PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr] AZATHIOPRINE-50

Azathioprine Tablets USP

50 mg

IMMUNOSUPPRESSIVE AGENT

PRO DOC LTÉE
2925, Boul. Industriel,
Laval, Quebec
H7L 3W9

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PrAZATHIOPRINE-50

Azathioprine Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablet / 50 mg	Lactose, magnesium stearate, microcrystalline cellulose and starch

INDICATIONS AND CLINICAL USE

Renal Homotransplantation

AZATHIOPRINE-50 (Azathioprine Tablets USP) is indicated as an adjunct for the prevention of rejection in renal homotransplantation.

Rheumatoid Arthritis

AZATHIOPRINE-50 is indicated only in adult patients meeting criteria for classic or definite rheumatoid arthritis as specified by the American Rheumatism Association. AZATHIOPRINE-50 should be restricted to patients with severe, active and erosive disease not responsive to conventional management including rest, acetylsalicylic acid or other non-steroidal drugs, or with disease-modifying antirheumatic drugs (DMARD's).

Geriatrics (>65 years of age):

No data are available.

Pediatrics (<18 years of age):

No data are available.

CONTRAINDICATIONS

- Patients who are hypersensitive to AZATHIOPRINE-50 or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions

- **AZATHIOPRINE-50 (Azathioprine Tablets USP) is mutagenic and carcinogenic and may increase the patients' risk of neoplasia, in particular lymphoproliferative disorders (including hepatosplenic T-cell lymphoma [HSTCL]) and skin cancer (see WARNINGS AND PRECAUTIONS, *General* and *Carcinogenesis and Mutagenesis*).**
- **Severe leukopenia and/or thrombocytopenia may occur in patients on AZATHIOPRINE-50 (see WARNINGS AND PRECAUTIONS, *General* and *Hematologic*).**
- **Macrophage activation syndrome (see WARNINGS AND PRECAUTIONS)**
- **Increased susceptibility to infection. (**see WARNINGS AND PRECAUTIONS**,** ***Immune*****).**
- **AZATHIOPRINE-50 can cause fetal harm when administered to a pregnant woman (see** WARNINGS AND PRECAUTIONS**, Special Populations,** ***Pregnant Women*****).**
- **Transplantation**
  Only physicians experienced in immunosuppressive therapy and management of organ transplant should prescribe AZATHIOPRINE-50. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.
- **Rheumatoid Arthritis**
  Careful monitoring of AZATHIOPRINE-50 treated patients is mandatory. AZATHIOPRINE-50 should only be prescribed for rheumatoid arthritis by physicians experienced with the use of immunosuppressants.

General

Physicians prescribing this drug should be very familiar with the mutagenic potential of the drug to both men and women and with its possible hematologic toxicities. Physicians should inform patients of the risk of malignancy with AZATHIOPRINE-50 (see WARNINGS AND PRECAUTIONS, ***Carcinogenesis and Mutagenesis*** and ***Hematologic***).

The dosage that will be tolerated or effective will vary from patient to patient. Therefore, careful management is necessary to obtain the optimum therapeutic effect and to reduce toxicity. Caution must be exercised to observe early signs of depression of the bone marrow which may result in leukopenia and eventually thrombocytopenia and bleeding. Since this drug may have a delayed action, it is important to withdraw the medication temporarily at the first sign of an

abnormally large fall in the white cell count or of abnormal depression of the bone marrow. It must be kept in mind that patients with impaired renal function may have slower elimination of the drug and a greater cumulative effect. Lower dose if there is impaired renal function. It is recommended that the drug be withheld if there is evidence of toxic hepatitis or biliary stasis.

A persistent negative nitrogen balance has been observed in some patients on continuous azathioprine dosage; if this should occur, the dose should be reduced as this has been found to correct the situation.

The combined use of azathioprine with DMARD's have not been studied for either added benefit or unexpected adverse effects. The use of azathioprine with these agents cannot be recommended.

