1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

IMURAN 50 mg film-coated tablets

IMURAN INJECTION 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of IMURAN contains 50 mg azathioprine.

Contains sugar: Lactose monohydrate 74 mg

For full list of excipients, see section 6.1.

Each vial of IMURAN INJECTION contains the equivalent of 50 mg azathioprine as its sodium salt, freeze dried.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

IMURAN:

Film-coated tablets.

IMURAN is a yellow film-coated, round, biconvex tablet, which is scored and branded ‘IM 5’.

IMURAN INJECTION:

Powder for solution for injection.

IMURAN INJECTION is a yellow to amber freeze-dried powder, which when reconstituted is a clear, or slightly opalescent, yellow solution, essentially free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

IMURAN is used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other medicines (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 is indicated for:

- **Transplantation**

  IMURAN, in combination with corticosteroids and/or other immunosuppressive medicines and procedures, is indicated to enhance the survival of organ transplants, such as renal transplants, cardiac transplants and hepatic transplants. It also reduces the corticosteroid requirement of renal transplant recipients.

  IMURAN INJECTION is used for the suppression of the immune response in organ transplantation, in patients who are unable to take oral medicine.

- **Inflammatory bowel disease**

  IMURAN is indicated for the treatment of moderate to severe inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis) 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.

- **Auto-immune diseases**

  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 active chronic hepatitis,
  - pemphigus vulgaris,
  - polyarteritis nodosa,
  - auto-immune haemolytic anaemia,
  - chronic refractory idiopathic thrombocytopenic purpura,
  - relapsing remittent multiple sclerosis.

4.2. Posology and method of administration

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

Powder for injection:

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 only by the IV route.

IMURAN tablets should be taken at least one hour before or three hours after food or milk.

Posology

Adults

Transplants

Depending on the immunosuppressive regimen employed, a loading dosage of up to 5,0 mg/kg bodyweight/day may be given orally or intravenously on the first day of therapy. Maintenance dosage should range from 1,0 to 4,0 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 the risk of graft rejection.

Multiple sclerosis

The dose recommended for the treatment of relapsing remittent multiple sclerosis is 2 to 3 mg/kg bodyweight/day. Treatment duration in excess of one year may be required to establish efficacy. Control of disease progression may not be apparent until after two years of therapy.

Other indications

In general, starting dosage is from 1 to 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

The dosage of IMURAN and the duration of treatment may vary according to the condition, its severity and the clinical response obtained. A therapeutic response in auto-immune disease may not be evident for a few days or even weeks after initiation of IMURAN therapy.

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 three months, consideration should be given to withdrawing IMURAN. Treatment is otherwise undertaken on a long-term basis unless the patient exhibits evidence of intolerance to IMURAN.

However, for patients with IBD, a treatment duration of at least twelve months should be considered and a response to treatment may not be clinically apparent until after three to four 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.

Special populations

Elderly population

There is limited experience of the administration of IMURAN to elderly patients. The dosage of IMURAN in the elderly has not been established. Although the available data do not provide evidence that the incidence of side effects among elderly patients is higher than that among other patients treated with IMURAN, it is advisable to monitor renal and hepatic function, and to consider dosage reduction if there is impairment.

It is recommended that the dosages used are at the lower end of the range given.

Renal impairment

IMURAN pharmacokinetics has not been formally studied in patients with renal insufficiency. No specific dose recommendations can be given. Since impaired renal function may result in slower elimination of azathioprine and its metabolites, IMURAN should be given at the lowest normal dose (see section 4.4).

Hepatic impairment

IMURAN pharmacokinetics has not been formally studied in patients with hepatic impairment. Since impaired hepatic function may result in reduced elimination of azathioprine and its metabolites, no specific dose recommendations can be given.
In patients with hepatic insufficiency, IMURAN should be given at the lowest normal dose (see section 4.4). Patients should be monitored for dose related adverse effects.

Interaction

When xanthine oxidase inhibitors, such as allopurinol, and azathioprine, as in IMURAN are administered concomitantly it is essential that only 25 % of the usual dose of IMURAN is given since allopurinol decreases the rate of catabolism of IMURAN (see section 4.5).

TPMT-deficient patients

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe toxicity from conventional doses of azathioprine, as in IMURAN, and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established (see section 4.4). Most patients with heterozygous TPMT deficiency can tolerate recommended IMURAN doses, but some may require dose reduction. Genotypic and phenotypic tests of TPMT are available (see section 4.4).

Fatal cases of myelosuppression in patients with low or absent TPMT activity treated with thiopurines have been reported. This problem could be exacerbated by coadministration with medicines that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine.

