Applicant: Teva Pharmaceuticals (Pty) Ltd	**Product name:** Azathioprine 50 PCH **Dosage form & strength:** Each tablet contains 50 mg Azathioprine

APPROVED PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

AZATHIOPRINE 50 PCH (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

AZATHIOPRINE 50 PCH:

Each tablet contains 50 mg azathioprine.

Contains sugar: 60 mg lactose monohydrate.

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

AZATHIOPRINE 50 PCH:

Yellow, biconvex tablets with score line and embossed description: AZP | 50 on one side and without marking and the score line on the other.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Transplantation:

AZATHIOPRINE 50 PCH is used mainly as an immunosuppressant for the prevention of rejection in organ and tissue transplantations. It is used in combination with corticosteroids and/or other immunosuppressive medicines and procedures.

Auto-immune diseases:

In combination with corticosteroids, AZATHIOPRINE 50 PCH is used to treat diseases with an auto-immune component such as chronically active and aggressive hepatitis, severe rheumatoid arthritis, systemic lupus erythematosus, and pemphigus vulgaris.

Its use in conjunction with corticosteroids may allow a lower dose of both medicines to be used, thus reducing adverse effects. Therapeutic effect may be evident only after weeks or months.

4.2 Posology and method of administration:

Posology:

The dosage of AZATHIOPRINE 50 PCH and the duration of the treatment depend on the nature and gravity of the disease and the clinical response obtained.

It may take several weeks before a therapeutic effect can be observed. If no discernible improvement occurs within 3 months, discontinuation of the therapy should be considered.

Treatment is otherwise undertaken on a long-term basis unless the patient exhibits evidence of intolerance to AZATHIOPRINE 50 PCH.

Transplantation:

Loading dose: A loading dose of 1,0 to 5,0 mg/kg body weight per day is usually given and depends partly on whether other medicines, such as corticosteroids, or radiotherapy are employed at the same time.

Maintenance dosage after transplantation: Usually 1,0 to 4,0 mg/kg body weight per day after transplantation.

Discontinuation of AZATHIOPRINE 50 PCH therapy, even after a period of years, carries a risk of rejection within a few weeks.

Auto-immune diseases:

For the treatment of chronic active hepatitis, the initial dose amounts to 1,0 to 1,5 mg/kg body weight per day.

Dosage for the treatment of severe rheumatoid arthritis, systemic lupus erythematosus, and pemphigus vulgaris is usually 1,0 to 2,5 mg/kg body weight per day depending on patient response.

Special populations:

Use in the elderly:

The dosage of AZATHIOPRINE 50 PCH in the elderly has not been established. It is recommended that the dosage used is at the lower end of the range given. The maintenance dosage should be reduced to the minimum required for clinical response.

Renal and hepatic impairment:

AZATHIOPRINE 50 PCH should be used with care in patients with renal or hepatic impairment. Dose reductions should be considered and the haematological response should be closely monitored. Dose reductions may also be necessary for patients with active chronic hepatitis (see **sections 4.4** and **5.2**).

Method of administration:

AZATHIOPRINE 50 PCH tablets are given by mouth.

AZATHIOPRINE 50 PCH tablets may be taken with food or on an empty stomach, but patients should standardise the method of administration (see **sections 4.5** and **5.2**).

Some patients experience nausea when first given AZATHIOPRINE 50 PCH. With oral administration, nausea appears to be relieved by administering the tablets after meals. However, administration of AZATHIOPRINE 50 PCH tablets after meals may reduce oral absorption, therefore monitoring for therapeutic efficacy should be considered after administration in this way (see **section 4.8**).

The dose should not be taken with milk or dairy products (see **sections 4.5** and **5.2**).

4.3 Contraindications:

AZATHIOPRINE 50 PCH is contraindicated in:

- Patients with a known hypersensitivity towards azathioprine, 6-mercaptopurine (6-MP) or to any of the excipients of AZATHIOPRINE 50 PCH listed in **section 6.1**.
- Severe infections.
- Severe hepatic impairment or bone marrow depression.
- Pancreatitis.
- Live vaccines, particularly tuberculosis (BCG), smallpox and yellow fever vaccines.
- AZATHIOPRINE 50 PCH should be avoided in pregnancy.

- Safety in lactation has not been established.

4.4 Special warnings and precautions for use:

Hypersensitivity:

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

In many cases, re-challenge has confirmed an association with AZATHIOPRINE 50 PCH.

It has been suggested that the imidazole sidechain gives rise to sensitivity, whereas the 6-MP molecule gives rise to cholestasis.

Allergic reactions including skin rashes, pruritus and erythema, often of an area previously irradiated, may occur. Anaphylaxis may also occur. Headache, hypotension, cardiac dysrhythmia, malaise-weakness, dizziness, vomiting, fever, rigors, muscular pains, arthralgia, disturbed liver functions, cholestatic jaundice and pancreatitis have been reported.

AZATHIOPRINE 50 PCH has been associated with gastrointestinal disorders, reversible alopecia and symptoms such as rash, muscle and joint pain, fever, shivering, pneumonitis, pancreatitis, tachycardia, renal dysfunction and hypotension. Some of these side effects may be an indication of a hypersensitivity reaction. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported less frequently (see **section 4.8**).

Immunisation:

When inactivated or toxoid vaccines are co-administered with AZATHIOPRINE 50 PCH, the immune response should be checked by titration.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, it is recommended that patients do not receive live organism vaccines until at least 3 months after the end of their treatment with azathioprine (see **section 4.5**).

Ribavirin:

Co-administration of ribavirin and azathioprine (e.g. AZATHIOPRINE 50 PCH) is not advised. Ribavirin may reduce efficacy and increase toxicity of AZATHIOPRINE 50 PCH (see **section 4.5**).