Carcinogenesis and Mutagenesis

AZATHIOPRINE-50 is carcinogenic and mutagenic in human and animal. Patients receiving immunosuppressive drugs, including azathioprine, particularly transplant patients receiving aggressive therapy, are known to have an increased risk of developing lymphoproliferative disorders (***including the rare, very aggressive and usually fatal hepatosplenic T-cell lymphoma [HSTCL]***) and other malignancies, notably skin cancer (melanoma and non-melanoma, sarcomas (Kaposi's and non-Kaposi's), uterine cervical cancer in situ, and reticulum cell or lymphomatous tumors. 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 lymphoproliferative disorders. 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. The degree of immunosuppression is determined not only by the immunosuppressive regimen, but also by a number of other patient factors. The number of immunosuppressive agents may not necessarily increase the risk of lymphomas. However, patients who receive multiple immunosuppressive agents may be at risk for over-immunosuppression; therefore, immunosuppressive drug therapy should be maintained at the lowest effective levels. 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. Information is available on the spontaneous neoplasia risk in rheumatoid arthritis, and on neoplasia following immunosuppressive therapy of other auto-immune diseases. It has not been possible to define the precise risk of neoplasia due to azathioprine. 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. However, acute myelogenous leukemia as well as solid tumors have been reported in patients with rheumatoid arthritis who have received azathioprine. Data on neoplasia in patients receiving azathioprine can be found under ADVERSE REACTIONS.
Patients with rheumatoid arthritis previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan or others) may have a prohibitive risk of neoplasia if treated with azathioprine.

Gastrointestinal

A gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting has been reported. These symptoms may also be accompanied by diarrhea, rash, fever, malaise, myalgias, elevations in liver enzymes, vasculitis, hepatic dysfunction, cholestatis and occasionally, hypotension. Symptoms of gastrointestinal toxicity may often develop within the first several weeks of azathioprine therapy and are reversible upon discontinuation of the drug. The reaction can recur within hours after rechallenge with a single dose of azathioprine.

Hematologic

Severe leukopenia and/or thrombocytopenia may occur in patients on azathioprine. Macrocytic anemia and severe bone marrow depression may also occur. Hematologic toxicities are dose related and may be more severe in renal transplant patients whose homograft is undergoing rejection. It is suggested that patients on azathioprine have complete blood counts, including platelet counts, weekly during the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage alterations or other therapy changes are necessary. Delayed hematologic suppression may occur. Prompt reduction in dosage or temporary withdrawal of the drug may be necessary if there is a rapid fall in, or persistently low leukocyte count or other evidence of bone marrow depression. Leukopenia does not correlate with therapeutic effect; therefore, the dose should not be increased intentionally to lower the white blood cell count.

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 coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. Also a possible association between decreased TPMT activity and secondary leukemias and myelodysplasia has been reported in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics. 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.

Immune

Patients receiving azathioprine alone or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to infections (e.g. fungal, viral and bacterial), including severe or atypical infection with varicella, herpes zoster and other infections agents (see ADVERSE REACTIONS). Fungal, viral, bacterial and protozoal infections may be fatal and should be treated vigorously. Reduction of azathioprine dosage and/or use of other drugs should be considered. 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.

Macrophage activation syndrome

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

Neuromuscular agents

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

Xanthine oxidase inhibitors

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

Sexual Function/Reproduction

Azathioprine has been reported to cause temporary depression in spermatogenesis and reduction in sperm viability and sperm count in mice at doses 10 times the human therapeutic dose; a reduced percentage of fertile matings occurred when animals received 5 mg/kg.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women therefore 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.

Azathioprine can cause fetal harm when administered to a pregnant woman.

Azathioprine should not be given during pregnancy or in patients of reproductive potential without careful weighing of risk versus benefit. Use of azathioprine in pregnant patients should be avoided whenever possible. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

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.
Azathioprine is teratogenic in rabbits and mice when given in doses equivalent to the human dose (5 mg/kg daily). Abnormalities included skeletal malformations and visceral anomalies.

