IMURAN
Azathioprine

1. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 50 mg of the active ingredient azathioprine.

2. PHARMACEUTICAL FORM
Film-coated tablet.

3. CLINICAL PARTICULARS
3.1 Indications
IMURAN is indicated for the treatment of patients who have received an organ transplant.

IMURAN has a significant therapeutic effect in a proportion patient suffering from chronic active hepatitis, severe rheumatoid arthritis, systemic lupus erythematosus (SLE), dermatomyositis, pemphigus vulgaris, polyarteritis nodosa, acquired haemolytic anemia, idiophatic thrombocytophenic purpura.

IMURAN is used in conditions other than transplantation when:
a) they are refractory to corticosteroids alone, or
b) they are controlled by corticosteroids in dosages producing or likely to produce severe side effects and the primary aim is to reduce the requirements of steroids, or
c) corticosteroids are contraindicated.

In pemphigus and rheumatoid arthritis *IMURAN* has been shown to have significant therapeutic activity when used without corticosteroids. In other conditions or where local registration authority approval has not yet been given for a particular condition, the use of *IMURAN* must be regarded as experimental. The risk as associated with therapy with *IMURAN* should be consider against the severity of patient's condition and the prospects of therapeutic benefit.

3.2 Posology and Method Administration
Adults and Children
In Transplants:
In renal transplantation the dose of *IMURAN* required to prevent rejection and minimize toxicity will vary with individual patients; this necessitates careful management. Initial dose usually 3 to 5 mg/kg daily, beginning at the time of transplant. *IMURAN* is usually given as a single daily dose on the day of, and in a minority of cases to three days before transplantation. *IMURAN* is often initiated with the intravenous administration of the sodium salt, with the subsequence use of film-coated tablets (at the same dose level) after post-operative period. Intravenous administration of the sodium salt is indicated only in patients unable to tolerate oral medications. Dose reduction to maintenance levels of 1 to 3 mg/kg daily is usually possible. The dose of *IMURAN* should not be increased to toxic levels because of threatened rejection. Discontinuation may be necessary for severe haematologic or other toxicity, even if rejection of hemograft may be a consequence of drug withdrawal.

Therapy with *IMURAN* should be maintained indefinitely unless positive contraindications should arise. Sometime only a very low dose is necessary if therapy is discontinued even after a period of years there is a high risk of graft rejection within a few weeks. In other conditions the dosage and duration of treatment may vary according to the condition, its severity and the clinical response obtained.

A therapeutic response may not be evident a few days or even weeks after initiation of therapy. If no improvement occurs in the patient's condition within three months, consideration should be given to withdrawing *IMURAN*.

For the treatment of most conditions the starting dose is 2 to 2.5 mg/kg orally which should be reduced if haematological or other complications occur.

In chronic active hepatitis the dose is 1 to 1.5 mg/kg/day orally. In rheumatoid arthritis lower doses can be effective.

3.3 Contraindications

Contraindicated in patients known to be hypersensitive to the active substance azathioprine or to any of the excipients listed in section 5.1. Hypersensitivity to 6-mercaptopurine should alert the prescriber to probable hypersensitivity to azathioprine.

3.4 Special Warnings and Precautions for Use
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 3.5*).

Co-administration of ribavirin and azathioprine is not advised. Ribavirin may reduce efficacy and increase toxicity of azathioprine (*see section 3.5*).

Monitoring
There are potential hazards in the use of azathioprine. 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.

Azathioprine may be given long-term unless the patient cannot tolerate the preparation. Withdrawal of an effective dose in certain instances e.g. SLE with nephritis, may result in a serious relapse of the condition.

In other instances, such as rheumatoid arthritis and certain haematological conditions treatment may be withdrawn after a suitable interval without any ill-effect. Withdrawal should always be gradual process perform under close supervision.

In the presence of severe renal or hepatic impairment, careful monitoring is initially required, since the dosage of azathioprine may have to be reduced.

Patients receiving azathioprine should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestations of bone marrow depression. Bone marrow suppression is reversible if azathioprine is withdrawn early enough.

Azathioprine 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 azathioprine immediately if jaundice becomes apparent.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine therapy (*see section 3.6*). Monitoring of 6-methyl mercaptopurine (6-MMP) should be considered in the presence of pruritus with elevated maternal total serum bile acids levels in second trimester of pregnancy to establish early diagnosis and minimise impact on the foetus. If cholestasis of pregnancy occurs, case by case assessment is necessary considering the risk-benefit profile of the product (potential withdrawal/dose reduction).

Thiopurine Methyltransferase (TPMT)
There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with azathioprine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. Also, a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics (*see section 3.8*). 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. When possible, concomitant administration of cytostatic drugs or drugs which may have a myelosuppression effect should be avoided (*see section 3.5*).

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 4.2*).

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.

Infection
Severe secondary infections, often with uncommon organisms are a hazard of immunosuppressive therapy. These are seen more frequently in transplant recipients than in patients being treated for other indications.

