7337566-9191

Imuran*

Tablats and Injection

To the Medical and Pharmaceutical Professions

Presentation

Tablets

Yellow, round, biconvex, film-coated tablets, scored and impressed 'GX/CH1' and containing 50 mg Azathioprine BP in each tablet.

Orange, round, biconvex, film-coated tablets, impressed 'GX/EL5' and containing 25 mg Azathioprine BP in each tablet.

Injection

A yellow to amber, sterile, freeze dried powder supplied in clear glass vials containing 50 mg Azathioprine BP as the sodium salt

The sodium ion content is approximately 4.5 mg (4.5 mEq)

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.

Therepeutic 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 immunosuppressant agents and procedures, is indicated to enhance the survival of organ transplants, such as renal transplants, cardiac transplants, and hepatic transplants; and to reduce the corticosteroid requirements of renal transplant recipients.

Imuran, 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, raconstitution and administration

Imuran Injection should be used ONLY when the oral route impractical, and should be discontinued as soon as oral therapy is tolerated. It must be administered only by the intravenous route

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

Dosage in transplentation – edults end children

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

Maintenance dosage should range from 1-4 mg/kg bodyweight/day and must be adjusted according to clinical requirements and haematological tolerance

Evidence indicates that Imuran therapy should be maintained indefinitely, even if only low doses are necessary, because of the risk of graft rejection.

Dosage in other conditions – adults and children

In general, starting dosage is from 1-3 mg/kg bodyweight/day, and should be adjusted, within these limits, depending on the clinical response (which may not be evident for weeks or months) and haematological tolerence

When therapeutic response is evident, consideration should be given to reducing the maintenance dosage to the lowest level compatible with the maintenance of that response. If no improvement occurs in the patient's condition within 3 months, consideration should be given to withdrawing **Imuran.**

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.

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

Use in the elderly (see **Renal and /or hepatic insufficiency**)

There is limited experience of the administration of **Imuran** to elderly patients. Although the available data do not provide evidence that the incidence of side effects among elderly patients is higher than that among other patients being 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

Reconstitution and dilution of **Imuran** Injection (see **Appendix**)

Precautions should always be taken when handling **Imuran** Injection (see Safe handling of **Imuran**)

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.

The contents of each vial should be reconstituted by the addition of 5 ml to 15 ml of Water for Injections BP

The reconstituted solution is stable for up to 5 days when stored between 5°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** 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) and Glucose (4.0% w/v) Intravenous Infusion BP

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

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

Imuran Injection should not be mixed with other drugs or fluids, except those specified above, before administration.

Administration of Imuran Injection

Imuran Injection, when reconstituted as directed, is a very irritant solution with a pH of 10 – 12

When the reconstituted solution is diluted as directed above, 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 is not practicable, the reconstituted solution should be injected slowly over a period of not less than one minute and followed immediately by not less than 50 ml of one of the recommended infusion solutions

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

Safe handling of Imuran

Health professionals who handle **Imuran** Injection should follow guidelines for the handling of cytotoxic drugs according to prevailing local recommendations and/or regulations (for example, the Royal Pharmaceutical Society of Great Britain Working Party Report on the handling of Cytotoxic Drugs, 1983)

Detailed precautions for handling **Imuran** Injection are given in the Appendix

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

Contra-indications

Imuren is contra-indicated in patients known to be hypersensitive to azathioprine. Hypersensitivity to 6-mercaptopurine (6-MP) should alert the prescriber to probable hypersensitivity to **Imuran**

Imuran therapy should not be initiated in patients who may be pregnant, or who are likely to become pregnant in the near future (see **Precautions and warnings**).

Precautions and warnings

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 duretion of therapy.

It is suggested that during the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than 3 months

Patients receiving **Imuran** should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestetions of bone marrow depression.

There are rare individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with **Imuran**

Renal and/or hepatic insufficiency

It has been suggested that the toxicity of **Imuran** may be enhanced in the presence of renal insufficiency, but controlled studies have not supported this suggestion. 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.