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

Limited immunologic and other abnormalities have occurred in a few infants born of renal allograft recipients on azathioprine. In a detailed case report, documented lymphopenia, diminished IgG and IgM levels, CMV infection, and a decreased thymic shadow were noted in an infant born to a mother receiving 150 mg azathioprine and 30 mg prednisone daily throughout pregnancy. At 10 weeks most features were normalized. Pancytopenia and severe immune deficiency has been reported in a preterm infant whose mother received 125 mg azathioprine and 12.5 mg prednisone daily. There have been two published reports of abnormal physical findings. In one study an infant born with preaxial polydactyly whose mother received azathioprine 200 mg daily and prednisone 20 mg every other day during pregnancy. The second study described an infant with a large myelomeningocele in the upper lumbar region, bilateral dislocated hips, and bilateral talipes equinovarus. The father was on long-term azathioprine therapy.

Nursing Women: The use of azathioprine in nursing mothers is not recommended. Azathioprine or its metabolites are transferred at low levels, both transplacentally and in breast milk. Because of the potential for tumorigenicity shown for azathioprine, a decision should be made on whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (<18 years of age): Safety and efficacy of azathioprine in children have not been established.

Azathioprine should not be used to treat children with rheumatoid arthritis.

Geriatrics (> 65 years of age): Safety and efficacy of azathioprine in geriatrics have not been established.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The principal and potentially serious toxic effects of azathioprine are hematologic and gastrointestinal. The risks of secondary infection and neoplasia are also significant (see WARNINGS AND PRECAUTIONS). The frequency and severity of adverse reactions depend on the dose and duration of azathioprine as well as on the patient's underlying disease or concomitant therapies. The incidence of hematologic toxicities and neoplasia encountered in groups of renal homograft recipients is significantly higher than that in studies employing azathioprine for rheumatoid arthritis.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The relative incidences in clinical studies are summarized below:

Toxicity	Renal Homograft	Rheumatoid Arthritis
Leukopenia Any Degree	>50%	28%
<2500/mm^3	16%	5.3%
Infections	20%	<1%
Neoplasia Lymphoma Others	 0.5% 2.8%	 *

* Data on the rate and risk of neoplasia among persons with rheumatoid arthritis treated with azathioprine are limited. The incidence of lymphoproliferative disease in patients with RA appears to be significantly higher than that in the general population. In one completed study, the rate of lymphoproliferative disease in RA patients receiving higher than recommended doses of azathioprine (5 mg/kg/day) was 1.8 cases per 1000 patient years of follow-up, compared with 0.8 cases per 1000 patient years of follow-up in those not receiving azathioprine. However, the proportion of the increased risk attributable to the azathioprine dosage or to other therapies (i.e., alkylating agents) received by patients treated with azathioprine cannot be determined.

Hematologic

Leukopenia and/or thrombocytopenia and rarely as agranulocytosis, pancytopenia and aplastic anemia are dose dependent and may occur late in the course of azathioprine therapy. Dose reduction or temporary withdrawal allows reversal of these toxicities. These adverse events occur particularly in patients predisposed to myelotoxicity, such as those with TPMT deficiency (see WARNINGS AND PRECAUTIONS) and renal or hepatic insufficiency and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol

therapy (see WARNINGS AND PRECAUTIONS). Infection may occur as a secondary manifestation of bone marrow suppression or leukopenia, but the incidence of infection is 30 to 60 times greater in renal homotransplantation than in rheumatoid arthritis. Macrocytic anemia and/or bleeding have been reported in patients on azathioprine.

Gastrointestinal
Nausea and vomiting may occur within the first few months of azathioprine therapy, and occurred in approximately 12% of 676 rheumatoid arthritis patients. The frequency of gastric disturbance can often be reduced by administration of the drug in divided doses and/or after meals. However, in some patients, nausea and vomiting may be severe and may be accompanied by symptoms such as diarrhea, fever, malaise, vasculitis, hepatic dysfunction, cholestatis and myalgias (see WARNINGS AND PRECAUTIONS). Vomiting with abdominal pain may occur rarely with a hypersensitivity pancreatitis.