Renal and/or Hepatic Impairment
Caution is advised during the administration of azathioprine in patients with renal impairment and/or hepatic impairment. Consideration should be given to reducing the dosage in these patients and haematological response should be carefully monitored (*see section 3.2 and section 4.2*).

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

Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes from the offspring of patients treated with azathioprine. Except in extremely rare cases, no overt physical evidence of abnormality has been observed in the offspring of patients treated with azathioprine.

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

Teratogenicity
The potential teratogenicity of azathioprine should be borne in mind. Although it has been shown to be teratogenic in laboratory animals clinical evidence suggests that the risk is not appreciable in man. There is no doubt that azathioprine and its metabolites cross the placenta. A temporary impairment of immune function has been noted following exposure in utero to azathioprine combined with prednisone. The long-term consequences of these properties of azathioprine are unknown, but many children exposed in utero have now completed the first decade of life without reported problems.

Carcinogenicity (*see section 3.8*)
An increased number of malignant tumors especially lymphoreticular and epithelial has been observed in transplant recipients. The skin tumours that have occurred in transplant patients have been primarily on sun exposed skin. Patients should be cautioned against undue sun exposure, and the skin should be examined at regular intervals. There is, however, as yet no conclusive evidence of an increased incidence of tumours in other azathioprine treated subjects. In such patients the risk may be indistinguishable from that accompanying some of the diseases under treatment.

The few cases reported show a different pattern from that seen in transplantation; tumour occurrence is much less common, has an increased latency, is seen mainly after prolonged continuous therapy, is less exclusively lymphoreticular and tends to occur in those patients also treated with alkylating agents.

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 azathioprine is used alone or in combination with anti-TNF agents 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 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 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.

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, especially in patients with IBD (Crohn's disease, colitis ulcerative). Diagnosis of pellagra should be considered in a patient presenting with localised pigmented rash (dermatitis); gastroenteritis (diarrhoea); and widespread neurologic deficits, including cognitive decline (dementia). Dose reduction or discontinuation of azathioprine treatment may not be required if appropriate medical care with niacin/nicotinamide supplementation is initiated. However, careful benefit-risk assessment is required on a case-by-case basis.

Varicella Zoster Virus Infection (*see section 3.8*)
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 azathioprine with other immunosuppressive agents. Immunosuppressive therapy should be withheld at the first sign or symptoms suggestive of PML and appropriate evaluation undertaken to establish a diagnosis (*see section 3.8*).

Hepatitis B (*see section 3.8*)
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.

Xanthine Oxide 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 3.2*).

Neuromuscular Agents
Special care is necessary when azathioprine is given concomitantly with neuromuscular acting agents like tubucurarine or succinylcholine (*see section 3.5*). It can also potentiate the neuromuscular block that is produced by depolarising agents such as succinylcholine (*see section 3.5*). Patients should be advised to inform their anaesthesiologist of their treatment with azathioprine prior to surgery.

3.5 Interactions with Other Medicinal Products and Other Form of Interaction
Vaccines
The immunosuppressive activity of azathioprine 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 azathioprine (*see section 3.4*).

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 and corticosteroids.

A small clinical study has indicated that standard therapeutic doses of azathioprine 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 Azathioprine
Ribavirin
Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin; therefore, co-administration is not advised (*see section 3.4*).

Cytostatic/myelosuppressive agents (*see section 3.4*)
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 azathioprine and trimethoprim/sulfamethoxazol.

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

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

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 azathioprine, the dose of 6-mercaptopurine and azathioprine should be reduced to 25% of the original dose (*see section 3.2*).

Other xanthine oxidase inhibitors, such as febuxostat may decrease the metabolism of azathioprine. Concomitant administration 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 azathioprine may need to be considered when administered concomitantly with aminosalicylate derivatives (*see section 3.4*).

Infliximab

An interaction has been observed between azathioprine 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.

Neuromuscular agents
There is clinical evidence that azathioprine antagonizes 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 3.4*).

Effect of Azathioprine on Other Drugs
Anticoagulants
Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with azathioprine; therefore, higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with azathioprine.

3.6 Fertility, Pregnancy and Lactation
Fertility
Relief of chronic renal insufficiency by renal transplantation involving the administration of azathioprine has been accompanied by improved fertility in both male and female transplant recipients.

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

Pregnancy
Substantial transplacental and transamniotic transmission of azathioprine and its metabolites from the mother to the foetus have been shown to occur.

Azathioprine 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 azathioprine in man is equivocal. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving azathioprine.

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

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

Cholestasis of pregnancy has occasionally been reported in association with azathioprine 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 3.4*).

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

3.7 Effects on Ability to Drive and Use Machines
There are no data on the effect of azathioprine on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the drug.

