

IMURAN Injection is supplied as a yellow to amber freeze-dried powder for solution for injection/infusion in a neutral glass vial with a rubber closure and aluminium collar.

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 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.

4.2 Dose and method of administration

IMURAN INJECTION SHOULD BE USED ONLY WHEN THE ORAL ROUTE IS IMPRACTICAL AND SHOULD BE DISCONTINUED AS SOON AS ORAL THERAPY IS TOLERATED. IT MUST BE ADMINISTERED BY THE INTRAVENOUS ROUTE.

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 intravenously 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 section 4.4 Special warnings and precautions for use).

TPMT-deficient patients

Patients with inherited little or no thiopruine 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.

Administration of IMURAN Injection
IMURAN Injection, when reconstituted as directed, is a very irritant solution with a pH of 10-12.

When the reconstituted solution is diluted as directed (see section 6.6 Special precautions for disposal (and other handling)), 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 product tissue damage.

4.3 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.

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.

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.

TPMT Testing
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. There have been fatal cases of myelosuppression in patients with low or absent TPMT activity treated with thiopurines. 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 section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Patients should be tested for TPMT activity before starting Imuran. TPMT testing cannot substitute for complete blood count monitoring in patients receiving Imuran. TPMT genotyping can be used to identify patients with absent
or reduced TPMT activity. Patients with low or absent TPMT activity (homozygous for non-functional alleles) are at an increased risk of developing severe, life-threatening myelotoxicity from Imuran if conventional doses are given. Alternative therapies may be considered for patients who have low or absent TPMT activity. Imuran should be administered with caution to patients having one non-functional allele (heterozygous) who are at risk for reduced TPMT activity that may lead to toxicity if conventional doses are given. Dosage reduction is recommended in patients with reduced TPMT activity. The dosage of azathioprine may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression.

TPMT testing is widely available through pathology laboratories and genetic testing services.

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 section 4.8 Undesirable 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 section 4.8 Undesirable Effects).

Hepatitis B (see section 4.8 UNDESIRABLE 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.

4.5 Interaction with other medicines and other forms of interaction

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 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.

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.

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.

4.6 Fertility, pregnancy and lactation

Use in 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.

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 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 ≥1/10, common ≥1/100, <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.

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).

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 section 4.4 Special warnings and precautions for use).

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

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.

Other Adverse Effects
Other adverse reactions include sores in the mouth and on the lips, meningitis, formication, acute febrile neutrophilic dermatosis (Sweet's Syndrome), exacerbation of myasthenia gravis and dermatomyositis and alterations in the senses of smell or taste.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

5.2 Pharmacokinetics

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 brain.

Plasma levels of azathioprine and 6-mercaptopurine 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 5-15 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, water for injection (removed during processing).
(NB: the sodium ion content of the injection is approximately 4.5 mg (0.2 mEq.))

6.2 Incompatibilities

IMURAN Injection should not be mixed with other drugs or fluids, except those specified in section 6.6 Special precautions for disposal (and other handling), before administration.

6.3 Shelf Life

3 years

6.4 Special Precautions for Storage

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

6.5 Nature and contents of container (and special equipment for use, administration or implantation)

Box contains 1 dose units: 50 mg glass vial.

6.6 Special precautions for disposal (and other handling)

Disposal

IMURAN Injection solution should be disposed of in an appropriate manner (for example deep burial or high-temperature incineration) according to local regulatory requirements.

Disposal of sharp objects, such as needles, syringes, administration sets and ampoules should be in rigid containers labelled with a suitable hazard warning seal. Personnel involved in disposal should be aware of the precautions to be observed, and the material should be destroyed in accordance with local regulatory requirements which may include incineration.

Instructions for Handling

Reconstitution and dilution of IMURAN Injection

Precautions should always be taken when handling IMURAN Injection (see Safe handling of IMURAN Injection).

No antimicrobial preservative is included. Therefore reconstitution and dilution must be carried out under full aseptic condition, preferably immediately before use. Any unused solution should be discarded.

The contents of each vial should be reconstituted by the addition of 5 mL to 15 mL of Water for Injections BP. The reconstituted solution is stable for up to 5 days when stored between 5^0C and 25^0C.

When diluted on the basis of 5 mL of reconstituted solution 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 (15^0C to 25^0C).:-

- Sodium chloride Intravenous Infusion BP (0.45% w/v and 0.9% w/v).
- Sodium chloride (0.18% w/v)
- Glucose (4.0% w/v) Intravenous Infusion BP.

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

IMURAN Injection should ONLY be reconstituted with the recommended volume of Water for Injections BP and should be diluted as specified above.

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

IMURAN Injection should be prepared for administration either by or under the direct supervision of a pharmacist, or by another specially trained person, who is familiar with its properties and has expertise in the safe handling of similar preparations.

IMURAN Injection should be prepared for use in the aseptic unit of a pharmacy, which is equipped with a suitable vertical laminar flow cabinet designed to ensure adequate protection of both operator and product and, preferably, reserved solely for cytotoxic preparations. Where such a facility does not exist, a specially designated side room of a ward or clinic may be used.

Personnel involved with the preparation of IMURAN Injection should wear the following protective clothing:-

- Polyvinylchloride disposable gloves of a suitable quality (rubber gloves are not adequate);
- Surgical facemask of suitable quality;
- Protective goggles or glasses which should be washed thoroughly with water after use;
- Disposable apron. In an aseptic facility, other suitable clothing will be required.

Any spillage should be dealt with immediately, by mopping with damp, disposable paper towels which are placed in a high-risk waste disposal bag after use. Contaminated surfaces should be washed with copious quantities of water.

Should IMURAN Injection solution come into contact with skin, the skin should be washed thoroughly with soap and plenty of cold water.

If the eyes are contaminated, immediate irrigation with sodium chloride eye wash should be carried out and medical attention sought without delay. If sodium chloride solution is not available, large volumes of clean tap water may be used.

Administration
The patient's eyes, skin and mucous membranes should be protected from contact with the reconstituted or diluted solution; care should be taken, however, to ensure that the patient is not made unduly anxious by the procedures used.

The patient's clothing, body and bedding should be protected by use of an absorbent disposable layer on top of a waterproof layer.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

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

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

2 September 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
Format of Data sheet	As per new European SmPC style format
4.4	Safety related changes
4.8	Safety related changes