PACKAGE LEAFLET: INFORMATION FOR THE PATIENT
Azathioprine 25mg and 50mg Film-Coated Tablets

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1 What Azathioprine is and what it is used for
Azathioprine belongs to a group of medicines called immunosuppressants. These work by reducing the strength of the body's immune system. Azathioprine may be taken long-term as it can take weeks or months before an effect is seen.

Azathioprine is used to treat the following:
- To prevent the body from rejecting kidney, liver or heart transplants
- Inflammatory bowel disease (Crohn's disease or ulcerative colitis)
- Severe inflammatory disease of the joints (rheumatoid arthritis)
- Long−term inflammation of skin and/or intestines (systemic lupus erythematosus)
- Inflammation of the skin and muscles (dermatomyositis, polymyositis)
- Inflammation of the liver (hepatitis)
- Inflammation of the walls of the arteries (polyarteritis nodosa)
- Increased breakdown of red blood cells due to the presence of auto-antibodies active at body temperature (warm) causing anaemia (looking pale and feeling tired)
- Autoimmune disorder where the number of platelets circulating is reduced by the immune system destroying them, causing a rash and an increased tendency to bleed, persisting longer than 6 months without a specific cause and is not responsive to conventional treatment (chronic refractory idiopathic thrombocytopenic purpura)
- Blistering of the skin (pemphigus vulgaris)

2 What you need to know before you take Azathioprine
Do not take Azathioprine if:
- You are allergic to Azathioprine, 6−mercaptopurine (a derivative of Azathioprine) or any of the other ingredients of this medicine (see section 6 "Contents of the pack and other information")

Warnings and precautions
Talk to your doctor before taking Azathioprine:
- If you are going to have a vaccination (see "Other medicines and Azathioprine" section)
- If you are currently taking ribavirin (see "Other medicines and Azathioprine" section)
- If you suffer from kidney or liver problems
- If you have had Hepatitis B, a liver disease caused by a virus
- If you suffer from Lesch−Nyhan Syndrome, a rare hereditary disorder caused by a deficiency of the enzyme HPRT (hypoxanthine-guanine-phosphoribosyltransferase)
- If you have, have been exposed to or have ever suffered from chickenpox or shingles (varicella zoster virus infection) as the infection can become severe if you are taking immunosuppressants
- If you are showing signs or symptoms (headache, loss of co-ordination, clumsiness, loss of speech, memory loss, vision problems, weakness of the legs and arms that gets worse) of having Progressive Multifocal Leukoencephalopathy [PML] (a rare infection caused by a virus that

damages the material covering and protecting nerves in the brain) as treatment with Azathioprine should be withheld (see section 4 “Possible side effects, Very rare side effects…”)
- If you have an inherited mutation in the NUDT15 gene (a gene which is involved in the break-down of Azathioprine in the body)
- If you suffer from an inherited condition where your body produces too little of the enzyme thiopurine methyltransferase (TPMT)
- If you or your partner are pregnant or planning to become pregnant (see section “Pregnancy, breast-feeding and fertility”)
- If you are receiving immunosuppressive therapy, taking Azathioprine could put you at greater risk of: tumours, including skin cancer. Therefore, avoid excessive exposure to sunlight and UV light, wear protective clothing and use a sunscreen with a high protection factor
- If you are receiving treatment with multiple immunosuppressants (including thiopurines) as this may increase the risk of a type of cancer called lymphoproliferative disorder and disorders of the lymph system due to a viral infection (Epstein-Barr virus (EBV)-associated lymphoproliferative disorders)
- If you suffer with autoimmune conditions such as inflammatory bowel disease (IBD), as this could put you at greater risk of developing a life-threatening disorder called Macrophage Activation Syndrome (excessive activation of white blood cells associated with inflammation)
- If you experience diarrhoea, localised pigmented rash (dermatitis), gastroenteritis (diarrhoea), decline in your memory, reasoning or other thinking skills (dementia), as these may be symptoms of vitamin B3 deficiency (nicotinic acid deficiency/pellagra)

Liver damage
Treatment with Azathioprine may affect the liver and your doctor will monitor your liver function regularly. Tell your doctor if you experience symptoms of liver damage (see section 4 “Possible side effects”).