3.8 Undesirable Effects
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 following convention has been utilised for the classification of frequency:

Tabulated summary of adverse reactions

Very common : ≥1/10;
Common : ≥1/100 to <1/10;
Uncommon : ≥1/1,000 to <1/100;
Rare : ≥1/10,000 to <1/1,000;
Very rare : <1/10,000;
Not known : cannot be estimated from the available data

System Organ Class	Frequency	Adverse Reaction
Infection and infestations	Very common	Viral, fungal and bacterial infections in transplant patients receiving azathioprine in combination with other immunosuppressants
	Uncommon	Viral, fungal and bacterial infection in other patient populations
	Very Rare	Cases of JC virus associated PML have been reported following the use of azathioprine in combination with other immunosuppressants (*see section 3.4*)
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) and uterine cervical cancer *in situ,* acute myeloid leukaemia and myelodysplastic syndrome (*see section 3.4*)
	Very Rare	Hepatosplenic T-cell lymphoma (*see section 3.4*)
Blood and lymphatic system disorders	Very common	Leukopenia, bone marrow depression
	Common	Thrombocytopenia
	Uncommon	Anaemia
	Rare	Agranulocytosis, pancytopenia, aplastic anaemia, anaemia megaloblastic
Immune system disorders	Uncommon	Hypersensitivity
	Very rare	Stevens-Johnson syndrome and toxic epidermal necrolysis
Respiratory, thoracic and mediastinal disorders	Very rare	Reversible pneumonitis
Gastrointestinal disorders	Common	Nausea
	Uncommon	Pancreatitis
	Very rare	Colitis, diverticulitis and intestinal perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population
Hepatobiliary disorders	Uncommon	Cholestasis
	Rare	Life-threatening liver injury
Skin and subcutaneous tissue disorders	Rare	Alopecia
	Not known	Acute febrile neutrophilic dermatosis (Sweet's syndrome), photosensitivity reaction
Investigations	Uncommon	Liver function test abnormal

Adverse events should be reported to GSK Indonesia via website https://gsk.public.reportum.com and Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan.
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

Description of Selected Adverse Reactions

Infections and infestations

Patients receiving azathioprine alone or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection and reactivation with VZV, hepatitis B and other infectious agents.

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

Blood and lymphatic system disorders
Azathioprine 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 azathioprine when receiving concurrent allopurinol therapy.

Reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content have occurred in association with azathioprine therapy. Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and erythroid hypoplasia are rare.

Immune system disorders
Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following administration of azathioprine. 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 section 3.8 – Hepatobiliary disorders*).

In many cases, re-challenge has confirmed an association with azathioprine.

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 azathioprine, the necessity for continued administration should be carefully considered on an individual basis.

Gastrointestinal disorders
Some patients experience nausea when first given 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 section 4.2*).

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 re-challenge, has been reported in patients treated with azathioprine 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 azathioprine 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 re-challenge has confirmed an association with azathioprine on occasions.

Hepatobiliary disorders
Cholestasis and deterioration of liver function have occasionally been reported in association with azathioprine therapy and are usually reversible on withdrawal of therapy. This may be associated with symptoms of a hypersensitivity reaction (*see section 3.8 – Immune system disorder*).

Rare, but life-threatening hepatic damage associated with chronic administration of azathioprine has been described primarily in transplant patients. Histological findings include sinusoidal dilatation, peliosis hepatis, venoocclusive disease and nodular regenerative hyperplasia. In some cases, withdrawal of azathioprine has resulted in either a temporary or permanent improvement in liver histology and symptoms.

Skin and subcutaneous tissue disorders
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.

3.9 Overdose
Symptoms
Unexplained infection, ulceration of the throat, bruising and bleeding are the main signs of overdosage with azathioprine and result from bone marrow depression, which may be maximal after nine 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 azathioprine. 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.

Management
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 azathioprine is not known, though azathioprine is partially dialyzable.

Symptomatic treatment should be administered. Azathioprine is known to be dialyzable and dialysis might be considered in severe cases. Subsequent monitoring, including haematological monitoring, is necessary to allow prompt treatment of any adverse effects which may develop.

4. PHARMACOLOGICAL PROPERTIES
4.1 Pharmacodynamic Properties
Mechanism of Action
Azathioprine is an imidazole derivate 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 that is inhibited by allopurinol. 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.

Pharmacodynamic Effects
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.

4.2 Pharmacokinetics 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 – 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 section 4.2*). Azathioprine should be administered at least one hour before or three hours after food or milk (*see section 3.2*).

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.

Biotransformation
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 3.2*). 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 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 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 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 section 3.2*).

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-∞) 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 section 3.2*).

Renal impairment
It has been suggested that the toxicity of azathioprine may be enhanced in the presence of renal insufficiency, but controlled studies have not supported this suggestion. Nevertheless, it is recommended that the dosage used should be at the lower end of the normal range and the haematological response should be carefully monitored. Dosage should be further reduced if haematological toxicity occurs.

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-mercaptopurine 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 3.2*).

Clinical Studies
No text

4.3 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 body weight/day.