Patients with NUDT15 variant

Patients with inherited mutated NUDT15 gene are at increased risk for severe thiopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy and generally require substantial dose reduction. Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population. The optimal starting dose for heterozygous or homozygous deficient patients has not been established.

Genotypic and phenotypic testing of NUDT15 variants should be considered before initiating thiopurine therapy in all patients (including paediatric patients) to reduce the risk of thiopurine-related severe leukocytopenia and alopecia, especially in Asian populations (see section 5.2).

Paediatric population

The use of IMURAN is not recommended in children with multiple sclerosis.

For transplants and other indications, the posology is as in adults.

Overweight paediatric population

Children considered to be overweight may require doses at the higher end of the dose range and therefore close monitoring of response to treatment is recommended (see section 5.2).

Method of administration

IMURAN:

For oral administration.

IMURAN tablets are given by mouth, but patients unable to take oral medicine may be given IMURAN INJECTION for a short period. It is seldom necessary to continue with the injection for more than a day or two and IMURAN tablets should be substituted as soon as possible.

IMURAN INJECTION:

For parental administration.

Precaution to be taken before manipulating or administering IMURAN INJECTION. For instructions on reconstitution and dilution of IMURAN INJECTION before administration, see section 6.6.

When IMURAN INJECTION is reconstituted as directed, it is a very irritant solution with a pH of 10 to 12. When the reconstituted solution is diluted as directed (see section 6.6), 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 of IMURAN INJECTION 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 (see section 6.6).

IMURAN INJECTION is given intravenously. 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. Should any visible turbidity or crystallisation appear in the reconstituted or diluted solution the preparation must be discarded.

4.3. Contraindications

IMURAN is contraindicated in:

- Patients with hypersensitivity to azathioprine or to any of the excipients in IMURAN (see section 6.1). Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to IMURAN.
- Pregnancy, lactation and patients who are likely to become pregnant in the near future.
- 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.
- Acute infections.

4.4. Special warnings and precautions for use

Hypersensitivity

Patients suspected to have previously presented a hypersensitivity reaction to 6-mercaptopurine (6-MP) should not be treated with its pro-drug azathioprine, after allergological tests have confirmed the medicine the patient is allergic to.

In many cases, re-challenge has confirmed an association with IMURAN. It has been suggested that the imidazole side-chain gives rise to sensitivity, whereas the 6-MP molecule gives rise to cholestasis.

Immunisation

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, it is recommended that patients do not receive live organism vaccines until at least three months after the end of their treatment with azathioprine (see section 4.5).

Ribavirin

Co-administration of ribavirin and IMURAN is not advised. Ribavirin may reduce efficacy and increase toxicity of IMURAN (see section 4.5).

Monitoring

THE RISKS ASSOCIATED WITH IMURAN THERAPY SHOULD BE CONSIDERED AGAINST THE SEVERITY OF THE PATIENT'S CONDITION AND THE EXPECTED BENEFICIAL CLINICAL EFFECT.

There are potential hazards in the use of IMURAN. IMURAN should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of the 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 no longer than three months.

At the first signs of an abnormal fall in blood counts, treatment should be interrupted immediately as leucocytes and platelets may continue to fall after treatment is stopped.

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

depression. Bone marrow suppression is reversible if IMURAN is withdrawn early enough.

IMURAN is hepatotoxic and liver function tests should be routinely monitored during treatment. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. The patient should be instructed to discontinue IMURAN immediately if jaundice becomes apparent.

If IMURAN is used in conjunction with, or soon after, withdrawal of another medicine known to have a depressive effect on the bone marrow, it is particularly important that frequent blood counts be taken. Since IMURAN may have a delayed action, it is important to reduce dosage or withdraw the medicine temporarily at the first sign of an abnormally large fall in leucocyte count and/or other evidence of persistent depression of the bone marrow. Such bone marrow depression is usually reversible at the doses recommended for auto-immune disease.

The effect on white cell count is not closely correlated with the immunosuppressive effect of IMURAN; a good immunosuppressive effect can often be obtained without change in the white cell count, but sometimes the count may be greatly reduced without any apparent immunosuppression.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine, as in IMURAN, therapy (see section 4.6). If cholestasis of pregnancy occurs, a case by case assessment is necessary considering the risk-benefit profile of the medicine (potential withdrawal/dose reduction).

Thiopurine methyltransferase

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine, as in IMURAN and prone to developing rapid bone marrow depression following the initiation of treatment with IMURAN. This problem could be exacerbated by coadministration with medicines 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-MP (the active metabolite of azathioprine) in combination with other cytotoxics (see section 4.8). 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 IMURAN may need to be reduced when IMURAN is combined with other medicines whose primary or secondary toxicity is myelosuppression (see section 4.5).