Other medicines and Azathioprine
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those obtained without a prescription. This includes herbal medicines.

Medicines which **may interact** with or be affected by Azathioprine:
Before a surgical procedure tell the anaesthesiologist that you are taking azathioprine because muscle relaxants used during anaesthesia may interact with Azathioprine
- Medicines used to treat gout such as allopurinol, oxipurinol, thiopurinol or other xanthine oxidase inhibitors, such as febuxostat. If these medicines are given concomitantly with Azathioprine, the dose of Azathioprine must be reduced to a quarter of the original dose
- Muscle relaxants such as atracurium, rocuronium, cisatracurium, pancuronium or suxamethonium (also known as succinylcholine) and tubocurarine (neuromuscular blocking agents)
- Medicines used to treat chronic inflammatory bowel diseases such as olsalazine, mesalazine, sulfasalazine (aminosalicylate derivatives) as lower doses of Azathioprine may need to be considered when given concomitantly
- Medicines used to thin the blood such as warfarin, acenocoumarol (anti−coagulants)
- Medicines used to treat high blood pressure or heart failure e.g. captopril (Angiotensin−Converting Enzyme [ACE] Inhibitors)
- Medicines used to treat infections such as trimethoprim, sulphamethoxazole also known as co-trimoxazole (antibiotics)
- Medicines used to treat stomach ulcers such as cimetidine (H2-receptor antagonist)
- Medicines used to treat certain rheumatic disorders such as indomethacin (Non-Steroidal Anti−Inflammatory Drugs [NSAIDs])
- Cytostatic medicines (used to treat cancer)
- Medicines which may have a myelosuppressive effect (decrease in bone marrow activity resulting in fewer red and white blood cells and platelets) such as penicillamine (mainly used in the treatment of rheumatoid arthritis)
- Live vaccines and also inactive vaccines such as hepatitis B (see section 2 “Warnings and precautions”)
- Ribavirin, used to treat chronic hepatitis C
- Methotrexate, used to treat auto-immune conditions and cancers
- Infliximab, mainly used in the treatment of ulcerative colitis and Crohn’s disease

Taking Azathioprine with food and drink
- Azathioprine may be taken with food or on an empty stomach.
- Azathioprine should be taken 1 hour before or 2 hours after milk or dairy products.

Pregnancy, breast-feeding and fertility
- If you are pregnant or breast−feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

- Women of childbearing potential should use effective contraceptive measures while being treated with Azathioprine and for one month following completion of treatment.
- Men should use effective contraceptive measures and not father a child while being treated with Azathioprine and for three months following completion of treatment.

Pregnancy
Do **not** take Azathioprine if you are pregnant, trying to become pregnant or think you may be pregnant.

If you experience intense itching (without a rash), nausea (feeling sick) and loss of appetite during your pregnancy, talk to your doctor immediately as you may have a condition called cholestasis of pregnancy (a condition which affects the liver during pregnancy).

Breast-feeding
It is recommended that women receiving Azathioprine should avoid breast-feeding (unless the benefits outweighs the potential risks) as 6-Mercaptopurine, a derivative of Azathioprine is passed into breast milk.

Fertility
The specific effect of Azathioprine on fertility is unknown. Adequate contraceptive precautions should be used when either partner is taking Azathioprine.

Driving and using machines
Azathioprine is not known to affect your ability to drive or use machinery. If you experience any side effect from this medicine, you may not be able to drive or operate machinery.

Azathioprine contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3 How to take Azathioprine
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- These tablets are to be taken orally and may be taken with food or on an empty stomach.
- These tablets should be taken at least 1 hour before or 2 hours after milk or dairy products.