5. PHARMACEUTICAL PARTICULARS
5.1 List of Excipients
Tablets:
Core tablet: lactose monohydrate, maize starch, pregelatinised starch, magnesium stearate, stearic acid, purified water.
Film coating: hypromellose, macrogol 400, purified water.

5.2 Incompatibilities
None reported for *IMURAN* tablets.

5.3 Shelf-Life
The expired date is indicated on the packaging.

5.4 Special Precautions for Storage
Store below 30°C. Protect from light.

5.5 Nature and Contents of Container
Box, 4 blister @ 25 film-coated tablet, Reg. No. DKI2159300117A1

5.6 Special Precautions for Disposal (and Other Handling)
Safe Handling
Health professionals who handle uncoated azathioprine 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 azathioprine tablets. Film-coated azathioprine tablets should not be divided and, provided the coating is intact, no additional precautions are required when handling them.

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

OBAT KERAS - HARUS DENGAN RESEP DOKTER

Manufactured by:
Aspen SA Operations (Pty) Ltd., Gqeberha, Republic of South Africa

Imported by:
PT Glaxo Wellcome Indonesia, Jakarta, Indonesia

Version number	: 01
Reference	: CCDS v27 (version date: 02Sep2022, MeDRA v25)
Date of local revision	: 21 Feb 2025

INFORMASI UNTUK PASIEN

Imuran Tablet Salut Selaput
Azathioprine 50 mg

Baca keseluruhan brosur ini secara teliti sebelum Anda mulai menggunakan obat ini karena mengandung informasi penting untuk Anda.
- Simpan brosur ini. Anda mungkin perlu membacanya kembali
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, perawat atau apoteker
- Obat ini hanya diresepkan untuk Anda. Jangan diberikan kepada orang lain. Hal tersebut dapat membahayakan mereka, meskipun gejala penyakit mereka sama dengan gejala Anda
- Jika Anda merasakan efek samping, konsultasikan dengan dokter, perawat atau apoteker. Hal ini termasuk kemungkinan efek samping lain yang tidak tertulis dalam brosur ini. *Lihat Bagian 4.*

Apa Saja yang Ada Dalam Brosur Ini:

1. Apa Itu IMURAN dan Digunakan Untuk Apa

IMURAN mengandung zat aktif azathioprine. Obat ini termasuk dalam imunosupresif yang membantu mengurangi kekuatan sistem kekebalan tubuh Anda.

IMURAN dapat digunakan untuk membantu tubuh Anda menerima transplantasi organ, seperti ginjal, jantung atau hati. Obat ini juga digunakan untuk mengobati beberapa penyakit di mana sistem kekebalan Anda bereaksi terhadap tubuh Anda sendiri (penyakit autoimun).

Penyakit autoimun di antaranya sebagai berikut:
- Rheumatoid arthritis yang parah (penyakit di mana sistem kekebalan menyerang sel-sel yang melapisi sendi sehingga menyebabkan pembengkakan, nyeri, dan kekakuan pada persendian)
- Lupus eritematosus sistemik (penyakit di mana sistem kekebalan menyerang banyak organ tubuh dan jaringan, termasuk kulit, persendian, ginjal, otak, dan organ lain yang menyebabkan kelelahan yang parah, demam, kaku dan nyeri sendi)
- Dermatomiositis (penyakit yang menyebabkan radang otot, kelemahan otot dan ruam kulit)
- Hepatitis aktif kronis autoimun (penyakit di mana sistem kekebalan menyerang sel hati yang menyebabkan radang hati, kelelahan, nyeri otot, kulit menguning dan demam)
- Pemfigus vulgaris (suatu penyakit di mana sistem imun menyerang sel kulit yang menyebabkan melepuh pada kulit, mulut, hidung, tenggorokan dan alat kelamin)
- Poliarteritis nodosa (penyakit langka yang menyebabkan pembengkakan pembuluh darah)
- Anemia hemolitik autoimun (kelainan darah serius di mana proses penghancuran sel darah merah oleh tubuh terjadi lebih cepat dibandingkan proses pembentukannya, dengan gejala kelemahan dan sesak nafas)
- Purpura trombositopenik idiopatik refrakter kronis (suatu kondisi dengan jumlah trombosit rendah, yang dapat menyebabkan mudah memar dan pendarahan).

Dokter Anda akan menyarankan obat ini sesuai dengan kondisi Anda.

IMURAN dapat digunakan secara tunggal, tetapi lebih sering digunakan bersamaan dengan obat lain.

2. Apa yang Perlu Anda Ketahui Sebelum Menggunakan IMURAN

Jangan gunakan IMURAN:
- Jika Anda alergi terhadap azathioprine atau salah satu kandungan dari obat ini (*Lihat Bagian 6*)
- Jika Anda alergi terhadap mercaptopurine (obat yang mirip dengan azathioprine).