NUDT15 mutation

Patients with inherited mutated NUDT15 gene are at increased risk for severe thiopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy and generally require substantial dose reduction. Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population. The optimal starting dose for heterozygous or homozygous deficient patients has not been established. Genotypic and phenotypic testing of NUDT15 variants should be considered before initiating thiopurine therapy in all patients (including paediatric patients) to reduce the risk of thiopurine-related severe leukocytopenia and alopecia, especially in Asian populations (see section 5.2).

Renal and/or hepatic impairment

Caution is advised during the administration of IMURAN in patients with renal impairment and/or hepatic impairment. Consideration should be given to reducing the starting dosage in these patients and haematological response should be carefully monitored (see section 4.2 and section 5.2).

The dosage of IMURAN must be reduced for the treatment of active chronic hepatitis. Patients with impaired renal and/or hepatic function may eliminate the medicine and its metabolites at a reduced rate with a consequent cumulative effect. The dosage of IMURAN should therefore be reduced in such cases, particularly in anuric patients. If there is evidence of toxic hepatitis or biliary stasis, consideration must be given to withholding IMURAN. Elevated serum bilirubin levels have been observed in some patients after initiation of IMURAN therapy (see section 4.8).

Lesch-Nyhan syndrome

Limited evidence suggests that IMURAN is not beneficial to patients with hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). Therefore, given the abnormal metabolism in these patients, they should not receive IMURAN.

Infection

IMURAN has an immunosuppressant effect involving both antibody and cell-mediated immunity. Infection, which is always a hazard of immunosuppressive therapy, particularly when corticosteroids are given, may require the dosage of immunosuppressive medicine to be reduced temporarily. Fungal, protozoal, viral and uncommon bacterial infections in patients on immunosuppressive therapy have occurred and should be treated vigorously. Some of these have proved fatal.

Gastrointestinal intolerance

IMURAN may cause anorexia, nausea, vomiting or diarrhoea. In such cases IMURAN therapy may have to be adjusted.

Other

Persistent negative nitrogen balance has been observed in some patients on continuous IMURAN and corticosteroid therapy. If this occurs, the dosage should be reduced.

The effects of azathioprine and its metabolite, mercaptopurine may persist after clearance is complete and therefore it is important to reduce or withdraw the medication at the first sign of abnormally large fall in the leucocyte count or other evidence of bone marrow depression.

Bone-marrow depression with main effect on the granulocytes and slight effect on platelets. The bone-marrow depression may be severe and irreversible and manifested by leucopenia, anaemia, thrombocytopenia and bleeding.

Medicine fever, pancreatitis, muscle wasting and skin rashes have been reported and oral lesions and skin reactions may occur.

IMURAN should be used with care in patients with liver damage or a history of liver disease. If infection develops during treatment IMURAN should be withdrawn.

Reduced doses may be required in patients with renal transplants.

Mutagenicity

Chromosomal abnormalities have been demonstrated in both male and female patients treated with azathioprine, as in IMURAN. It is difficult to assess the role of IMURAN in the development of these abnormalities.

Chromosomal abnormalities, which disappear in time, have been demonstrated in lymphocytes from the offspring 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 (see section 4.6).

Azathioprine, as in IMURAN, and long-wave ultraviolet light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine, as in IMURAN, for a range of disorders.

Carcinogenicity

Patients receiving immunosuppressive therapy, including IMURAN, are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

Reports of hepatosplenic T-cell lymphoma have been received when azathioprine, as in IMURAN, is used alone or in combination with anti-TNF medicines or other immunosuppressants. Although most reported cases occurred in the IBD population, there have also been cases reported outside of this population.

Patients receiving multiple immunosuppressive medicines 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.

Contraception

The recommended duration of contraception in males and females should be until the end of relevant systemic exposure to the genotoxic compound incl. potential genotoxic metabolites (i.e. five half-lives after the last dose) plus three and six months, respectively, afterwards (see section 4.6).

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with IBD, and there could potentially be an increased susceptibility for developing the condition with the use of IMURAN. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with IMURAN should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Metabolism and nutrition disorders

Administration of purine analogues, azathioprine and mercaptopurine, may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency (pellagra). Few cases have been reported with the use of azathioprine, as in IMURAN, especially in patients with IBD (Crohn's disease, ulcerative colitis). Diagnosis of pellagra should be considered in a patient presenting with localised pigmented rash (dermatitis); gastroenteritis (diarrhoea); or neurologic deficits, including cognitive decline(dementia).