Monitoring:

THE RISKS ASSOCIATED WITH AZATHIOPRINE 50 PCH THERAPY SHOULD BE CONSIDERED AGAINST THE SEVERITY OF THE PATIENT'S CONDITION AND THE EXPECTED BENEFICIAL CLINICAL EFFECT.

There are potential hazards in the use of AZATHIOPRINE 50 PCH. AZATHIOPRINE 50 PCH should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of the therapy.

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

IT IS SUGGESTED THAT DURING THE FIRST EIGHT WEEKS OF AZATHIOPRINE 50 PCH THERAPY, COMPLETE BLOOD COUNTS, INCLUDING PLATELET COUNTS MUST BE PERFORMED AT LEAST 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 after eight weeks. It is suggested that full blood counts are repeated monthly or at least at intervals of no longer than 3 months, even if patients are stabilised with long-term therapy.

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

During the course of therapy, AZATHIOPRINE 50 PCH may have to be discontinued because of haematopoietic toxicity. The maximum effect of AZATHIOPRINE 50 PCH on the white cell count usually manifests within the first two weeks of initiating treatment, but thereafter the risk of complications gradually declines as the duration of therapy increases.

Patients receiving AZATHIOPRINE 50 PCH 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 50 PCH is withdrawn early enough.

AZATHIOPRINE 50 PCH 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.

Cases of non-cirrhotic portal hypertension/ portosinusoidal vascular disease have been reported. Early clinical signs include liver enzyme abnormalities, mild jaundice, thrombocytopenia, and splenomegaly (see **section 4.8**). The patient should be informed about the symptoms of liver injury and advised to contact their medical practitioner immediately if these occur.

If AZATHIOPRINE 50 PCH is used in conjunction with, or soon after, withdrawal of another medicine known to have a depressive effect on the bone marrow, it is particularly important that frequent blood counts be taken. Since AZATHIOPRINE 50 PCH may have a delayed action, it is important to reduce dosage or withdraw the medicine temporarily at the first sign of an abnormally large fall in leukocyte count and/or other evidence of persistent depression of the bone marrow.

Such bone marrow depression is usually reversible at the doses recommended for auto-immune disease.

The effect on white cell count is not closely correlated with the immunosuppressive effect of AZATHIOPRINE 50 PCH; a good immunosuppressive effect can often be obtained without change in the white cell count, but sometimes the count may be greatly reduced without any apparent immunosuppression.

The frequency of blood count monitoring should be increased

- if high doses of AZATHIOPRINE 50 PCH are used,
- in elderly patients,
- in patients with renal impairment or hypersplenism,
- in the presence of mild to moderate hepatic impairment,

- in the presence of mild to moderate bone marrow depression.

Close monitoring of blood counts is required when azathioprine is given concurrently with allopurinol, oxipurinol or thiopurinol, aminosalicylic acid derivatives such as mesalazine, olsalazine or sulfasalazine, ACE inhibitors, trimethoprim/sulfamethoxazole, cimetidine or indomethacin, cytotoxic and/or bone marrow suppressive medicines (see **section 4.5**).

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, as in AZATHIOPRINE 50 PCH and prone to developing rapid bone marrow depression following the initiation of treatment with AZATHIOPRINE 50 PCH.

This problem could be exacerbated by coadministration with medicines that inhibit TPMT (aminosalicylate derivatives), such as olsalazine, mesalazine or sulphasalazine. Also, a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving 6-MP (the active metabolite of azathioprine) in combination with other cytotoxics (see **section 4.8**).

Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore, close monitoring of blood counts is still necessary.

The patient's phenotype or genotype should be determined before administration of AZATHIOPRINE 50 PCH to establish whether thiopurine methyltransferase deficiency is involved. TPMT deficiency and impaired hepatic or renal function increase the predisposition for azathioprine-induced bone marrow toxicity.

The dosage of AZATHIOPRINE 50 PCH may need to be reduced when AZATHIOPRINE 50 PCH is combined with other medicines whose primary or secondary toxicity is myelosuppression (see **section 4.5**).

Patients with NUDT15 variant:

Patients with inherited mutated NUDT15 gene are at increased risk for severe azathioprine toxicity, such as early leukopenia and alopecia, from conventional doses of AZATHIOPRINE 50 PCH therapy and generally require substantial dose reduction.

Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population.

The optimal starting dose for heterozygous or homozygous deficient patients has not been established.

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

Renal and/or hepatic impairment:

Caution is advised during the administration of AZATHIOPRINE 50 PCH in patients with renal impairment and/or hepatic impairment. Consideration should be given to reducing the starting dosage in these patients and haematological response should be carefully monitored (see **section 4.2** and **section 5.2**).

The dosage of AZATHIOPRINE 50 PCH must be reduced for the treatment of active chronic hepatitis.

Patients with impaired renal and/or hepatic function may eliminate the medicine and its metabolites at a reduced rate with a consequent cumulative effect. The dosage of AZATHIOPRINE 50 PCH should therefore be reduced in such cases, particularly in anuric patients.

If there is evidence of toxic hepatitis or biliary stasis, consideration must be given to withholding AZATHIOPRINE 50 PCH. Elevated serum bilirubin levels have been observed in some patients after initiation of AZATHIOPRINE 50 PCH therapy (see **section 4.8**).

Lesch-Nyhan syndrome:

AZATHIOPRINE 50 PCH is not beneficial to patients with the hereditary hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome). Therefore, given the abnormal metabolism in these patients, they should not receive AZATHIOPRINE 50 PCH.

Infections:

AZATHIOPRINE 50 PCH has an immunosuppressant effect involving both antibody and cell-mediated immunity. Infection, which is always a hazard of immunosuppressive therapy, particularly when corticosteroids are given, may require the dosage of immunosuppressive medicines to be reduced temporarily.