Adults
You should be adequately monitored throughout the duration of treatment. Particular care should be taken to monitor your response and to reduce the maintenance dose to the lowest dose possible.

Organ transplants
- An initial dose of up to 5mg per kg of bodyweight per day may be given.
- The maintenance dose should range from 1−4mg per kg of bodyweight per day.
- Treatment with Azathioprine should be maintained indefinitely, even if only low doses are necessary, because of the risk of rejection.

Other conditions

- The starting dose is 1−3mg per kg of bodyweight per day and should be adjusted (within these limits) according to the effectiveness of treatment (which may be evident only after weeks or months).
- The maintenance dose should be reduced to the lowest dose possible. If no improvement occurs within 3 months, consideration should be given to withdrawing this medicine. However, for patients with inflammatory bowel disease, a treatment duration of at least 12 months should be considered as a response to treatment may not be apparent until after 3-4 months of treatment.

Kidney and/or liver disorders
If you suffer from kidney and/or mild to moderate liver disorders, the dose should be given at the lower end of the normal range.

TPMT (thiopurine S-methyltransferase) deficiency
- If you have (inherited) little or no TPMT activity (metabolic abnormality that increases the risk of adverse drug effects if you are treated with thiopurine medicines), you are at increased risk of severe toxicity from conventional doses of Azathioprine and generally will require substantial dose reduction.
- Most patients with heterozygous TPMT deficiency (intermediate TPMT enzyme activity) can tolerate recommended Azathioprine doses, but some may require dose reduction.

NUDT15 gene mutation
If you have an inherited mutation in the NUDT15 gene (a gene which is involved in the break-down of Azathioprine in the body), you are at increased risk of severe toxicity and generally will require dose reduction.

Elderly
It is advisable to monitor kidney and liver function and to consider reducing the dose if there is impairment.

Use in children
The recommended doses are the same as those given for adults.

Children considered to be overweight may require doses at the higher end of the range and therefore close monitoring of response to treatment is recommended.

If you take more Azathioprine than you should
If you accidentally take too many tablets, contact your doctor or nearest hospital emergency department **immediately** for advice. Remember to take this leaflet or any remaining tablets with you. **Symptoms of overdose include:** ulcers in the throat, unexplained infections, bruising and bleeding. These signs are more likely to occur following long-term overdose rather than a single sudden overdose. Effects of a single overdose may include feeling and/or being sick (nausea, vomiting), diarrhoea, mild reduction in white blood cells (leukopenia) and mild abnormalities in liver function.

If you forget to take Azathioprine
Take it as soon as you remember, unless it is time for your next dose. If you miss a dose **do not** take a double dose to make up for a forgotten dose.

If you stop taking Azathioprine
It is important that you keep taking Azathioprine for as long as your doctor has told you to. Withdrawal of Azathioprine should always be a gradual process performed under close monitoring.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4 Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any of the following serious side effects, talk to your doctor or go to hospital immediately:
- Allergic reactions: swelling of the face, throat or tongue, difficulty breathing or dizziness.

- Severe blistering of the skin (toxic epidermal necrolysis), mouth, eyes and genitals (Stevens-Johnson syndrome)
- Various types of cancers including blood, lymph and skin cancers (see section 2, “Warnings and precautions”)
- You may develop a rash (raised red, pink or purple lumps which are sore to touch), particularly on your arms, hands, fingers, face and neck, which may also be accompanied by a fever (Sweet’s Syndrome, also known as acute febrile neutrophilic dermatosis). The rate at which these side effects occur is not known (cannot be estimated from available data).
- A certain type of lymphomas (hepatosplenic T-cell lymphoma)
- Any evidence of infections, unexpected bruising or bleeding as these may be signs of bone marrow depression. This condition is reversible if Azathioprine is withdrawn early enough
- If you come into contact with anyone who is suffering from chickenpox or shingles
- Severe liver damage which can be life threatening, especially in patients who receive long-term treatment (like liver injury, non-cirrhotic portal hypertension, portosinusoidal vascular disease). Tell your doctor if you experience any of the following symptoms: yellowing of the skin and the whites of the eyes (jaundice), bruising easily, abdominal discomfort, loss of appetite, fatigue, nausea, or vomiting.