Appropriate medical care with niacin/nicotinamide supplementation must be initiated, and dose reduction or discontinuation of azathioprine must be considered.

Varicella Zoster virus infection

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.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by the John Cunningham virus (JC virus), has been reported in patients receiving azathioprine, as in IMURAN, with other immunosuppressive medicines. 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).

Hepatitis B

Hepatitis B virus (HBV) 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 medicines are at risk of reactivation of HBV replication, with asymptomatic increases in serum HBV DNA and ALT levels. Local guidelines may be considered including prophylactic therapy with oral anti-HBV medicines (see section 4.8).

Xanthine oxidase inhibitors

If allopurinol, oxipurinol and/or thiopurinol are given concomitantly with azathioprine, as in IMURAN, the dosage of IMURAN must be reduced to a quarter of the original dose (see section 4.2).

Neuromuscular medicines

Special care is necessary when muscle relaxants are administered to patients taking IMURAN as the action of non-depolarising neuromuscular blockers may be inhibited (see section 4.5). IMURAN can also potentiate the neuromuscular block that is produced by depolarising medicines such as succinylcholine (see section 4.5). Patients should be advised to inform their anaesthesiologist of their treatment with IMURAN prior to surgery.

Excipients

IMURAN (tablet)

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take IMURAN.

IMURAN INJECTION

IMURAN INJECTION contains approximately 4,5 mg (0,2 mEq) sodium (main component of cooking/tablet salt) in each 50 mg vial.

4.5. Interaction with other medicines and other forms of interaction

Vaccines

The immunosuppressive activity of azathioprine, as in IMURAN, could result in an atypical and potentially deleterious response to live vaccines. It is therefore recommended that patients do not receive live vaccines until at least three months after the end of their treatment with IMURAN (see section 4.4).

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, as in IMURAN, and corticosteroids. Contributing causes to a suboptimal response to the hepatitis B vaccine include genetic predisposition, immunosuppression, certain chronic illnesses (for example, HIV and AIDS, chronic kidney disease) and age.

A small clinical study has indicated that standard therapeutic doses of azathioprine, as in 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, as in IMURAN, and ribavirin; therefore, co-administration is not advised (see section 4.4).

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors

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-MP or azathioprine, as in IMURAN, the dose of 6-MP and IMURAN should be reduced to 25 % of the original dose.

Other xanthine oxidase inhibitors, such as febuxostat may decrease the metabolism of azathioprine, as in IMURAN. Concomitant administration is not recommended as data are insufficient to determine an adequate dose reduction.

Neuromuscular blocking medicines

Azathioprine inhibits phosphodiesterase activity in motor nerve terminals increasing the release of acetylcholine. There is clinical evidence that azathioprine antagonises the effect of non-depolarising muscle relaxants such as curare, d-tubocurarine and pancuronium. Experimental data confirm that IMURAN reverses the neuromuscular blockade produced by d-tubocurarine and show that IMURAN potentiates the neuromuscular blockade produced by succinylcholine (see section 4.4).

Cytostatic/myelosuppressive medicines

Where possible, concomitant administration of cytostatic medicines, or medicines which may have a myelosuppressive effect, such as penicillamine, should be avoided.

There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between azathioprine, as in IMURAN, and trimethoprim/sulfamethoxazole also known as co-trimoxazole. Medicines which may affect leukocyte production, including co-trimoxazole, may lead to exaggerated leukopenia, especially in renal transplant recipients.

There have been case reports suggesting that haematological abnormalities may develop due to the concomitant administration of IMURAN and angiotensin converting enzyme (ACE) inhibitors (e.g. captopril).

The use of ACE inhibitors to control hypertension in patients on azathioprine, as in IMURAN, has been reported to induce severe leukopenia.

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

Diuretics

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

Aminosalicylates

There is *in vitro* and *in vivo* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme. Therefore, lower doses of IMURAN may need to be considered when administered concomitantly with aminosalicylate derivatives (see section 4.4).

Methotrexate

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

Infliximab

An interaction has been observed between azathioprine, as in IMURAN, and infliximab. Patients receiving ongoing azathioprine experienced transient increases in 6-TGN (6-thioguanine nucleotide, an active metabolite of azathioprine) levels and a decrease in the mean leukocyte count in the initial weeks following infliximab infusion, which returned to previous levels after three months.

Anticoagulants

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with azathioprine, as in IMURAN; therefore, higher doses of the anticoagulant may be needed. It is recommended that coagulation tests (INR and/or PT) are closely monitored when oral anticoagulants (warfarin) are concurrently administered with IMURAN.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

As with all cytotoxic treatments, male and female patients who use azathioprine, as in IMURAN, should use effective and reliable contraceptive methods during the treatment and for a period of three and six months following the cessation of treatment, respectively.