Infections and Infestations
Infections (i.e. viral, fungal and bacterial) occur very commonly in transplant patients receiving azathioprine in combination with other immunosuppressants and uncommonly in other patient populations (See WARNINGS AND PRECAUTIONS).

Hepatic
Hepatotoxicity manifested by elevation of serum alkaline phosphatase, bilirubin and/or serum transaminases is known to occur with thiopurines including azathioprine and Purinethol® (6-mercaptopurine). This toxic hepatitis with biliary stasis is known to occur in homograft recipients. Hepatotoxicity has been uncommon in rheumatoid arthritis patients on azathioprine (less than 1%). Hepatotoxicity following transplantation most often occurs within 6 months of transplantation and is generally reversible after interruption of azathioprine. Rare but life-threatening hepatic damage associated with chronic administration of azathioprine has been described primarily in transplant patients and in one patient receiving azathioprine for panuveitis. Histological findings include sinusoidal dilation, peliosis hepatis, veno-occlusive disease and nodular regenerative hyperplasia. Periodic measurement of serum transaminases, alkaline phosphatase, and bilirubin is indicated for early detection of hepatotoxicity. If hepatic veno-occlusive disease is clinically suspected, azathioprine should be permanently withdrawn. In some cases withdrawal of azathioprine has resulted in either a temporary or permanent improvement in liver histology and symptoms.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Additional side effects of low frequency have been reported. These include skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea, negative nitrogen balance, and reversible interstitial pneumonitis.

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

There have been reports of neoplasms (frequency rare ≥1/10,000 to <1/1000) including lymphoproliferative disorders, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's), uterine cervical cancer *in situ*, acute myeloid leukemia and myelodysplastic syndrome (some in association with chromosomal abnormalities).

Post-Market Adverse Drug Reactions

Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported very rarely in post-marketing surveillance.

Cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported.
Cases of progressive multifocal leukoencephalopathy (PML) have been reported with the use of azathioprine.

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

Xanthine oxidase inhibitors*:* The principal pathway for detoxification of azathioprine is inhibited by xanthine oxidase inhibitors. If xanthine oxidase inhibitors, such as allopurinol, oxipurinol and/or thiopurinol, are given concomitantly with azathioprine, the dosage of azathioprine must be reduced to a quarter of the original dose. Subsequent adjustment of doses of azathioprine should be made on the basis of therapeutic response and any toxic effects.

Other agents affecting myelopoesis: Drugs which may affect leukocyte production, including trimethoprim/sulfamethoxazole, may lead to exaggerated leukopenia, especially in renal transplant recipients.

Angiotensin converting enzyme inhibitors: The use of angiotensin converting enzyme inhibitors to control hypertension in patients on azathioprine has been reported to induce anemia and severe leukopenia.

Warfarin*:* Azathioprine may inhibit the anticoagulant effect of warfarin.

Non-depolarizing muscle relaxants*:* There is clinical evidence that azathioprine antagonizes the effect of non-depolarizing muscle relaxants such as curare, d-tubocurarine and pancuronium. Experimental data confirm that azathioprine reverses the neuromuscular blockade caused by d-tubocurarine, and show that azathioprine potentiates the neuromuscular blockade caused by succinylcholine (see WARNINGS AND PRECAUTIONS).

As there is *in vitro* evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent azathioprine therapy (See WARNINGS AND PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Renal Homotransplantation
The dose of AZATHIOPRINE-50 (Azathioprine Tablets USP) required to prevent rejection and minimize toxicity will vary with individual patients; this necessitates careful management. The initial dose is usually 3 to 5 mg/kg daily, beginning at the time of transplant. Azathioprine is usually given as a single daily dose on the day of, and in a minority of cases one to three days before, transplantation. Azathioprine is often initiated with the intravenous administration of the sodium salt, with subsequent use of tablets (at the same dose level) after the 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 azathioprine should not be increased to toxic levels because of threatened rejection. Discontinuation may be necessary for severe hematologic or other toxicity, even if rejection of the homograft may be a consequence of drug withdrawal.