Very Common side effects (may affect more than 1 in 10 people)
- Viral, fungal and bacterial infections (if you are a transplant patient receiving Azathioprine in combination with other immunosuppressants)
- A reduction in white blood cells (leukopenia)
- Reduction of bone marrow function

Common side effects (may affect up to 1 in 10 people)
- A reduction in blood platelets, which increases risk of bleeding or bruising (thrombocytopenia)
- Feeling sick (nausea). This may be relieved by taking the tablets after meals

Uncommon side effects (may affect up to 1 in 100 people)
- Allergic reactions. The signs may include:
    - swelling of the eyelids, face or lips
    - redness of the skin, skin nodules or a skin rash (including blisters, itching or peeling skin)
- Viral, fungal and bacterial infections in other patient populations
- Looking pale and feeling tired (anaemia)
- Inflammation of the pancreas (pancreatitis)
- Build-up of bile acids in the bloodstream causing persistent itch (cholestasis), cholestasis of pregnancy (see Pregnancy section), worsening of liver function tests (usually reversible on withdrawal of treatment)

Rare side effects (may affect up to 1 in 1000 people)
- Various types of cancers including soft tissue (sarcomas), uterine and cervical (see section 2, “Warnings and precautions”)
- Life-threatening liver damage
- Hair loss (alopecia)
- Blood and bone marrow disorders

Very rare side effects (may affect up to 1 in 10,000 people)
- Virus-associated PML following the use of Azathioprine in combination with other immunosuppressants (see section 2, “Warnings and precautions”)
- Inflammation of the lungs (reversible pneumonitis)
- Inflammation which causes abdominal pain or diarrhoea (colitis/diverticulitis)
- Bowel perforation if you are a transplant patient
- Severe diarrhoea if you suffer from inflammatory bowel disease

Not known (frequency cannot be estimated from the available data)
- Abnormal sensitivity of the skin to sunlight (photosensitivity)
- Vitamin B3 deficiency (nicotinic acid deficiency/pellagra) (see section 2, “Warnings and precautions”)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Azathioprine
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton/blister after EXP. The expiry date refers to the last day of that month.
- Store below 25°C. Protect from light.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6 Contents of the pack and other information
What Azathioprine contains:
- Each 25mg tablet contains 25mg of Azathioprine
- Each 50mg tablet contains 50mg of Azathioprine

The other ingredients are: lactose monohydrate, maize starch, povidone, colloidal silicon dioxide, magnesium stearate, hypromellose, microcrystalline cellulose, polyoxyl−8−stearate, talc and titanium dioxide (E171).

What Azathioprine looks like and contents of the pack:
- Azathioprine 25mg are white to yellowish-white, round, biconvex, film-coated tablets of diameter 6.0-6.4mm and height of 3.1-3.7mm, with no score-line
- Azathioprine 50mg are white to yellowish-white, biconvex, film-coated tablets, of diameter 7.9-8.3mm and height of 3.6-4.2mm with a score-line on one side

Azathioprine is available in:
Azathioprine tablets are available in blister packs of:
- Azathioprine 25mg Tablets: 20, 28, 30, 50 or 100 tablets.
- Azathioprine 50mg Tablets: 30, 50, 56 or 100 tablets.

Not all pack sizes may be marketed.

Product Licence Numbers:
- Azathioprine 25mg Tablets: PL 11311/0475
- Azathioprine 50mg Tablets: PL 11311/0476

Marketing Authorisation Holder and Manufacturer:
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