The final decision regarding the additional time period on contraception should be taken by the doctor.

It is recommended to have a consultation on sperm cryopreservation and/or individual genetic counselling for male and female patients intending to have a child after treatment with IMURAN.

The use of IMURAN is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

IMURAN can cause foetal harm when administered to pregnant women.

Substantial transplacental and trans-amniotic transmission of azathioprine, as in IMURAN, and its metabolites from the mother to the foetus have been shown to occur.

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

Evidence of the teratogenicity of IMURAN in man is equivocal.

There have been a few reports of congenital deformity when the father was receiving IMURAN at the time of conception.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine, as in IMURAN, therapy. Early diagnosis and discontinuation of azathioprine may minimise impact on the foetus. However, a careful assessment of benefit to the mother and impact on the foetus should be performed, if cholestasis of pregnancy is confirmed (see section 4.4).

Mutagenicity

Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes from the offspring 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, as in IMURAN, and long-wave ultraviolet light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine, as in IMURAN, for a range of disorders (see section 4.4).

There have been reports of intra-uterine growth retardation, premature birth and low birth weight following maternal exposure to azathioprine, as in IMURAN, particularly in combination with corticosteroids.

There have also been reports of spontaneous abortion following either maternal or paternal exposure.

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

Extra care in haematological monitoring is advised during pregnancy.

Breastfeeding

IMURAN and/or its metabolites, such as 6-MP, have been identified in the colostrum and breastmilk of women receiving treatment with azathioprine, as in IMURAN.

It is recommended that mothers receiving IMURAN should not breastfeed.

If a decision is made to breastfeed, the breastfed infant should be closely monitored for signs of immunosuppression, leukopenia, thrombocytopenia, hepatotoxicity, pancreatitis or other symptoms of 6-mercaptopurine exposure.

Fertility

The specific effect of azathioprine, as in IMURAN, therapy on human fertility is unknown but there are reports of successful fatherhood/motherhood after receiving treatment. Several studies report that azathioprine, as in IMURAN, at standard doses does not appear to affect male 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.

4.7. Effects on ability to drive and use machines

IMURAN has a moderate influence on the ability to drive and use machines.

Since adverse reactions such as dizziness and retinopathy have been reported in patients receiving IMURAN, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that IMURAN does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

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 most important adverse reactions include bone marrow depression, most frequently expressed as leukopenia, thrombocytopenia or anaemia; viral, fungal and bacterial infections; life-threatening liver injury; hypersensitivity, Stevens- Johnson syndrome and toxic epidermal necrolysis

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Viral, fungal and bacterial infections in transplant patients receiving IMURAN in combination with immunosuppressants	Viral, fungal and bacterial infections in other patient populations, cases of JC virus associated PML have been reported following the use of IMURAN in combination with other immunosuppressants	Protozoal and uncommon bacterial infections
Neoplasm benign, malignant and unspecified (including cysts and polyps)		Neoplasms including lymphoproliferative disorders, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*, acute myeloid leukaemia and myelodysplastic syndrome	Hepatosplenic T-cell lymphoma

Blood and the lymphatic system disorders	Leukopenia, bone marrow depression, thrombocytopenia	Anaemia, agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, bone marrow failure, erythroid hypoplasia	
Immune system disorders		Hypersensitivity (including skin rashes, pruritus and erythema, often of an area previously irradiated), erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)	Anaphylaxis
Metabolism and nutrition disorders			Hyperphosphataemia, anorexia
Nervous system disorders			Headache, dizziness
Eye disorders			Retinopathy
Cardiac disorders			Cardiac dysrhythmia
Vascular disorders			Hypotension, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders		Reversible pneumonitis	Pulmonary oedema
Gastrointestinal disorders	Nausea	Pancreatitis, colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population	Vomiting, stomatitis, mouth ulceration, oesophagitis, abdominal pain, intestinal haemorrhage, ulceration, peritoneal haemorrhage
Hepatobiliary disorders		Cholestasis (biliary stasis) and cholestasis of pregnancy, life-threatening liver injury	Disturbed liver functions, cholestatic jaundice, toxic hepatitis
Skin and subcutaneous tissue disorders		Alopecia	Vesicant or irritant effects on the skin and mucous membranes, pigmentation of the skin and nails, acute febrile neutrophilic dermatosis (Sweet's syndrome), photosensitivity
Musculoskeletal and connective tissue disorders			Muscular pains, arthralgia
Renal and urinary disorders			Hyperuricaemia and acute renal failure due to uric acid nephropathy

Reproductive system and breast disorders			Suppression of ovarian and testicular function with amenorrhoea and inhibition of spermatogenesis
Congenital and familial/genetic disorders			Chromosomal abnormalities
General disorders and administrative site conditions			Medicine fever, serum sickness, malaise, fever, rigors, weakness
Investigations		Liver function test abnormal (elevated serum bilirubin levels)	Persistent negative nitrogen balance

c) Description of selected adverse reactions

Infections and infestations

Patients receiving azathioprine, as in 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 (see section 4.4).