Fungal, protozoal, viral and uncommon bacterial infections in patients on immunosuppressive therapy have occurred and should be treated vigorously. Some of these have proved fatal.

Special caution is required with patients with untreated acute infections (see **section 4.3**).

The infectious disease and complications may be more severe in these patients than in non-treated patients. The patients should be instructed to immediately report any evidence of ulceration of the throat, fever, infections, bruising or bleeding or other manifestations of bone marrow depression (see s**ection 4.9**).

Cases of neutropenic sepsis have been reported in patients receiving 6-mercaptopurine.

Gastrointestinal intolerance:

AZATHIOPRINE 50 PCH may cause anorexia, nausea, vomiting or diarrhoea. In such cases AZATHIOPRINE 50 PCH therapy may have to be adjusted, by giving AZATHIOPRINE 50 PCH in divided doses and/or with meals. Stomatitis, mouth ulceration, oesophagitis, abdominal pain, intestinal haemorrhage, ulceration and perforation may occur.

There is an increased susceptibility to infection in patients with inflammatory bowel disease.

Metabolism and nutrition disorders:

Purine analogues, azathioprine and mercaptopurine (i.e., AZATHIOPRINE 50 PCH), may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency (pellagra). Cases of pellagra have been reported with the use of azathioprine, as in AZATHIOPRINE 50 PCH, particularly in patients with chronic inflammatory bowel disease. The diagnosis of pellagra should be considered in patients with a localised pigmented rash; gastroenteritis and extensive neurological deficits including cognitive deterioration.

Appropriate medical care with niacin/ nicotinamide supplementation must be initiated, and dose reduction or discontinuation of AZATHIOPRINE 50 PCH must be considered.

Posterior reversible encephalopathy syndrome (PRES)

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients using azathioprine. If patients taking azathioprine present with symptoms indicating PRES such as headache, altered mental status, seizures, hypertension, and visual disturbances, a diagnostic imaging should be performed. If PRES is diagnosed, adequate blood pressure and seizure control and immediate discontinuation of azathioprine is advised. Most cases reported resolved following discontinuation of azathioprine and appropriate treatment.

Other:

Persistent negative nitrogen balance has been observed in some patients on continuous AZATHIOPRINE 50 PCH and corticosteroid therapy. If this occurs the dosage should be reduced.

Other reported complications include medicine fever, serum-sickness, pulmonary oedema, reversible pneumonitis, peritoneal haemorrhage, retinopathy, alopecia (resolves despite continuing therapy), arthralgia and Raynaud's phenomenon. Hyperuricaemia and acute renal failure due to uric acid nephropathy, hyperphosphataemia and pigmentation of the skin and nails may also occur.

Carcinogenicity:

Some homograft recipients, whose immune responses have been suppressed, appear to be vulnerable to neoplasia either in the transplanted organ or at some other unrelated site, during the first few weeks or months after transplantation. This is a known risk after transplantation and it could also occur when immunosuppressive therapy such as AZATHIOPRINE 50 PCH is used in the treatment of auto-immune disease.

Patients receiving immunosuppressive therapy, including AZATHIOPRINE 50 PCH 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 such as AZATHIOPRINE 50 PCH may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines such as AZATHIOPRINE 50 PCH) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

Reports of hepatosplenic T-cell lymphoma have been received when azathioprine, as in AZATHIOPRINE 50 PCH, is used alone or in combination with anti-TNF medicines or other immunosuppressants. Although most reported cases occurred in the inflammatory bowel disease (IBD) population, there have also been cases reported outside of this population.

Patients receiving multiple immunosuppressive medicines may be at risk of over-immunosuppression, therefore such therapy should be maintained at the lowest effective level.

As is usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet irradiation/ UV light should be limited, and patients should wear protective clothing and use a sunscreen with a high protection factor.
Patients on concomitant cytotoxic treatment should only be given AZATHIOPRINE 50 PCH under close supervision.

Mutagenicity:

Chromosomal abnormalities have been demonstrated in both male and female patients treated with azathioprine, as in AZATHIOPRINE 50 PCH. It is difficult to assess the role of AZATHIOPRINE 50 PCH in the development of these abnormalities.

Chromosomal abnormalities which disappear in time, have been demonstrated in lymphocytes from the offspring of patients treated with AZATHIOPRINE 50 PCH.
AZATHIOPRINE 50 PCH has long-term effects on the gonads, and may suppress ovarian and testicular function with amenorrhoea and inhibition of spermatogenesis.
Except in extremely less frequent cases, no overt physical evidence of abnormality has been observed in the offspring (children) of patients treated with AZATHIOPRINE 50 PCH (see **section 4.6**).

Azathioprine, as in AZATHIOPRINE 50 PCH, and long-wave ultraviolet (UV) light have been shown to have a synergistic clastogenic effect in patients treated with AZATHIOPRINE 50 PCH for a range of disorders.

Macrophage activation syndrome (MAS):

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with auto-immune conditions, in particular with inflammatory bowel disease (IBD), and there could potentially be an increased susceptibility for developing MAS with the use of AZATHIOPRINE 50 PCH. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with AZATHIOPRINE 50 PCH should be discontinued. Medical practitioners should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Varicella zoster virus (VZV) infection:

Infection with varicella zoster virus (VZV; chickenpox and herpes zoster) may become severe during the administration of immunosuppressants such as AZATHIOPRINE 50 PCH. Caution should be exercised especially with respect to the following:

Before starting the administration of AZATHIOPRINE 50 PCH, 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 John Cunningham virus (JC virus), has been reported in patients receiving AZATHIOPRINE 50 PCH in combination with other immunosuppressive medicines. Immunosuppression therapy should be withheld at the first signs or symptoms suggestive of PML and appropriate evaluation undertaken to establish a diagnosis (see **section 4.8**).