Perhatian dan pencegahan
Konsultasikan dengan dokter atau apoteker Anda sebelum menggunakan IMURAN

- Jika Anda baru saja atau akan melakukan vaksinasi. Jika Anda menggunakan IMURAN, Anda tidak boleh mendapatkan vaksin yang berisi organisme hidup (misalnya: vaksin flu, vaksin campak, vaksin BCG, dll.) sampai dinyatakan aman oleh dokter Anda untuk melakukan vaksinasi. Hal ini dikarenakan beberapa vaksin dapat menyebabkan infeksi apabila digunakan bersamaan dengan IMURAN.
- Jika Anda memiliki masalah hati atau ginjal
- Jika Anda memiliki kondisi genetik yang disebut defisiensi TPMT (di mana tubuh Anda memproduksi terlalu sedikit enzim thiopurine methyltransferase)
- Jika Anda pernah menderita cacar air atau herpes zoster
- Jika Anda pernah menderita hepatitis B (penyakit hati yang disebabkan oleh virus)
- Jika Anda akan menjalani operasi (ini karena obat-obatan termasuk tubocurarine atau succinylcholine yang digunakan sebagai pelemas otot selama operasi dapat berinteraksi dengan IMURAN). Anda harus memberi tahu ahli anestesi tentang pengobatan Anda menggunakan IMURAN sebelum operasi.

Jika Anda tidak yakin dengan keadaan di atas, konsultasikan dengan dokter, perawat, atau apoteker Anda sebelum menggunakan IMURAN.

Dokter Anda akan melakukan pengambilan sampel darah secara rutin selama Anda menggunakan IMURAN untuk memeriksa setiap perubahan (*Lihat Bagian 3* - Cara menggunakan IMURAN). Frekuensi pemeriksaan darah biasanya akan berkurang semakin lama Anda menggunakan IMURAN.

Jika Anda menerima terapi imunosupresif, penggunaan IMURAN dapat membuat Anda memiliki risiko lebih besar untuk mengalami keadaan di bawah ini:

- Tumor, termasuk kanker kulit. Oleh karena itu, saat menggunakan IMURAN hindari terkena sinar matahari berlebihan, kenakan pakaian pelindung dan gunakan tabir surya.
- Gangguan limfoproliferatif:
  - Pengobatan dengan IMURAN meningkatkan risiko Anda terkena jenis kanker yang disebut gangguan limfoproliferatif. Dengan rejimen pengobatan yang mengandung banyak imunosupresan (termasuk tiopurin), hal ini dapat menyebabkan kematian.
  - Kombinasi beberapa imunosupresan yang diberikan secara bersamaan akan meningkatkan risiko gangguan pada sistem getah bening karena infeksi virus (virus Epstein-Barr (EBV) terkait gangguan limfoproliferatif)
- Berkembangnya kondisi serius yang disebut sindrom aktivasi makrofag (aktivasi berlebihan sel darah putih yang berhubungan dengan peradangan), yang biasanya terjadi pada orang yang mengalami jenis radang sendi tertentu, cacar air parah atau infeksi herpes zoster. Oleh karena itu, saat menggunakan IMURAN hindari kontak dengan penderita cacar air atau herpes zoster
- Infeksi hepatitis B sebelumnya dapat menjadi aktif kembali
- Infeksi lain seperti *Progressive Multifocal Leukoencephalopathy* (PML) yang merupakan penyakit infeksi oportunistik. Jika Anda mengalami tanda-tanda infeksi, harap hubungi dokter Anda (*Lihat Bagian 4* – Efek samping yang mungkin terjadi).

Anda perlu menginformasikan dokter secepatnya apabila merasakan gatal yang sangat intens, namun tanpa adanya ruam/kemerahan selama masa kehamilan, terutama pada trimester kedua. Anda mungkin juga merasakan mual dan kehilangan nafsu makan secara bersamaan dengan gatal-gatal. Hal ini menunjukkan bahwa Anda mengalami kondisi kesehatan yang disebut dengan kolestasis kehamilan (keadaan yang mempengaruhi organ hati pada masa kehamilan). Dokter mungkin akan meminta Anda untuk melakukan tes darah pada saat Anda sedang menggunakan azathioprine, dimana dari hasil tes tersebut, dokter mungkin akan melakukan penyesuaian dosis atau menghentikan penggunaan obat ini.

Segera informasikan pada dokter apabila Anda mengalami diare, ruam/kemerahan di area tertentu (dermatitis), dan penurunan ingatan, penalaran, atau keterampilan berpikir lainnya (demensia) karena gejala tersebut mungkin menunjukkan kekurangan vitamin B3 (kekurangan asam nikotinat/pellagra). Dokter mungkin akan meresepkan suplemen vitamin (niasin/nikotinamid) untuk membantu memperbaiki kondisi Anda.

