IMURAN

Azathioprine

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg or 50 mg of the active ingredient azathioprine.

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

PHARMACEUTICAL FORM

Tablet or film-coated tablet.

Powder for solution for injection/infusion.

CLINICAL PARTICULARS

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. It also reduces the corticosteroid requirements of renal transplant recipients.

IMURAN, either alone or more usually in combination with corticosteroids and/or other drugs and procedures, has been used with clinical benefit (which may include reduction of dosage or discontinuation of corticosteroids) in a proportion of patients suffering from the following:

severe rheumatoid arthritis

systemic lupus erythematosus

dermatomyositis and polymyositis

auto-immune chronic active hepatitis

pemphigus vulgaris

polyarteritis nodosa

auto-immune haemolytic anaemia

chronic refractory idiopathic thrombocytopenic purpura

Dosage and Administration

IMURAN tablets should be administered at least 1 hour before or 3 hours after food or milk (see Pharmacological Properties: Pharmacokinetics; Absorption).

***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 i.v. route.**

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 Instructions for Use/Handling - Reconstitution and dilution of IMURAN injection)*, the pH of the resulting solution may be expected to be within the range of 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 Instructions for Use/Handling - Reconstitution and dilution of IMURAN injection).*

Care must be taken to avoid perivenous injection, which may produce tissue damage.

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

- **Adults**

Transplants

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

Maintenance dosage should range from 1 to 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.

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.

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*. 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.

- **Children**
  - Overweight children

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 Pharmacological Properties: Special Patient Populations; Overweight children).

Transplants and Other Indications

See Dosage and Administration – Adults.

Elderly

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.

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

- **Renal impairment**

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

- **Hepatic impairment**

In patients with hepatic insufficiency, dosages should be given at the lower end of the normal range (see Warnings and Precautions and Pharmacological Properties: Special Patient Populations; Hepatic Impairment).

- ***Drug interactions***

The principal pathway for detoxification of *IMURAN* is inhibited by allopurinol. In patients receiving *IMURAN*, the concomitant administration of allopurinol will require a reduction in dose to approximately 1/3 to 1/4 of the usual dose of *IMURAN*. Subsequent adjustment of doses of *IMURAN* should be made on the basis of therapeutic response and any toxic effects *(see Interactions*).

- **TPMT-deficient patients**

Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe *IMURAN* toxicity from conventional doses of *IMURAN* and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established (see Warnings and Precautions: Monitoring and Pharmacokinetics).

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 Warnings and Precautions: Monitoring and Pharmacokinetics).

Contraindications

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

Warnings and Precautions

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 3 months after the end of their treatment with azathioprine (see Interactions).

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

Hypersensitivity

Patients suspected to have previously presented a hypersensitivity reaction to 6-mercaptopurine should not be recommended to use its pro-drug azathioprine, and vice-versa, unless the patient has been confirmed as hypersensitive to the culprit drug with allergological tests, and tested negative for the other.

Effects on fertility

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

Relief of chronic renal insufficiency by renal transplantation involving the administration of azathioprine has been accompanied by increased fertility in both male and female transplant recipients. 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 eight 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 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.

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of *IMURAN* and prone to developing rapid bone marrow depression following the initiation of treatment with *IMURAN*. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6-mercaptopurine (the active metabolite of *IMURAN*) in combination with other cytotoxics *(see Adverse Reactions*). Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is still necessary.

The dosage of *IMURAN* may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression (see Interactions: Cytostatic/ myelosuppressive agents).

Renal and/or hepatic impairment

It is impossible to relate plasma levels of *IMURAN* or 6-mercaptopurine to therapeutic efficacy or toxicity. Conversion of 6-thioinosinic acid to 6-thiouric acid by xanthine oxidase is not dependent on intact hepatic and/or renal function (see Dosage and Administration and Pharmacological Properties: Special Populations).

Nevertheless, it is recommended that the dosages used should be at the lower end of the normal range and that haematological response should be carefully monitored. Dosage should be further reduced if haematological toxicity occurs. Caution is necessary during the administration of *IMURAN* to patients with hepatic dysfunction, and regular complete blood counts and liver function tests should be undertaken. In such patients the metabolism of *IMURAN* may be impaired, and the dosage of *IMURAN* should therefore be reduced to the lower end of the recommended range. Dosage should be further reduced if hepatic or haematological toxicity occurs.

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, 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*.

IMURAN and long-wave ultraviolet light (UV) have been shown to have a synergistic clastogenic effect in patients treated with *IMURAN* for a range of disorders.