Hepatitis B:

Hepatitis B virus (HBV) carriers (defined as patients positive for hepatitis B surface antigen [HBsAg] for more than six months), or patients with documented past HBV infection, who receive immunosuppressive medicines are at risk of reactivation of HBV replication, with asymptomatic increases in serum HBV DNA and ALT levels. Local guidelines may be considered including prophylactic therapy with oral anti-HBV medicines (see **section 4.8**). Serologic testing prior to starting AZATHIOPRINE 50 PCH treatment should be considered with respect to hepatitis B.

Xanthine oxidase inhibitors:

If allopurinol, oxipurinol and/or thiopurinol are given concomitantly with AZATHIOPRINE 50 PCH, the dosage of AZATHIOPRINE 50 PCH must be reduced to a quarter of the original dosage.

Failure to reduce the dosage of AZATHIOPRINE 50 PCH in the presence of allopurinol can result in severe bone marrow depression (see **section 4.5**).

Neuromuscular blocking medicines:

Special care is necessary when AZATHIOPRINE 50 PCH is given concomitantly with neuromuscular blocking medicines such as atracurium, rocuronium, cisatracurium, tubocurarine or suxamethonium (also known as succinylcholine) (see **section 4.5**).

AZATHIOPRINE 50 PCH can also potentiate the neuromuscular block that is produced by depolarising medicines such as succinylcholine (see **section 4.5**).

Patients should be advised to inform their anaesthesiologist of their treatment with AZATHIOPRINE 50 PCH prior to surgery.

Concomitant medicines and/or surgery:

Patients receiving anticoagulants of the coumarin type concomitantly with AZATHIOPRINE 50 PCH should be monitored closely for coagulation (see **section 4.5**).

Discontinuation:

Discontinuation of AZATHIOPRINE 50 PCH may seriously complicate the condition, for instance in patients with systemic lupus erythematosus by nephritis.

AZATHIOPRINE 50 PCH must always be withdrawn gradually and under close supervision.

Excipients:

AZATHIOPRINE 50 PCH contains lactose. Patients with rare hereditary problems or galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take AZATHIOPRINE 50 PCH.

4.5 Interaction with other medicines and other forms of interaction:

Food, milk and dairy products:

The administration of azathioprine, as in AZATHIOPRINE 50 PCH, with food may decrease systemic exposure slightly but this is unlikely to be of clinical significance (see **section 4.8**). Therefore, AZATHIOPRINE 50 PCH may be taken with food or on an empty stomach, but patients should standardise the method of administration.
The dose should not be taken with milk or dairy products since they contain xanthine oxidase, an enzyme which metabolises 6–mercaptopurine and might therefore lead to reduced plasma concentrations of 6–mercaptopurine (see **section 4.2** and **5.2**).

Vaccines:

The immunosuppressive activity of azathioprine, as in AZATHIOPRINE 50 PCH, 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 50 PCH (see **section 4.4**).

A diminished response to killed vaccines is likely and such a response to hepatitis B vaccine has been observed among patients treated with a combination of azathioprine, as in AZATHIOPRINE 50 PCH, and corticosteroids.

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

A small clinical study has indicated that standard therapeutic doses of azathioprine, as in AZATHIOPRINE 50 PCH, do not deleteriously affect the response to polyvalent pneumococcal vaccine, as assessed on the basis of mean anti-capsular specific antibody concentration
Immunisation with oral poliovirus vaccine should be postponed in persons in close contact with the patient (especially family members).

Effect of concomitant medicines on AZATHIOPRINE 50 PCH:

Ribavirin:

Ribavirin inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant

administration of azathioprine, as in AZATHIOPRINE 50 PCH, and ribavirin ; therefore, co-administration is not advised (see **section 4.4**).

Allopurinol/ oxipurinol / thiopurinol and other xanthine oxidase inhibitors:

Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid.

When allopurinol, oxipurinol and/or thiopurinol are given concomitantly with 6-MP or azathioprine, as in AZATHIOPRINE 50 PCH, the dose of 6-MP and AZATHIOPRINE 50 PCH should be reduced to 25 % (one-quarter) of the original dose (see **section 4.4**). Fatal cases have been reported in patients treated concomitantly with azathioprine and allopurinol.

Other xanthine oxidase inhibitors, such as febuxostat may decrease the metabolism of azathioprine, as in AZATHIOPRINE 50 PCH. Concomitant administration is not recommended, as data are insufficient to determine an adequate dose reduction.

Neuromuscular blocking medicines:

AZATHIOPRINE 50 PCH inhibits phosphodiesterase activity in motor nerve terminals increasing the release of acetylcholine.

There is clinical evidence that azathioprine, as in AZATHIOPRINE 50 PCH, antagonises the effect of non-depolarising muscle relaxants such as curare, d-tubocurarine and pancuronium.

Experimental data confirm that AZATHIOPRINE 50 PCH reverses the neuromuscular blockade produced by d-tubocurarine and show that AZATHIOPRINE 50 PCH potentiates the neuromuscular blockade produced by succinylcholine (see **section 4.4**).

Cytostatic medicines/ myelosuppressive medicines:

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

There are conflicting clinical reports of interactions, resulting in serious haematological abnormalities, between azathioprine, as in AZATHIOPRINE 50 PCH, and trimethoprim/sulfamethoxazole also known as co-trimoxazole.

Medicines which may affect leukocyte production, including co-trimoxazole, may lead to exaggerated leukopenia, especially in renal transplant recipients.

There have been case reports suggesting that haematological abnormalities may develop due to the concomitant administration of AZATHIOPRINE 50 PCH and angiotensin converting enzyme (ACE) inhibitors (e.g. captopril). The use of ACE inhibitors to control hypertension in patients on azathioprine, as in AZATHIOPRINE 50 PCH, has been reported to induce severe leukopenia.