Rheumatoid Arthritis
Azathioprine is usually given on a daily basis. The initial dose should be approximately 1.0 mg/kg (50 to 100 mg) given as a single dose or on a twice daily schedule. The dose may be increased, beginning at six to eight weeks and thereafter by steps at four-week intervals, if there are no serious toxicities and if initial response is unsatisfactory. Dose increments should be 0.5 mg/kg daily, up to a maximum dose of 2.5 mg/kg/day. Therapeutic response occurs after several weeks of treatment, usually six to eight; an adequate trial should be a minimum of 12 weeks. Patients not improved after twelve weeks can be considered refractory. AZATHIOPRINE-50 may be continued long-term in patients with clinical response, but patients should be monitored carefully, and gradual dosage reduction should be attempted to reduce risk of toxicities. Maintenance therapy should be at the lowest effective dose, and the dose given can be lowered, with decremental changes of 0.5 mg/kg or approximately 25 mg daily every four weeks, while other therapy is kept constant. The optimum duration of maintenance azathioprine has not been determined. AZATHIOPRINE-50 can be discontinued abruptly, but delayed effects are possible.

Rest, physiotherapy and salicylates should be continued while AZATHIOPRINE-50 is given, but it may be possible to reduce the dose of corticosteroids in patients on AZATHIOPRINE-50.

Use in Renal Dysfunction
Relatively oliguric patients, especially those with tubular necrosis in the immediate post-cadaveric transplant period, may have delayed clearance of azathioprine or its metabolites, or be particularly sensitive to this drug, and are usually given lower doses.

OVERDOSAGE

For the management of a suspected overdose, contact your regional Poison Control Centre.

Initial symptoms are nausea and vomiting; and symptoms appearing later are leukopenia, thrombocytopenia, hepatic necrosis and anorexia.

For the treatment of overdosage, activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

About 30% of azathioprine is bound to serum proteins, but approximately 45% is removed during an 8-hour hemodialysis. A single case has been reported of a renal transplant patient who ingested a single dose of 7500 mg azathioprine. The immediate toxic reactions were nausea, vomiting, and diarrhea, followed by mild leukopenia and mild abnormalities in liver function. The white blood cell count, AST, and bilirubin returned to normal 6 days after the overdose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Homograft Survival
Although the use of azathioprine for inhibition of renal homograft rejection is well established, the mechanism(s) for this action are somewhat obscure. The drug suppresses hypersensitivities of the cell-mediated type and causes variable alterations in antibody production. Suppression of T-cell effects, including ablation of T-cell suppression, is dependent on the temporal relationship to antigenic stimulus or engraftment. This agent has little effect on established graft rejections or secondary responses.

Alterations in specific immune responses or immunologic functions in transplant recipients are difficult to relate specifically to immunosuppression by azathioprine. These patients have subnormal responses to vaccines, low numbers of T-cells, and abnormal phagocytosis by peripheral blood cells, but their mitogenic responses, serum immunoglobulins and secondary antibody responses are usually normal.

Immunoinflammatory Response
Azathioprine suppresses disease manifestations as well as underlying pathology in animal models of auto-immune disease. For example, the severity of adjuvant arthritis is reduced by azathioprine.

The mechanisms whereby azathioprine affects auto-immune diseases are not known. Azathioprine is immunosuppressive, delayed hypersensitivity and cellular cytotoxicity tests

being suppressed to a greater degree than are antibody responses. In the rat model of adjuvant arthritis, azathioprine has been shown to inhibit the lymph node hyperplasia which precedes the onset of the signs of the disease. Both the immunosuppressive and therapeutic effects in animal models are dose-related. Azathioprine is considered a slow-acting drug and effects may persist after the drug has been discontinued.