Carcinogenicity *(see Adverse Reactions)*

Patients receiving immunosuppressive therapy, including azathioprine 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 *IMURAN* is used alone or in combination with anti-TNF agents or other immunosuppressants. Although most reported cases occurred in the IBD population (un-licensed indication), there have also been cases reported outside of this population.

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.

Macrophage activation syndrome

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

Xanthine oxidase inhibitors

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

Neuromuscular agents

Special care is necessary when azathioprine is given concomitantly with neuromuscular acting agents like tubocurarine or succinylcholine *(see section 4.5)*. It can also potentiate the neuromuscular block that is produced by depolarising agents such as succinylcholine *(see section 4.5)*. Patients should be advised to inform their anaesthesiologist of their treatment with azathioprine prior to surgery.

Varicella Zoster Virus Infection *(see Adverse Reactions)*

Infection with varicella zoster virus (VZV; chickenpox and herpes zoster) may become severe during the administration of immunosuppressants. Caution should be exercised especially with respect to the following.

Before starting the administration of immunosuppressants, the prescriber should check to see if the patient has a history of VZV. Serologic testing may be useful in determining previous exposure. Patients who have no history of exposure should avoid contact with individuals with chickenpox or herpes zoster. If the patient is exposed to VZV, special care must be taken to avoid patients developing chickenpox or herpes zoster, and passive immunisation with varicella-zoster immunoglobulin (VZIG) may be considered.

If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.

Progressive Multifocal Leukoencephalopathy (PML)

PML, an opportunistic infection caused by the JC virus, has been reported in patients receiving *IMURAN* with other immunosuppressive agents. Immunosuppressive therapy should be withheld at the first sign or symptoms suggestive of PML and appropriate evaluation undertaken to establish a diagnosis (see Adverse Reactions).

Hepatitis B *(see Adverse Reactions)*

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. Local guidelines may be considered including prophylactic therapy with oral anti-HBV agents.

Interactions

Vaccines

The immunosuppressive activity of *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 3 months after the end of their treatment with azathioprine (see Warnings and Precautions).

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 *IMURAN* 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.

Effect of concomitant drugs on IMURAN

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 *IMURAN* and ribavirin; therefore co-administration is not advised (see Warnings and Precautions and Pharmacokinetics: Metabolism).

Cytostatic/myelosuppressive agents *(see Warnings and Precautions)*

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 trimethoprim/sulfamethoxazole.

There have been case reports suggesting that haematological abnormalities may develop due to the concomitant administration of *IMURAN* and ACE Inhibitors.

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

Neuromuscular agents

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 azathioprine reverses the neuromuscular blockade produced by d-tubocurarine, and show that azathioprine potentiates the neuromuscular blockade produced by succinylcholine *(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-mercaptopurine or *IMURAN*, the dose of 6-mercaptopurine and *IMURAN* should be reduced to 25% of the original dose (see Dosage and Administration: Drug Interactions).

Other xanthine oxidase inhibitors, such as febuxostat may decrease the metabolism of aza-thioprine. Concomitant admin-istration is not recommended as data are insufficient to determine an adequate dose reduction.

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 Warnings and Precautions).

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 *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 ob-served between azathioprine and infliximab. Patients receiving ongoing azathioprine experi-enced transient increases in 6-TGN (6-thioguanine nucleotide, an active metabolite of azathio-prine) levels and a decrease in the mean leukocyte count in the initial weeks following inflixi-mab infusion, which returned to previous levels after 3 months.

Effect of azathioprine on other drugs

Anticoagulants

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with *IMURAN*; therefore higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with *IMURAN*.

Pregnancy and Lactation

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.

Substantial transplacental and transamniotic transmission of azathioprine 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. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving *IMURAN*.

There have been reports of intra-uterine growth retardation, premature birth and low birth weight following maternal exposure to *IMURAN*, particularly in combination with corticosteroids. There have also been reports of spontaneous abortion following either maternal or paternal exposure.

Leucopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took *IMURAN* throughout their pregnancies. Extra care in haematological monitoring is advised during pregnancy.

6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving *IMURAN* treatment. It is recommended that mothers receiving *IMURAN* should not breastfeed.

Fertility

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

See Warnings and Precautions – Effects on fertility.

Effects on Ability to Drive and Use Machines

There are no data on the effect of *IMURAN* on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the drug.

Adverse Reactions

For *IMURAN*, there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication. The following convention has been utilised for the classification of frequency: Very common 1/10; common 1/100, <1/10; uncommon 1/1000 and <1/100; rare 1/10,000 and <1/100 ; very rare <1/10,000.

Infections and infestations

Very common: viral, fungal and bacterial infections in transplant patients receiving IMURAN in combination with other immunosuppressants.