It has been suggested that cimetidine and indomethacin may have myelosuppressive effects, which may be enhanced by concomitant administration of AZATHIOPRINE 50 PCH.

When AZATHIOPRINE 50 PCH is combined with other immunosuppressants such as ciclosporin or tacrolimus, it is important to be aware of the increased risk of unusually high immunosuppression.

Diuretics:

Furosemide has been shown to impair the metabolism of azathioprine, as in AZATHIOPRINE 50 PCH by human hepatic tissue *in vitro*. The clinical significance is unknown.

Aminosalicylates:

Concomitant administration with aminosalicylate derivatives such as olsalazine, mesalazine and sulfasalazine may involve a risk of increased myelosuppressive action as a result of inhibited degradation in the liver.
There is *in vitro* and *in vivo* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulfasalazine) inhibit the TPMT enzyme.
Therefore, lower doses of azathioprine (i.e., AZATHIOPRINE 50 PCH) may need to be considered when administered concomitantly with aminosalicylate derivatives (see **section 4.4**).

Methotrexate:

Methotrexate (20 mg/m^2 orally) increased the AUC of 6-mercaptopurine (the primary metabolite of azathioprine) by approximately 31 % and methotrexate (2 or 5 g/m^2 intravenously) increased the AUC of 6-mercaptopurine by 69 % and 93 % respectively.

Therefore, when AZATHIOPRINE 50 PCH is administered concomitantly with high doses methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.

Infliximab:

An interaction has been observed between azathioprine, as in AZATHIOPRINE 50 PCH 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.

Effect of AZATHIOPRINE 50 PCH on other medicines:

Anticoagulants:

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with azathioprine, as in AZATHIOPRINE 50 PCH; therefore, higher doses of the anticoagulant may be needed.

It is recommended that coagulation tests (INR and/or PT) are closely monitored when oral anticoagulants (warfarin) are concurrently administered with AZATHIOPRINE 50 PCH.

4.6 Fertility, pregnancy and lactation:

Women of childbearing potential/contraception in males and females:

Due to the genotoxic potential of azathioprine (see **sections 4.4** and **5.3**), women of childbearing potential should use effective contraceptive measures while being treated with AZATHIOPRINE 50 PCH and for 6 months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving AZATHIOPRINE 50 PCH and for 3 months following completion of treatment.

Pregnancy:

The safety of AZATHIOPRINE 50 PCH in pregnancy has not been established.

AZATHIOPRINE 50 PCH can cause foetal harm when administered to pregnant women.

AZATHIOPRINE 50 PCH should not be given to patients who are pregnant or likely to become pregnant in the near future.

Substantial transplacental and trans-amniotic transmission of azathioprine, as in AZATHIOPRINE 50 PCH, and its metabolites from the mother to the foetus have been shown to occur.

Evidence of the teratogenicity of AZATHIOPRINE 50 PCH in man is equivocal. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving AZATHIOPRINE 50 PCH (see **section 5.3**).

There have been a few reports of congenital deformity when the father was receiving AZATHIOPRINE 50 PCH at the time of conception.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine therapy (i.e., AZATHIOPRINE 50 PCH). Early diagnosis and discontinuation of AZATHIOPRINE 50 PCH may minimise impact on the foetus. A careful assessment should be performed, if cholestasis of pregnancy is confirmed.

Mutagenicity:

Chromosomal abnormalities, which disappear with time, have been demonstrated in lymphocytes from the offspring of patients treated with AZATHIOPRINE 50 PCH. Except in extremely less frequent cases, no overt physical evidence of abnormality has been observed in the offspring of patients treated with AZATHIOPRINE 50 PCH.

Azathioprine, as in AZATHIOPRINE 50 PCH, and long-wave ultraviolet light have been shown to have a synergistic clastogenic effect in patients treated with azathioprine, as in AZATHIOPRINE 50 PCH, for a range of disorders (see **section 4.4)**.

Leukopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took azathioprine, as in AZATHIOPRINE 50 PCH, throughout their pregnancies.

Extra care in haematological monitoring is advised during pregnancy.

AZATHIOPRINE 50 PCH has been reported to inhibit the efficacy of intrauterine contraceptive devices.

There have been reports of intrauterine growth retardation (IUGR), premature birth and low birth weight following maternal exposure to azathioprine, as in AZATHIOPRINE 50 PCH, particularly in combination with prednisolone.

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

The long-term consequences of these effects of AZATHIOPRINE 50 PCH are not known; however, many children who had been exposed to AZATHIOPRINE 50 PCH in the womb have now reached the age of 10 years without any reports of adverse effects.

Breastfeeding:

The safety of AZATHIOPRINE 50 PCH in lactation has not been established.

AZATHIOPRINE 50 PCH and/or its metabolites, such as 6-mercaptopurine (6-MP) have been identified in the colostrum and breast milk of women receiving treatment with azathioprine, as in AZATHIOPRINE 50 PCH.

AZATHIOPRINE 50 PCH is distributed, in low concentrations, into breast milk.

It is recommended that women receiving azathioprine (i.e., AZATHIOPRINE 50 PCH) should not breastfeed.

Fertility:

The specific effect of azathioprine therapy (i.e., AZATHIOPRINE 50 PCH) on human fertility is unknown.

Several studies report that azathioprine, as in AZATHIOPRINE 50 PCH, at standard doses does not appear to affect male fertility.

Relief of chronic renal insufficiency by renal transplantation involving the administration of AZATHIOPRINE 50 PCH has been accompanied by increased fertility in both male and female transplant recipients.

4.7 Effects on ability to drive and use machines:

AZATHIOPRINE 50 PCH has a moderate influence on the ability to drive and operate machinery.