Pengobatan lain dan IMURAN

Informasikan kepada dokter Anda jika Anda sedang, baru saja atau mungkin akan menggunakan obat lain. Hal ini karena IMURAN dapat mempengaruhi cara kerja beberapa obat dan juga beberapa obat lain dapat mempengaruhi cara kerja IMURAN. Informasikan kepada dokter Anda jika Anda sedang atau berencana untuk menggunakan obat di bawah ini:

- Ribavirin (digunakan untuk mengobati infeksi virus)
- Allopurinol, oksipurinol, tiopurinol atau penghambat xantin oksidase lainnya, seperti febuxostat (terutama digunakan untuk mengobati asam urat)
- Penicillamine (terutama digunakan dalam pengobatan rheumatoid arthritis)
- Penghambat *Angiotensin-Converter Enzyme* (ACE) (terutama digunakan untuk mengobati tekanan darah tinggi - hipertensi)
- Antikoagulan seperti warfarin atau acenocoumarol (digunakan untuk mencegah penggumpalan darah)
- Simetidin (digunakan untuk mengobati sakit maag dan gangguan pencernaan)
- Indometasin (digunakan sebagai pereda nyeri dan antiradang)
- Obat sitostatik (obat yang digunakan untuk mengobati berbagai jenis kanker)
- Aminosalicylates, misalnya: olsalazine, mesalazine atau sulfasalazine (terutama digunakan dalam pengobatan kolitis ulserativa dan penyakit Crohn)
- Kotrimoksazol (antibiotik, digunakan untuk mengobati infeksi yang disebabkan oleh bakteri)
- Infliximab (terutama digunakan untuk pengobatan kolitis ulserativa dan penyakit Crohn)
- Pelemas otot misalnya tubocurarine atau succinylcholine (digunakan selama operasi) yang dapat berinteraksi dengan IMURAN. Anda harus memberi tahu ahli anestesi tentang pengobatan Anda menggunakan IMURAN sebelum operasi.

Jika Anda tidak yakin dengan hal-hal di atas, konsultasikan dengan dokter atau apoteker Anda sebelum menggunakan IMURAN.

Melakukan vaksinasi ketika Anda menggunakan IMURAN
Jika Anda akan melakukan vaksinasi, konsultasikan dengan dokter atau perawat Anda sebelumnya. Jika Anda menggunakan IMURAN, Anda tidak boleh mendapatkan vaksin yang berisi organisme hidup (misalnya: vaksin flu, vaksin campak, vaksin BCG, dll.) sampai dinyatakan aman oleh dokter Anda untuk melakukan vaksinasi. Hal ini dikarenakan beberapa vaksin dapat menyebabkan infeksi apabila digunakan bersamaan dengan IMURAN.

IMURAN dengan makanan dan minuman
Anda harus menggunakan IMURAN setidaknya 1 jam sebelum atau 3 jam setelah mengonsumsi susu atau makanan.

Kehamilan, menyusui dan kesuburan
Apabila Anda sedang hamil atau menyusui, akan hamil maupun merencanakan kehamilan, konsultasikan dengan dokter atau apoteker sebelum menggunakan IMURAN.

Kehamilan
Tindakan pencegahan menggunakan kontrasepsi harus dilakukan untuk menghindari kehamilan pada saat Anda atau pasangan Anda menggunakan IMURAN.

Jika Anda hamil, dokter Anda akan mempertimbangkan kembali penggunaan obat ini berdasarkan kajian risiko dan manfaat pengobatan.

Menyusui
IMURAN ditemukan di dalam ASI. Wanita yang menggunakan IMURAN dianjurkan untuk menghindari menyusui.

Kesuburan
Efek IMURAN pada kesuburan tidak diketahui.

Mengemudi dan menggunakan mesin
Penggunaan IMURAN tidak diketahui mempengaruhi kemampuan Anda untuk mengemudi atau menggunakan mesin. Jika Anda mengalami efek samping dari obat ini, Anda mungkin tidak dapat mengemudi atau menggunakan mesin.

Tablet IMURAN mengandung laktosa
Tablet IMURAN mengandung lactose monohydrate. Jika Anda intoleransi terhadap beberapa jenis gula, konsultasikan dengan dokter Anda sebelum menggunakan obat ini.

3. Cara Menggunakan IMURAN

Selalu gunakan obat ini sesuai saran dokter, perawat atau apoteker pada Anda. Konsultasikan dengan dokter, perawat atau apoteker jika Anda tidak yakin.

Jumlah tablet IMURAN yang digunakan setiap pasien dapat bervariasi dan akan ditentukan oleh dokter Anda sesuai dengan kondisi Anda saat ini.

Anda dapat menggunakan IMURAN bersamaan dengan makanan atau pada saat perut kosong, tetapi pilihan metodenya harus dilakukan secara konsisten dari hari ke hari. Beberapa pasien merasa mual saat pertama kali menggunakan IMURAN dan mungkin akan hilang ketika menggunakan obat ini setelah makan.