Limited evidence suggests that **Imuran** is not beneficial to patients with hypoxanthine-guaninephosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). Therefore, given the abnormal metabolism in these patients, it is not prudent to recommend that these patients should receive **Imuran**.

Mutegenicity

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 **Imuren**. Azathioprine and longwave ultraviolet light have been shown to have synergistic clastogenic effect in patients treated with azathioprine for a range of disorders

Teratogenicity

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

Evidence of the teratogenicity of **Imuran** in a man is equivocal. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving **Imuran**

Carcinogenicity

There is no clear evidence that, in therapeutic doses, **Imuran** per se is oncogenic in man, but the issues remains unresolved.

The risk of developing post-transplant lymphomas is increased in patients who receive aggressive treatment with immunosuppressive drugs, and such therapy should be maintained at the lowest effective levels. The increased risk of developing lymphomas in immunosuppressed rheumatoid arthritis patients compared with the general population appears to be related to at least in part to the disease itself. There have been reports of increased incidences of skin cancers in renal transplant recipients compared with the general population, which may be in part associated with immunosuppressive therapy

Use in pregnancy and lactation

Imuran should not be given during pregnancy without careful assessment of risk versus benefit

Azathioprine and/or its metabolites have been found in low concentrations in foetal blood and amniotic fluid after maternal administration of azathioprine.

Leucopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mother took azathioprine 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 azathioprine treatment

Effects on fertility

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

Adverse reactions

Hypersensitivity reactions

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, myalgia, arthralgia, renal dysfunction and hypotension. In many cases, rechallenge has confirmed an association with **Imuren**.

Immediate withdrawal of azathioprine and institution of circulatory support where appropriate have led to recovery in the majority of cases. Other marked underlying pathology has contributed to the very rare deaths reported.

Following a hypersensitivity reaction to **Imuran**, the necessity for continued administration of **Imuran** should be carefully considered on an individual basis.

Haematopoiesis

Therapeutic use of **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

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.

Failure to reduce the dosage of **Imuran** in the presence of allopurinol can result in severe bone marrow suppression and pancytopenia

Susceptibility to infection

Transplant recipients receiving **Imuran** and corticosteroids have shown increased susceptibility to viral, fungal and bacterial infections evident both in skin and other body systems. The use of **Imuran** in other conditions does not appear to give rise to a marked increase in susceptibility to such infections

Gastro-intestinal reactions

A minority of patients experience nausea when first given **Imuran**. This appears to be relieved by administering the tablets after meals.

Serious complications, including colitis, diverticulitis and bowel perforation, have been described in transplant recipients receiving immunosuppressive therapy. However, the aetiology is not clearly established and high-dose corticosteroids may be implicated. Severe diarrhoea, recurring on rechallenge, has been reported in patients treated with **Imuran** for inflammatory bowel disease. The possibility that exacerbation of symptoms might be drug related should be borne in mind when treating such patients.

Pancreatitis has been reported in a small percentage of patients on **Imuran** therapy, particularly in renal transplant patients and those diagnosed as having inflammatory bowel disease. There are difficulties in relating the pancreatitis to the administration of one particular drug, although rechallenge has confirmed an association with **Imuran** on occasions

Cholestasis and deterioration of liver function have occasionally been reported in association with **Imuran** therapy and are usually reversible on withdrawal of therapy

A rare, but lifethreatening hepatic veno-occlusive disease associated with chronic administration of azathioprine has been described, primarily in transplant patients. In some cases withdrawal of azathioprine has resulted in either a temporary or permanent improvement in liver histology and symptoms

Pulmonary reactions

Reversible pneumonitis has been described very rarely

Alopecia

Hair loss has been described on a number of occasions in patients receiving azathioprine and other immunosuppressive agents. In many instances the condition resolved spontaneously despite continuing therapy. The relationship between alopecia and azathioprine treatment is uncertain.