Uncommon: viral, fungal and bacterial infections in other patient populations.

Patients receiving *IMURAN* alone or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection. Reactivation of varicella zoster virus, hepatitis B and other infectious agents are also uncommon. (see Warnings and Precautions).

Very rare: cases of JC virus associated PML have been reported following the use of azathioprine in combination with other immunosuppressants (see Warnings and Precautions).

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

Rare: neoplasms including lymphoproliferative disorders, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's), uterine cervical cancer *in situ*, acute myeloid leukaemia and myelodysplastic syndrome *(see Warnings and Precautions)*.

Patients receiving immunosuppressive therapy, including azathioprine 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.

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

Very rare: Hepatosplenic T-cell lymphoma (see Warnings and Precautions).

Blood and lymphatic system disorders

Very common: depression of bone marrow function; leucopenia.

Common: thrombocytopenia.

Uncommon: anaemia.

Rare: agranulocytosis, pancytopenia, aplastic anaemia, 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

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Replacement: 576545	
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Drawing Ref. Number: PE-PIL-007-01	
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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

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, erythema nodosum, myalgia, arthralgia, hypotension, renal dysfunction, hepatic dysfunction and cholestasis *(see Adverse Reactions - Hepato-biliary disorders)*.

In many cases, rechallenge has confirmed an association with *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 of *IMURAN* should be carefully considered on an individual basis.

Respiratory, thoracic and mediastinal disorders

Very rare: reversible pneumonitis.

Gastrointestinal disorders

Tablets:

Common: nausea

Uncommon: pancreatitis.

Very rare: colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population (un-licensed indication).

Some patients experience nausea when first given oral azathioprine. With oral administration, nausea appears to be relieved by administering the tablets after meals. However, administration of azathioprine tablets after meals may reduce oral absorption, therefore monitoring for therapeutic efficacy should be considered after administration in this way (see Clinical Pharmacology: Absorption)
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 (un-licensed indication). 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 (un-licensed indication). 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.

Rare: life-threatening liver injury.

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 Adverse Reactions - Immune system disorders)*.

Rare, but life-threatening hepatic damage associated with chronic administration of *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 *IMURAN* 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 *IMURAN* and other immunosuppressive agents. In many instances the condition resolved spontaneously despite continuing therapy. The relationship between alopecia and *IMURAN* treatment is uncertain.

Not known: Sweet's syndrome (acute febrile neutrophilic dermatosis).

Overdose

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with *IMURAN* and result from bone marrow depression, which may be maximal after 9 to 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 *IMURAN*. 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.

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 *IMURAN* overdose unless the procedure can be undertaken within 60 minutes of ingestion.

Gastric lavage has been used. Subsequent monitoring, including haematological monitoring, is necessary to allow prompt treatment of any adverse effects which may develop. 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 *IMURAN* is partially dialysable.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action

IMURAN is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down in vivo into 6-MP and 1-methyl-4-nitro-5-thiomidazole. 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid. *IMURAN* has an effect on both immunological reaction and tumour growth. Its major role has been as an agent for suppressing the immune response, and although the precise mechanism by which this effect is achieved is not known, the following mechanisms of action have been suggested:

i. The action of the released 6-MP as a purine antimetabolite.

ii. The possible blockade of -SH groups by alkylation.

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

iv. Damage to deoxyribonucleic acid (DNA) through incorporation of purine thioanalogues.

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

The activity of the methylnitroimidazole moiety, a metabolite of *IMURAN* 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.

Pharmacodynamic Effects

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

Pharmacokinetics

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 – 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) *(see* Pharmacokinetics: Metabolism). Azathioprine should be administered at least 1 hour before or 3 hours after food or milk (see Dosage and Administration).

Distribution

The volume of distribution at steady state (Vdss) of azathioprine is unknown. The mean (± SD) apparent Vdss 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.

Metabolism

Azathioprine is rapidly broken down in vivo into 6-MP by glutathione-S-transferase and a methylnitroimidazole moiety. The 6-MP readily crosses cell membranes and is extensively metabolized 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 Warnings and Precautions: Monitoring and Interactions: Aminosalicylates), xanthine oxidase (see Interactions: Allopurinol/oxipurinol/thiopurinol and Pharmacokinetics: Absorption), inosine monophosphate dehydrogenase (IMPDH) (see Interactions: Ribavirin), and hypoxanthine guanine phosphoribosyltransferase (HPGRT). 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 metabolized 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)

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.