- Ketika Anda menggunakan IMURAN, dokter Anda akan secara rutin melakukan tes darah. Hal ini dilakukan untuk memeriksa jumlah dan tipe sel dalam darah Anda, dan untuk memastikan hati Anda bekerja dengan baik.
- Dokter Anda akan meminta untuk melakukan tes darah dan urin untuk memantau kerja ginjal Anda dan mengukur kadar asam urat. Asam urat adalah bahan alami yang diproduksi di dalam tubuh dan kadar asam urat Anda dapat meningkat ketika Anda menggunakan IMURAN. Kadar asam urat yang tinggi dapat merusak ginjal Anda. Dokter Anda mungkin akan mengubah dosis IMURAN berdasarkan hasil tes ini.

Telan tablet IMURAN secara utuh. Jangan mengunyah tabletnya. Tablet tidak boleh pecah atau dihancurkan.

Penting untuk mengetahui cara penggunaan yang aman terhadap obat ini. Jika Anda bersentuhan dengan tablet yang rusak, segera cuci tangan Anda. Silahkan konsultasikan dengan dokter atau apoteker Anda.

Dosis yang dianjurkan
Dokter akan memberitahukan berapa dosis IMURAN yang akan diberikan kepada Anda. Dosis yang diberikan tergantung pada kondisi, berat badan dan respon Anda terhadap pengobatan. Dokter mungkin akan melakukan penyesuaian dosis awal yang Anda terima hingga didapatkan respon pengobatan yang baik. Selama pengobatan dengan IMURAN, dokter akan meminta Anda untuk melakukan pemeriksaan darah secara berkala. Hal ini dilakukan untuk memeriksa jumlah sel darah Anda dan untuk menentukan apakah perlu dilakukan perubahan dosis.

Apabila Anda menggunakan IMURAN lebih dari yang seharusnya
Jika Anda menggunakan IMURAN lebih dari yang dianjurkan dokter Anda, konsultasikan dengan dokter atau apoteker Anda sesegera mungkin.

Apabila Anda lupa menggunakan IMURAN
Jangan menggunakan dosis tambahan IMURAN untuk menggantikan dosis yang terlewatkan. Informasikan ke dokter Anda jika melewatkan dosis tersebut.

Jika sudah dekat dengan waktu penggunaan selanjutnya, tunggu hingga waktu tersebut.

Jika tidak dekat dengan waktu penggunaan selanjutnya, segera gunakan obat ini setelah Anda ingat. Lalu lanjutkan penggunaan IMURAN seperti jadwal biasanya.

Apabila Anda berhenti menggunakan IMURAN
Konsultasikan dengan dokter Anda sebelum Anda berhenti menggunakan IMURAN. Jangan berhenti menggunakan secara tiba-tiba sampai dokter Anda memberi tahu bahwa aman untuk dilakukan.
Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

4. Efek Samping yang Mungkin Terjadi

Seperti semua obat-obatan lain, IMURAN dapat menyebabkan efek samping, tetapi tidak semua orang akan mengalaminya. Berikut efek samping yang mungkin terjadi dengan obat ini:

Hentikan penggunaan IMURAN dan beritahu dokter Anda dengan segera, jika Anda menyadari ada efek samping yang serius, Anda mungkin membutuhkan penanganan medis:

- Reaksi alergi (efek samping yang jarang terjadi hingga 1 dari 100 orang). Tanda-tanda yang terjadi:
  - Kelelahan, pusing, perasaan mual, sakit (muntah), diare atau sakit perut
  - Pembengkakan pada kelopak mata, wajah atau bibir
  - Kemerahan pada kulit atau ruam kulit (termasuk melepuh, gatal atau kulit mengelupas)
  - Nyeri pada otot atau persendian
  - Sesak nafas tiba-tiba, batuk atau kesulitan bernafas

  Dalam kasus yang parah, reaksi ini dapat mengancam jiwa (jarang terjadi hingga 1 dari 10.000 orang).
- Ruam kulit atau kemerahan yang dapat berkembang menjadi reaksi kulit yang mengancam jiwa termasuk ruam yang melepuh dan kulit mengelupas, terutama terjadi di sekitar mulut, hidung, mata dan alat kelamin (*Stevens-Johnson Syndrome*), pengelupasan kulit yang luas (*toxic epidermal necrolysis*) (efek samping yang sangat jarang terjadi hingga 1 dari 10.000 orang), benjolan kemerahan pada kulit yang terasa nyeri (*erythema nodosum*).
- Pneumonitis reversibel (radang paru-paru yang menyebabkan sesak nafas, batuk dan demam) (efek samping yang sangat jarang terjadi hingga 1 dari 10.000 orang).
- Masalah dengan darah dan sumsum tulang Anda, tanda-tanda termasuk kelemahan, kelelahan, pucat, mudah memar, pendarahan yang tidak biasa atau infeksi (efek samping yang sangat umum terjadi hingga 1 dari 10 orang).
- Jika menggunakan IMURAN bersamaan dengan imunosupresif lainnya, Anda mungkin terkena virus yang menyebabkan kerusakan pada otak Anda. Ini dapat menyebabkan sakit kepala, perubahan perilaku gangguan bicara, memburuknya daya ingat, perhatian dan pengambilan keputusan (penurunan kognitif) dan dapat berakibat fatal (kondisi yang dikenal sebagai *JC virus associated progressive multifocal leukoencephalopathy*) (efek samping yang sangat jarang terjadi hingga 1 dari 10.000 orang).