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Patients receiving immunosuppressive therapy, including IMURAN, are at an increased risk of developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and nonmelanoma), sarcomas, (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ.* The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

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

Blood and lymphatic system disorders

Azathioprine, as in IMURAN, may be associated with a dose-related, generally reversible, depression of bone marrow function, most frequently expressed as leukopenia, 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 (see section 4.4).

Immune system disorders

Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following administration of azathioprine, as in IMURAN. Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, vasculitis, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis.

In many cases, rechallenge has confirmed an association with azathioprine, as in IMURAN.

Immediate withdrawal of IMURAN 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 should be carefully considered on an individual basis.

Gastrointestinal disorders

Some patients experience nausea when first given IMURAN. With oral administration, nausea appears to be relieved by administering the tablets after meals. However, administration of IMURAN tablets after meals may reduce oral absorption, therefore monitoring for therapeutic efficacy should be considered after administration in this way (see section 4.2 and section 5.2).

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 IBD. The possibility that exacerbation of symptoms might be medicine-related should be borne in mind when treating such patients.

Pancreatitis has been reported in a small percentage of patients on azathioprine, as in IMURAN therapy, particularly in renal transplant patients and those diagnosed as having IBD.

There are difficulties in relating the pancreatitis to the administration of one particular medicine, although re-challenge has confirmed an association with IMURAN on occasions.

Hepatobiliary disorders

Cholestasis and deterioration of liver function have occasionally been reported in association with azathioprine, as in IMURAN, therapy and are usually reversible on withdrawal of therapy. This may be associated with symptoms of a hypersensitivity reaction (see section 4.4).

Life-threatening hepatic damage associated with chronic administration of azathioprine, as in IMURAN, 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, as in IMURAN, has resulted in either a temporary or permanent improvement in liver histology and symptoms.

Skin and subcutaneous tissue disorders

Hair loss has been described on a number of occasions in patients receiving azathioprine, as in IMURAN, and other immunosuppressive medicines. In many instances the condition resolved spontaneously despite continuing therapy.

The relationship between alopecia and IMURAN treatment is uncertain.

d) Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to: **SAHPRA** via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdose with IMURAN and result from bone marrow depression which may be maximal after 9 to 14 days. These signs are more likely to 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, as in IMURAN. The immediate toxic effects of this overdose were nausea, vomiting and diarrhoea, followed by mild leukopenia and mild abnormalities in liver function. Recovery was uneventful.

Treatment

Treatment is symptomatic and supportive. As there is no specific antidote, blood counts should be closely monitored and general supportive measures, together with appropriate blood transfusion, instituted if necessary. Active measures (such as the use of activated charcoal) may not be effective in the event of azathioprine overdose unless the procedure can be undertaken within 60 minutes of ingestion.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, Immunosuppressants.

ATC code: L04AX01

Mechanism of action

Azathioprine, a derivative of mercaptopurine, is an antimetabolite of the purine class and possesses immunosuppressive properties.

Azathioprine is a pro-drug of 6-MP. 6-MP is inactive but acts as a purine antagonist and requires cellular uptake and intracellular anabolism to thioguanine nucleotides (TGNs) for immunosuppression. The TGNs and other metabolites (e.g. 6-methyl-mecaptopurine ribonucleotides) inhibit *de novo* purine synthesis and purine nucleotide interconversions. The TGNs are also incorporated into nucleic acids and this contributes to the immunosuppressive effects of the medicine. Other potential mechanisms of azathioprine include the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response. Because of these mechanisms, the therapeutic effect of azathioprine may be evident only after several weeks or months of treatment.

The activity of the methylnitroimidazole moiety, a metabolite of azathioprine but not 6-MP, has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP.

Plasma levels of azathioprine and 6-MP do not correlate well with the therapeutic efficacy or toxicity of azathioprine, and therefore have no prognostic value.

5.2. Pharmacokinetic properties

Absorption

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

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

Distribution

The volume of distribution at steady state (V_{dss}) of azathioprine is unknown. The mean (± SD) apparent V_{dss} of 6-MP is 0,9 (± 0,8) L/kg, although this may be an underestimate because 6-MP is cleared throughout the body (and not just in the liver).
Approximately 30 % of azathioprine is protein bound.