Since adverse reactions such as dizziness and retinopathy have been reported in patients receiving AZATHIOPRINE 50 PCH, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that AZATHIOPRINE 50 PCH does not adversely affect their ability to do so (see **section 4.8**).

4.8 Undesirable effects:

a. Summary of the safety profile:

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

b. Tabulated list of adverse reactions:

Infections and infestations:	
Frequent:	Fungal, protozoal, viral and bacterial infections in transplant patients receiving AZATHIOPRINE 50 PCH in combination with immunosuppressants (see **section 4.4**), increased sensitivity to infection in patients with inflammatory bowel disease.
Less frequent:	Viral, fungal and bacterial infections in other patient populations, cases of JC virus associated PML have been reported following the use of azathioprine in combination with other immunosuppressants (see s**ection 4.4**).
Frequency unknown:	Protozoal and uncommon bacterial infections.
Neoplasms benign malignant and unspecified (including cysts and polyps):	
Frequent:	Squamous cell skin carcinoma, non-Hodgkin's lymphoma, cervical cancer, Kaposi's sarcoma, vulval cancer.
Less frequent:	Post-transplantation lymphoproliferative disorder, neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ* (see **section 4.4**), acute myeloid leukaemia and myelodysplastic syndrome.
Frequency unknown:	Hepatosplenic T-cell lymphoma (see **section 4.4**)
Blood and lymphatic system disorders:	
Frequent:	Leukopenia, thrombocytopenia, bone marrow depression.

Less frequent:	Anaemia, macrocytosis, neutropenia, bone marrow aplasia, granulocytopenia, agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia.
Frequency unknown:	Reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content.
Metabolism and nutrition disorders:	
Frequency unknown:	Hyperphosphataemia, anorexia and other disturbances of the electrolyte balance, pellagra (see **section 4.4**)
Immune system disorders:	
Less frequent:	Hypersensitivity reaction (including skin rashes, exanthema, pruritus, erythema, often of an area previously irradiated), erythema nodosum, Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) (see **section 4.4**).
Frequency unknown:	Anaphylaxis
Nervous system disorders:	
Frequency unknown:	Headache, dizziness, Posterior reversible encephalopathy syndrome (PRES), tremor
Eye disorders:	
Frequency unknown:	Retinopathy.
Cardiac disorders:	
Frequency unknown:	Cardiac dysrhythmia
Vascular disorders:	
Frequency unknown:	Hypotension, Raynaud's phenomenon.
Respiratory, thoracic and mediastinal disorders:	
Less frequent:	Pulmonary oedema, interstitial pneumonia (reversible).
Gastrointestinal disorders:	
Frequent:	Nausea and vomiting.
Less frequent:	Pancreatitis, abdominal pain, oral ulceration and soreness,

	oesophagitis, gastric ulcer and intestinal/peritoneal haemorrhage, necrosis or perforation, steatorrhea, colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population.
Frequency unknown:	Stomatitis, sialadenitis
Hepato-biliary disorders:	
Frequent:	Hepatic impairment (including destructive cholangitis, peliosis hepatitis, peri-sinusoidal fibrosis, nodular regenerative hyperplasia).
Less frequent:	Cholestasis (biliary stasis) and cholestasis of pregnancy, toxic hepatitis, hepatitis, endophlebitis hepatica obliterans, life-threatening liver injury.
Frequency unknown:	Non-cirrhotic portal hypertension, portosinusoidal vascular disease, cholestatic jaundice.
Skin and subcutaneous disorders:	
Less frequent:	Skin rash, photosensitivity, alopecia.
Frequency unknown:	Vesicant or irritant effects on the skin and mucous membranes, pigmentation of the skin and nails (may occasionally be part of Addison's disease), acute febrile neutrophilic dermatosis (Sweet's syndrome).
Musculoskeletal, connective tissue and bone disorders:	
Frequency unknown:	Muscular pains (myalgia), arthralgia.
Renal and urinary disorders:	
Frequency unknown:	Hyperuricaemia and acute renal failure due to uric acid nephropathy, chromaturia.
Reproductive system and breast disorders:	
Frequency unknown:	Suppression of ovarian and testicular function with amenorrhoea and inhibition of spermatogenesis.

Congenital, familial, and genetic disorders:	
Frequency unknown:	Chromosomal abnormalities.
General disorders and administrative site conditions:	
Frequency unknown:	Medicine fever, serum sickness, malaise, fever, rigors, general weakness.
Investigations:	
Frequency unknown:	Liver function tests abnormal (elevated serum bilirubin levels), persistent negative nitrogen balance

c. Description of selected adverse reactions:

Infections and infestations:

Patients receiving azathioprine, as in AZATHIOPRINE 50 PCH, 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 medicines (see **section 4.4**).

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

The risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer *in situ*, is increased in patients who receive immunosuppressants, particularly in transplant recipients receiving aggressive treatment and such therapy should be maintained at the lowest effective levels.

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.

The increased risk of developing non-Hodgkin's lymphomas in immunosuppressed rheumatoid arthritis patients compared with the general population appears to be related at least in part to the disease itself.

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

Blood and lymphatic system disorders:

Azathioprine, as in AZATHIOPRINE 50 PCH, 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 less frequently 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, as in AZATHIOPRINE 50 PCH, when receiving concurrent allopurinol therapy.

Reversible, dose-related increases in mean corpuscular volume and red cell haemoglobin content have occurred in association with azathioprine (i.e., AZATHIOPRINE 50 PCH) therapy.

Megaloblastic bone marrow changes have also been observed but severe megaloblastic anaemia and erythroid hypoplasia are less frequent.