Jika Anda mengalami salah satu efek samping yang serius berikut ini, segera konsultasikan dengan dokter atau dokter spesialis Anda, Anda mungkin membutuhkan penanganan medis segera:

- Anda mengalami demam atau tanda-tanda infeksi lain seperti nyeri menelan, rasa tidak nyaman di mulut, masalah kencing, atau infeksi dada yang menyebabkan sesak nafas dan batuk (efek samping yang sangat umum terjadi hingga 1 dari 10 orang).
- Masalah pada hati Anda, tanda-tandanya termasuk kulit atau bagian putih mata Anda menguning (penyakit kuning) (efek samping yang tidak umum terjadi hingga 1 dari 100 orang).
- Berbagai jenis kanker termasuk kanker darah, getah bening dan kulit (*Lihat Bagian 2* – Perhatian dan pencegahan) (efek samping yang jarang terjadi hingga 1 dari 1.000 orang).
- *Sweet's Syndrome*, (dikenal juga sebagai *acute febrile neutrophilic dermatosis*). Ruam Anda dapat mengembang menjadi benjolan merah, merah muda atau ungu yang terasa sakit saat disentuh, terutama di lengan, tangan, jari, wajah dan leher, yang juga bisa disertai demam (tingkat terjadinya efek samping ini tidak diketahui – tidak dapat diperkirakan dari data yang tersedia)
- Jenis limfoma tertentu (*hepatosplenic T-cell lymphoma*). Anda mungkin mengalami mimisan, kelelahan, keringat malam yang signifikan, penurunan berat badan dan demam yang tidak dapat dijelaskan (tingkat terjadinya efek samping ini tidak diketahui – tidak dapat diperkirakan dari data yang tersedia).

Jika Anda mengalami hal-hal di atas, segera hentikan penggunaan IMURAN dan segera hubungi dokter.

Efek samping lainnya yang mungkin terjadi:
Sangat umum (terjadi hingga lebih dari 1 dari 10 orang)

- Tingkat sel darah putih yang rendah dalam tes darah yang dapat menyebabkan infeksi umum.

Umum (terjadi hingga dari 1 dari 10 orang)

- Mual.

Tidak umum (terjadi hingga 1 dari 100 orang)
- Anemia (tingkat sel darah merah rendah)
- Pankreatitis (radang pankreas), yang dapat menyebabkan sakit perut bagian atas yang parah.

Jarang (terjadi hingga 1 dari 1.000 orang)
- Anda mungkin memperhatikan beberapa rambut akan rontok saat menggunakan IMURAN. Rambut akan tumbuh kembali meskipun Anda terus menggunakan IMURAN. Jika Anda khawatir, konsultasikan dengan dokter Anda.

Sangat jarang (terjadi pada hingga 1 dari 10.000 orang)
- Masalah pada usus Anda yang menyebabkan diare, sakit perut, sembelit, perasaan atau sedang sakit (perforasi usus)
- Radang paru-paru yang menyebabkan sesak nafas, batuk dan demam.

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)
- Fotosensitivitas (kepekaan terhadap cahaya atau sinar matahari).

Pelaporan efek samping
Jika efek samping menjadi serius, atau jika Anda melihat terdapat efek samping yang tidak tercantum dalam brosur ini, segera konsultasikan pada dokter atau apoteker Anda.

Laporkan Kejadian Tidak Diinginkan (KTD) ke GSK Indonesia melalui situs web https://gsk.public.reportum.com.

5. Bagaimana Cara Penyimpanan IMURAN

Simpan di bawah suhu 30°C. Lindungi dari cahaya.

Jangan menggunakan obat setelah tanggal kedaluwarsa yang tertulis pada kemasan. Tanggal kedaluwarsa merujuk pada hari terakhir pada bulan tersebut.

Jangan membuang obat apapun di air limbah atau limbah rumah tangga. Tanyakan pada apoteker bagaimana membuang obat yang tidak digunakan lagi.

6. Isi dari Kemasan dan Informasi Lain

Kandungan pada IMURAN
- Bahan aktif azathioprine
- Komponen lainnya adalah *lactose monohydrate, pregelatinised starch, maize starch, stearic acid, magnesium stearate, hypromellose,* dan *macrogol 400*
- Tidak ada pewarnaan pada tablet kuning.

HARUS DENGAN RESEP DOKTER

Dus, 4 blister @ 25 tablet salut selaput Reg. No. DKI2159300117A1

Diproduksi oleh:
Aspen SA Operations (Pty) Ltd., Gqeberha, Afrika Selatan

Diimpor oleh:
PT Glaxo Wellcome Indonesia, Jakarta, Indonesia

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