It is recommended that consideration be given to either genotype or phenotype patients for TPMT. Phenotyping and genotyping methods are commercially available. The most common non-functional alleles associated with reduced levels of TPMT activity are TPMT*2, TPMT*3A and TPMT*3C. Patients with two nonfunctional alleles (homozygous) have low or absent TPMT activity and those with one non-functional allele (heterozygous) have intermediate activity. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions. TPMT testing may also be considered in patients with abnormal CBC results that do not respond to dose reduction. Early drug discontinuation in these patients is advisable. TPMT TESTING CANNOT SUBSTITUTE FOR COMPLETE BLOOD COUNT (CBC) MONITORING IN PATIENTS RECEIVING *IMURAN* (see Warnings and Precautions).

Elimination

After oral administration of 100mg 35S-azathioprine, 50% of the radioactivity was excreted in the urine over 24 hours and 12% in the faeces after 24 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 3L/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/m2 and 0.9 hr respectively.

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

Special Patient Populations

Elderly

No specific studies have been carried out in the elderly *(see Dosage and Administration)*.

Overweight children

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-∞) of 6-MP 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 (see Dosage and Administration).

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, dosages should be given at the lower endof the normal rang in patients with impaired renal function (see Dosage and Administration).

Azathioprine and/or its metabolites are eliminated by haemodialysis, with approximately 45% of radioactive metabolites eliminated during dialysis of 8 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-mercaptopurine exposure was 1.6 times higher in patients with hepatic impairment (but no cirrhosis) and 6 times higher in patients with hepatic impairment and cirrhosis, compared to patients without liver disease. Therefore, dosages should be given at the lower end of the normal range in patients with impaired hepatic function (see Dosage and Administration).

Pre-clinical Safety Data

Mutagenicity

Azathioprine was found to be mutagenic in a number of in vitro and in vivo genotoxicity assays

Carcinogenicity

Long-term carcinogenicity studies of azathioprine showed an increased incidence of lymphosarcomas, as well as epithelial tumours and carcinomas in mice and rats, respectively, at dosages of up to 2-fold the human therapeutic dose and at lower dosages in immunocompromised mice.

Reproductive toxicology

Studies in pregnant rats, mice and rabbits using azathioprine in dosages from 5 to 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablets:

Lactose Monohydrate, Maize Starch, Pregelatinised Starch, Magnesium Stearate, Stearic Acid, Water, Purified, Hypromellose, Macrogol 400

Injection:

Sodium hydroxide
Water for Injection (removed during processing).

The sodium ion content of the injection formulation is approximately 4.5 mg (0.2 mEq).

Incompatibilities

None reported for *IMURAN* tablets.

IMURAN injection should not be mixed with other drugs or fluids, except those specified in *Instructions for Use/Handling*.

Shelf-Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Store below 30°C.

Protect from light.

Injection:

Keep dry.

Nature and Contents of Container

White opaque PVC/aluminium foil blister packs.

Tablets:

Pack of 100's.

Injection:

IMURAN injection is supplied as a white freeze-dried powder in a neutral glass vial with a rubber closure and aluminium collar.

Instructions for Use/Handling

Tablets:

Safe handling

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

Provided that the film-coating is intact, there is no risk in handling film-coated *IMURAN* tablets. Film-coated *IMURAN* tablets should not be divided and, provided the coating is intact, no additional precautions are required when handling them.

Disposal

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

Injection:

Safe handling

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 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 *(see Instructions for Use/ Handling - Safe handling)*.

No antimicrobial preservative is included, therefore reconstitution and dilution must be carried out under full aseptic conditions, preferably immediately before use. Any unused solution should be discarded *(see Disposal)*.

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 five 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, azathioprine is stable for up to 24 hours 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 of pH 8.0 to 9.5 (the greater the dilution, the lower the pH).

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.

Not all presentations are available in every country.

Name and address of Manufacturers

Aspen Port Elizabeth (Pty) Ltd, Corners of Fairclough Rd and Gibaud Rd, Korsten, Port Elizabeth 6020, South Africa and Excella GmbH & Co. KG, Nurnberger Str. 12,90537 Feucht, Germany

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ASPEN Artwork Panel

AW Version:	Page:
5	2 of 2

New Item Code: 576882

Replacement: 576545

Market: Singapore

Product Name: Imuran

Number of Colours: 1

BLACK

Manufacturing Site: Aspen Port Elizabeth

Drawing Ref. Number: PE-PIL-007-01

Drawing Version: 01

Originated by: Sami Hajredin

Originated at: ASPEN Dandenong

Originated on: 30-JUN-2021

Amended on: 01-APR-2022

160 mm Measuring Bar

ASPEN Artwork Panel • May 2013 • Version 5