Drug interactions

Allopurinol/oxipurinol/thiopurinol

Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol which results in reduced conversion of biologically active 6 thioinosinic acid to biologically inactive 6-thiouric acid. When allopurinol, oxipurinol and/or thiopurinol are given concomitantly with 6-mercaptopurine or azathioprine, the dose of 6-mercaptopurine and azathioprine should be reduced to one-quarter of the original dose

Neuromuscular blocking agents

Imuran can potentiate the neuromuscular blockade produced by depolarising agents such as succinylcholine and can reduce the blockade produced by non-depolarising agents such as tubocurarine

There is considerable variation in the potency of this interaction

Warfarin

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

Cytostatic/myelosuppressive agents

Where possible, concomitant administration of cytostatic drugs, or drugs which may have a myelosuppressive effect, such as penicillamine, should be avoided. There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between **Imuran** and co trimoxazole

There has been a case report suggesting that haematological abnormalities may develop due to the concomitant administretion of **Imuran** and captopril

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

Other interactions

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

Vaccines

The immunosuppressive activity of **Imuran** could result in an atypical and potentially deleterious response to live vaccines and so the administration of live vaccines to patients receiving **Imuran** therapy is contraindicated on theoretical grounds

A diminished response to killed vaccines is likely and such a response to hepatitis B vaccine has been observed among patients treated with a combination of azathioprine and corticosteroids

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 anticapsular specific antibody concentration

Overdosage

Symptoms and signs

Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with **Imuran** and result from bone marrow depression which may be maximal after 9-14 days. These signs are more likely to be manifest following chronic overdosage, rather than alter a single acute overdose. There has been a report of a patient who ingested a single overdose of 7.5 g of azathioprine. The immediate toxic effects of this overdose were nausea, vomiting and diarrhoea, followed by mild leucopenia and mild abnormalities in liver function. Recovery was uneventful

Treatment

There is no specific antidote. Gastric lavage has been used. Subsequent monitoring, including haematological monitoring, is necessary to allow prompt treatment of any adverse effects which may develop. The value of dialysis in patients who have taken an overdose of **Imuran** is not known, though azathioprine is partially dialysable.

Pharmaceutical precautions

Tablets: Store below 25°C and protect from light

Injection: Store below 25°C in a dry place and protect from light

Furthar information

Pharmacology

Azathioprine is an imidazole derivative of 6-mercaptopurine (6-MP). It is rapidly broken down in vivo into 6-MP and a methylnitroimidazole moiety. The 6-MP readily crosses cell membranes and is converted intracellularly into a number of purine thioanalogues, which include the main active nucleotide, thioinosinic acid. The rate of conversion varies from one person to another. Nucleotides do not traverse cell membranes and therefore do not circulate in body fluids Irrespective of whether it is given directly or is derived in vivo from azathioprine, 6 MP is eliminated mainly as the inactive oxidised metabolite thiouric acid. This oxidation is brought about by xanthine oxidase, an enzyme which is inhibited by allopurinol. The activity of the methylnitroimidazole moiety has not been defined clearly. However, in several systems it appears to modify the activity of azathioprine as compared with that of 6-MP Determinations of plasma concentrations of azathioprine or 6-MP have no prognostic value as regards effectiveness or toxicity of these compounds

Mode of action

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

1. the release of 6-MP which acts as a purine antimetabolite
2. the possible blockade of –SH groups by alkylation
3. the inhibition of many pathways in nucleic acid biosynthesis, hence preventing proliferation of cells involved in determination and amplification of the immune response.
4. damage to deoxyribonucleic acid (DNA) through incorporation of purine thio-analogues

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

Imuran appears to be well absorbed from the upper gastro-intestinal tract.

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

Plasma levels of azathioprine and 6-mercaptopurine do not correlate well with the therapeutic efficacy or oxicity of **Imuran.**

Shelf Life

The expiry date is indicated on the packaging.

Appendix

Safe handling of Imuran* Injection

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

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 hightemperature 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

HIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

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