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

Biotransformation

Azathioprine is rapidly broken down *in vivo* by glutathione-S-transferase into 6-MP and a methyl-nitroimidazole moiety. The 6-MP readily crosses cell membranes and is extensively metabolised by many multi-step pathways to active and inactive metabolites, with no one enzyme predominating. Because of the complex metabolism, inhibition of one enzyme does not explain all cases of lack of efficacy and/or pronounced myelosuppression. The predominant enzymes responsible for the metabolism of 6-MP or its downstream metabolites are: the polymorphic enzyme thiopurine S-methyltransferase (TPMT) (see section 4.4), xanthine oxidase (see section 4.5), inosine monophosphate dehydrogenase (IMPDH) (see section 4.5), and hypoxanthine guanine phosphoribosyl transferase (HPRT). Additional enzymes involved in the formation of active and inactive metabolites are: guanosine monophosphate synthetase (GMPS, which form TGNs) and inosine triphosphate pyrophosphatase (ITPase). Azathioprine itself is also metabolised by aldehyde oxidase to form 8-hydroxy azathioprine, which may be active. There are also multiple inactive metabolites formed via other pathways.

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

Thiopurine S-Methyl transferase

TPMT activity is inversely related to red blood cell 6-MP derived thioguanine nucleotide concentration, with higher thioguanine nucleotide concentrations resulting in greater reductions in white blood cell and neutrophil counts. Individuals with TPMT deficiency develop very high cytotoxic thioguanine nucleotide concentrations.

Genotypic testing can determine the allelic pattern of a patient. Currently, three alleles—TPMT*2, TPMT*3A and TPMT*3C—account for about 95 % of individuals with reduced levels of TPMT activity. Approximately 0,3 % (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity. Approximately 10 % of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90 % of individuals have normal TPMT activity with two functional alleles. There may also be a group of approximately 2 % who have very high TPMT activity. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in red blood cells and can also be informative (see section 4.4).

NUDT15 R139C (NUDT15 c.415C>T) Variant

Recent studies indicate that a strong association exists between the NUDT15 variant NUDT15 c.415C>T (p.Arg139Cys) (also known as NUDT15 R139C (rs116855232)), which is thought to lead to a loss of function of the NUDT15 enzyme, and thiopurine-mediated toxicity such as leukopenia and alopecia. The frequency of NUDT15 c.415C>T has an ethnic variability of 9,8 % in East Asians, 3,9 % in Hispanics, 0,2 % in Europeans and 0,0 % in Africans, indicating an increased risk for the Asian population. Patients who are NUDT15 variant homozygotes (NUDT15 T risk alleles) are at an excessive risk of thiopurine toxicity compared with the C homozygotes.

Reduced thiopurine doses for patients who carry the NUDT15 variants may decrease their risk of toxicity. Therefore, genotypic analysis determining NUDT15 genotype should be determined for all patients, including paediatric patients, prior to initiating thiopurine treatment (see section 4.2). The prescribing physician is advised to establish whether dose reduction is required based on patient response to treatment as well as their genetic profile.

Patients with variants in both the NUDT15 and TPMT enzymes are significantly less tolerant of thiopurines than those with risk alleles in only one of these two genes.

The precise mechanism of NUDT15-associated thiopurine-related toxicity is not understood.

Elimination

After oral administration of 100 mg 35S-azathioprine, 50 % of the radioactivity was excreted in the urine over 24 hours and 12 % in the faeces after 48 hours. In the urine, the major compound was the inactive oxidised metabolite thiouric acid. Less than 2 % was excreted in the urine as azathioprine or 6-MP. Azathioprine has a high extraction ratio with a total clearance greater than 3 L/min in normal volunteers. There are no data on the renal clearance or half-life of azathioprine. The renal clearance of 6-MP and the half-life of 6-MP are 191 mL/min/m^2 and 0,9 hour respectively.

Mercaptopurine, a metabolite of azathioprine, has been identified in the colostrum and breastmilk of women receiving azathioprine treatment.

Special patient populations

Elderly

No specific studies have been carried out in the elderly.

Overweight paediatric population

In a US clinical study, 18 children (aged 3 to 14 years) were evenly divided into two groups; either a weight to height ratio above or below the 75th percentile. Each child was on maintenance treatment of 6-MP and the dosage was calculated based on their body surface area. The mean AUC (0-∞) in the group above the 75th percentile was 2,4 times lower than

that for the group below the 75th percentile. Therefore, children considered to be overweight may require azathioprine doses at the higher end of the dose range and close monitoring of response to treatment is recommended.