Immune system disorders:

Several different clinical syndromes, which appear to be idiosyncratic manifestations of hypersensitivity, have been described occasionally following administration of azathioprine, as in AZATHIOPRINE 50 PCH, Clinical features include general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, erythema nodosum, vasculitis, myalgia, arthralgia, hypotension, cardiac dysfunction, renal dysfunction, hepatic dysfunction and cholestasis (see **section 4.8 - Hepatobiliary disorders**).

In many cases, rechallenge has confirmed an association with azathioprine, as in AZATHIOPRINE 50 PCH.

Immediate withdrawal of AZATHIOPRINE 50 PCH 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 50 PCH, the necessity for continued administration should be carefully considered on an individual basis.

Gastrointestinal disorders:

Some patients experience nausea when first given azathioprine (i.e., AZATHIOPRINE 50 PCH). With oral administration, nausea appears to be relieved by administering the tablets after meals. However, administration of azathioprine tablets (i.e., AZATHIOPRINE 50 PCH) after meals may reduce oral absorption, therefore monitoring for therapeutic efficacy should be considered after administration in this way (see **section 4.2** and **section 5.2**).

Serious complications, including colitis, diverticulitis and bowel perforation, have been described in transplant recipients receiving immunosuppressive therapy. However, the aetiology is not clearly established and high-dose corticosteroids may be implicated.

Severe diarrhoea, recurring on re-challenge, has been reported in patients treated with azathioprine, as in AZATHIOPRINE 50 PCH for inflammatory bowel disease (IBD). The possibility that exacerbation of symptoms might be related to the medicine 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 medicine, although re-challenge has confirmed an association with azathioprine as in AZATHIOPRINE 50 PCH on occasions.

Hepatobiliary disorders:

Cholestasis and deterioration of liver function have occasionally been reported in association with azathioprine, as in AZATHIOPRINE 50 PCH, therapy and are usually reversible on withdrawal of therapy. This may be associated with symptoms of a hypersensitivity reaction (see **section 4.8 - Immune system disorders**).

Life-threatening hepatic damage associated with chronic administration of azathioprine, as in AZATHIOPRINE 50 PCH, has been described primarily in transplant patients. Histological findings include sinusoidal dilatation, peliosis hepatis, veno-occlusive disease and nodular regenerative hyperplasia. In some cases, withdrawal of azathioprine, as in AZATHIOPRINE 50 PCH, has resulted in either a temporary or permanent improvement in liver histology and symptoms.

Skin and subcutaneous tissue disorders:

Hair loss has been described on a number of occasions in patients receiving azathioprine, as in AZATHIOPRINE 50 PCH, and other immunosuppressive medicines. In many instances the condition resolved spontaneously despite continuing therapy. The relationship between alopecia and AZATHIOPRINE 50 PCH treatment is uncertain.

Renal and urinary disorders:

A minority of patients receiving azathioprine, as in AZATHIOPRINE 50 PCH, develop chromaturia, often presenting as bright yellow urine. Chromaturia may occur independent of, or because of, renal or hepatic disorder. Other urine discolorations or darkening are indicative of an underlying renal or hepatic pathology and may require investigation.

Paediatric population:

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

Reporting of suspected adverse reactions:

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

4.9 Overdose:

Symptoms:

Unexplained infections, ulceration of the throat, bruising and bleeding are the main signs of overdose with AZATHIOPRINE 50 PCH and result from bone marrow depression which may be maximal after 9 to 14 days. These signs are more likely to manifest following chronic overdosage, rather than after a single acute overdose. There has been a report of a patient who ingested a single overdose of 7,5 g of azathioprine, as in AZATHIOPRINE 50 PCH. The immediate toxic effects of this overdose were nausea, vomiting and diarrhoea, followed by mild leukopenia and mild abnormalities in liver function. Recovery was uneventful.

Treatment:

Treatment is symptomatic and supportive. Monitoring the patient's blood counts and liver function is particularly important. General supportive measures, together with appropriate blood transfusion, should be 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 50 PCH is not known, though azathioprine is partially dialysable.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, Immunosuppressants.

ATC code: L04AX01

Mechanism of action:

Azathioprine, a derivative of 6-mercaptopurine, is a purine antimetabolite with immunosuppressive properties. Azathioprine is cleaved by nucleophiles such as glutathione, to 6-mercaptopurine, which in turn can be converted into 6-mercaptopurine nucleotides.

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.

5. Because of these mechanisms, the therapeutic effect of AZATHIOPRINE 50 PCH may be evident only after several weeks or months of treatment.

AZATHIOPRINE 50 PCH appears to be well absorbed from the upper gastro-intestinal tract.

5.2 Pharmacokinetic properties:

Absorption:

The absorption of azathioprine is incomplete and variable. The median (range) absolute bioavailability of 6-MP after administration of azathioprine 50 mg is 47 % (27 % to 80 %).

The extent of absorption of azathioprine is similar across the gastrointestinal tract, including the stomach, jejunum, and cecum. However, the extent of 6-MP absorption, after azathioprine administration is variable and differs between the sites of absorption, with the highest extent of absorption in the jejunum, followed by the stomach and then the cecum.

Azathioprine is well absorbed from the gastrointestinal tract, with peak levels at 1 to 2 hours after oral administration.

Although there are no food effect studies with azathioprine, pharmacokinetic studies with 6-mercaptopurine have been conducted that are relevant to azathioprine.

The mean relative bioavailability of 6-mercaptopurine was approximately 27 % lower following administration with food and milk compared to an overnight fast. 6-mercaptopurine is not stable in milk due to the presence of xanthine oxidase (30 % degradation within 30 minutes).

Azathioprine may be taken with food or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken with milk or dairy products (see **section 4.2**).

Distribution:

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

Both azathioprine and mercaptopurine are about 30 % bound to plasma proteins.