Renal impairment

Studies with azathioprine have shown no difference in 6-MP pharmacokinetics in uremic patients compared to renal transplant patients. Since little is known about the active metabolites of azathioprine in renal impairment, consideration should be given to reducing the dosage in patients with impaired renal function (see section 4.2). Azathioprine and/or its metabolites are eliminated by haemodialysis, with approximately 45 % of radioactive metabolites eliminated during dialysis of eight hours.

Hepatic impairment

A study with azathioprine was performed in three groups of renal transplant patients: those without liver disease, those with hepatic impairment (but no cirrhosis) and those with hepatic impairment and cirrhosis. The study demonstrated that 6-MP exposure was 1,6 times higher in patients with hepatic impairment (but no cirrhosis) and six times higher in patients with hepatic impairment and cirrhosis, compared to patients without liver disease. Therefore, consideration should be given to reducing the dosage in patients with impaired hepatic function (see section 4.2).

5.3. Preclinical safety data

Teratogenicity

Studies in pregnant rats, mice and rabbits using azathioprine, as in IMURAN, in dosages from 5 to 15 mg/kg body weight/day over the period of organogenesis have shown varying degrees of foetal abnormalities. Teratogenicity was evident in rabbits at 10 mg/kg body weight/day. Studies with pregnant rabbits and Swiss-Webster mice have shown that

azathioprine produces resorptions and skeletal anomalies even when administered as late as the midpoint of gestation.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

IMURAN:

Lactose monohydrate, magnesium stearate, maize starch, pregelatinised starch, stearic acid.

Film-coating: Methylhydroxypropylcellulose (hypromellose), polyethylene glycol 400 (macrogol).

IMURAN INJECTION:

Sodium hydroxide (for pH adjustment)

Water for injection.

6.2. Incompatibilities

IMURAN: Not applicable.

IMURAN INJECTION should not be mixed with other medicines or fluids, except those specified in section 6.6.

Addition of reconstituted IMURAN INJECTION to any other infusion or intravenous admixture containing medicines is not recommended.

6.3. Shelf life

IMURAN: 60 months.

IMURAN INJECTION: 36 months. Reconstituted IMURAN INJECTION is stable for up to 6 days at ambient or refrigerator temperatures.

6.4. Special precautions for storage

Store at or below 25 °C.

Keep dry and protect from light.

Keep in original packaging until required for use.

6.5. Nature and contents of container

IMURAN: White opaque polyvinyl chloride and aluminium blisters of 100 film-coated tablets are packed into preprinted cartons together with a leaflet.

IMURAN INJECTION: Glass vials containing the equivalent of 50 mg azathioprine as its sodium salt, freeze dried. The vials are fitted with a light grey bromobutyl rubber stopper and a polypropylene with aluminium flip-off seal. The sealed vial is packed into a preprinted carton together with a leaflet.

Not all packs and pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

IMURAN tablets:

Safe handling

Film-coated tablets should not be divided, and provided the coating is intact, no additional precautions are required when handling IMURAN tablets.

Disposal

IMURAN tablets should be disposed of in a manner appropriate to the prevailing local regulatory requirements for the destruction of dangerous substances.

IMURAN INJECTION:

Safe handling

Healthcare professionals who handle IMURAN INJECTION should follow guidelines for the handling of cytotoxic medicines 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 cytotoxic medicines.

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 and medicine and, preferably, reserved solely for cytotoxic preparations. Where operator 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 the 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.

Reconstitution and dilution of IMURAN INJECTION

Precautions should always be taken when handling IMURAN INJECTION.

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

IMURAN INJECTION is given intravenously. The contents of each vial should be reconstituted by the addition of 5 ml to 15 ml of Water for Injection BP. The reconstituted solution is stable for up to six days when stored between 5 °C and 25 °C.

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 INJECTION is stable for up to 24 h at room temperature (15 °C to 25 °C):

- 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 Injection BP and should be diluted as specified above.

When IMURAN INJECTION is reconstituted as directed, it is a very irritant solution with a pH of 10 to 12.

When the reconstituted solution is diluted as directed, 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) and must therefore be given slowly, preferably by injecting it into the tubing of an intravenous saline or glucose saline drip while the fluid is being infused.

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.

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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBERS

IMURAN: D/26/98

IMURAN INJECTION: H2746 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

IMURAN: 10 May 1974

IMURAN INJECTION: Old medicine

10. DATE OF REVISION OF TEXT

23 February 2026

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

Botswana: IMURAN TABLETS 50 mg: BOT1703039 S2

Namibia: IMURAN TABLETS 50 mg: NS2 90/26/00580