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

Biotransformation:

Azathioprine is metabolised either by methylation of the sulfhydryl group and subsequent oxidation of the methylated derivatives or by xanthine oxidase to 6-thiouric acid.

Azathioprine is rapidly broken down *in vivo* by glutathione-S-transferase into 6-MP and a methyl-nitroimidazole moiety. The 6-MP readily crosses cell membranes and is extensively metabolised by many multi-step pathways to active and inactive metabolites, with no one enzyme predominating. Because of the complex metabolism, inhibition of one enzyme does not explain all cases of lack of efficacy and/or pronounced myelosuppression.

The predominant enzymes responsible for the metabolism of 6-MP or its downstream metabolites are: the polymorphic enzyme thiopurine S-methyltransferase (TPMT) (see **section 4.4**), xanthine oxidase (see **section 4.5**), inosine monophosphate dehydrogenase (IMPDH) (see **section 4.5**), and hypoxanthine guanine phosphoribosyl transferase (HPRT).

Additional enzymes involved in the formation of active and inactive metabolites are: guanosine monophosphate synthetase (GMPS, which form TGNs) and inosine triphosphate pyrophosphatase (ITPase). Azathioprine itself is also metabolised by aldehyde oxidase to form 8-hydroxy azathioprine, which may be active.

There are also multiple inactive metabolites formed via other pathways.

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

Thiopurine S-Methyl Transferase (TPMT):

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

Genotypic testing can determine the allelic pattern of a patient. Currently, three alleles—TPMT*2, TPMT*3A and TPMT*3C—account for about 95 % of individuals with reduced levels of TPMT activity. Approximately 0,3 % (1:300) of patients have two non-functional alleles (homozygous-deficient) of the TPMT gene and have little or no detectable enzyme activity.

Approximately 10 % of patients have one TPMT non-functional allele (heterozygous) leading to low or intermediate TPMT activity and 90 % of individuals have normal TPMT activity with two functional alleles. There may also be a group of approximately 2 % who have very high TPMT activity. Phenotypic testing determines the level of thiopurine nucleotides or TPMT activity in red blood cells and can also be informative (see **section 4.4**).

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

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

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

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

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

Elimination:

After oral administration of 100 mg [35S]-azathioprine, 50 % of the radioactivity was excreted in the urine over 24 hours and 12 % in the faeces after 48 hours.

In the urine, the major compound was the inactive oxidised metabolite thiouric acid. Less than 2 % was excreted in the urine as azathioprine or 6-MP. Azathioprine has a high extraction ratio with a total clearance greater than 3 L/min in normal volunteers.

There are no data on the renal clearance or half-life of azathioprine. The renal clearance of 6-MP and the half-life of 6-MP are 191 mL/min/m^2 and 0,9 hour respectively.

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

Special patient populations:

Elderly:

No specific studies have been carried out in the elderly.

Overweight paediatric population:

In a US clinical study, 18 children (aged 3 to 14 years) were evenly divided into two groups; either a weight to height ratio above or below the 75th percentile. Each child was on maintenance treatment of 6-MP and the dosage was calculated based on their body surface area. The mean AUC (0-∞) in the group above the 75th percentile was 2,4 times lower than that for the group below the 75th percentile. Therefore, children considered to be overweight may require azathioprine doses at the higher end of the dose range and close monitoring of response to treatment is recommended.

Patients with renal impairment:

Studies with azathioprine have shown no difference in 6-mercaptopurine pharmacokinetics in uremic patients compared to renal transplant patients.

Since little is known about the active metabolites of azathioprine in renal impairment, consideration should be given to reducing the dosage in patients with impaired renal function (see **section 4.2**).

Azathioprine and/or its metabolites are eliminated by haemodialysis, with approximately 45 % of radioactive metabolites eliminated during dialysis of 8 hours.

Azathioprine and its metabolites are excreted primarily in the urine.

Patients with hepatic impairment:

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

5.3. Preclinical safety data:

Teratogenicity:

Studies in pregnant rats, mice and rabbits using azathioprine, as in AZATHIOPRINE 50 PCH, in dosages from 5 to 15 mg/kg body weight/day over the period of organogenesis have shown varying degrees of foetal abnormalities. Teratogenicity was evident in rabbits at 10 mg/kg body weight/day. Studies with pregnant rabbits and Swiss-Webster mice have shown that azathioprine produces resorptions and skeletal anomalies even when administered as late as the midpoint of gestation.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Colloidal anhydrous silica

Lactose monohydrate

Magnesium stearate

Potato starch

Povidone.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

5 years.

6.4 Special precautions for storage:

Store at or below 25 ºC and protect from light.

Keep blister in carton until required for use.

6.5 Nature and contents of container:

AZATHIOPRINE 50 PCH tablets are provided in:

Aluminium/PVC/PVDC and transparent green PVC foil blister strips. 10 Tablets per blister and 10 blister strips per outer carton.

White HDPE containers with white PP closure with space filler (polyurethane). Pack sizes of 90, 100, 150 or 250 tablets.

6.6 Special precautions for disposal and other handling:

AZATHIOPRINE 50 PCH is mutagenic and potentially carcinogenic.

AZATHIOPRINE 50 PCH should only be handled while taking appropriate precautions, especially for pregnant females.

If it is necessary to divide the film-coated tablet, precautions must be taken to prevent exposure to the skin from tablet dust or broken tablet surfaces.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd,

Maxwell Office Park,

Magwa Crescent West,

Waterfall City,

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8. REGISTRATION NUMBER:

37/26/0692

9. DATE OF FIRST AUTHORISATION:

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10. DATE OF REVISION OF TEXT:

19 June 2026

Namibia

Reg. No.: 13/26/0126

NS2

Botswana:

10 x 10's PVC/Alu blister Reg. No.: BOT1803358

S2