Pharmacodynamics

In view of the observations by Schwartz *et al.* that mercaptopurine suppressed the antibody response in rabbits injected with bovine serum albumin, the effects of azathioprine on the formation of antibodies were investigated. In the suppression of the formation of antibodies in mice to sheep red cells, as determined by hemagglutinin titers, azathioprine was found to be superior to mercaptopurine. Whereas mercaptopurine was active only at its maximum tolerated dose of 75 mg/kg, azathioprine was active at 25 mg/kg and was tolerated in doses up to 60 mg/kg for the dosage schedule employed (intraperitoneal injection for 4 successive days beginning at the time of the antigenic stimulus). The anti-immune effects of azathioprine are not due entirely to the mercaptopurine derived therefrom by splitting *in vivo*.

Another line of evidence which suggests that part of the activity of azathioprine may be due to its reaction with sulfhydryl compounds is the potentiation of its anti-immune effect by the simultaneous administration of MYLERAN® (busulfan). (Busulfan is also known to react with sulfhydryl groups in tissues.) Thus the combination of azathioprine (10 mg/kg) and busulfan (30 mg/kg) produced a marked suppression of the antibody response, whereas the minimum effective dose of azathioprine alone is 25 mg/kg, and busulfan alone is inactive at its maximum tolerated dose of 40 mg/kg. The combination of mercaptopurine (25 mg/kg) and busulfan (25 mg/kg) is inactive.

Pharmacokinetics

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 i.v. or oral administration of 6-MP.

Metabolism

Azathioprine is well absorbed following oral administration. Maximum serum radioactivity occurs at one to two hours after oral 35S-azathioprine and decays with a half-life of five hours. This is not an estimate of the half-life of azathioprine itself but is the decay rate for all 35S-containing metabolites of the drug. Because of extensive metabolism, only a fraction of the radioactivity is present as azathioprine. Usual doses produce blood levels of azathioprine, and of mercaptopurine derived from it, which are low (<1 mcg/mL). Blood levels are of little predictive value for therapy since the magnitude and duration of clinical effects correlate with thiopurine nucleotide levels in tissues rather than with plasma drug levels. Azathioprine and

mercaptopurine are moderately bound to serum proteins (30%) and are partially dialyzable.

Azathioprine is cleaved *in vivo* to mercaptopurine. Both compounds are rapidly eliminated from blood and are oxidized or methylated in erythrocytes and liver; no azathioprine or mercaptopurine is detectable in urine after eight hours. Conversion to inactive 6-thiouric acid by xanthine oxidase is an important degradative pathway, and the inhibition of this pathway in patients receiving ZYLOPRIM® (allopurinol) is the basis for the azathioprine dosage reduction required in these patients (see Drug Interactions under PRECAUTIONS). Proportions of metabolites are different in individual patients, and this presumably accounts for variable magnitude and duration of drug effects. Renal clearance is probably not important in predicting biological effectiveness or toxicities, although dose reduction is practiced in patients with poor renal function.

Elimination
After oral administration of 100mg 35S-azathioprine, 50% of the radioactivity was excreted in the urine over 24 hours and 12% in the faeces after 24 hours. In the urine, the major compound was the inactive oxidised metabolite thiouric acid. Less than 2% was excreted in the urine as azathioprine or 6-MP. Azathioprine has a high extraction ratio with a total clearance greater than 3L/min in normal volunteers. There are no data on the renal clearance or half-life of azathioprine. The renal clearance of 6-MP and the half-life of 6-MP are 191 mL/min/m2 and 0.9 hr respectively.

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

STORAGE AND STABILITY

Store at room temperature (15°C to 30°C), protected from light.

SPECIAL HANDLING INSTRUCTIONS

Tablets should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

All materials which have come in contact with cytotoxic drugs should be segregated and incinerated at 1000°C or more. Sealed containers may explode.

Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

In addition to azathioprine, each AZATHIOPRINE-50 Tablet contains the non-medicinal ingredients lactose, magnesium stearate, microcrystalline cellulose and starch.

Packaging

AZATHIOPRINE-50 (azathioprine) 50 mg Tablets are pale yellow, peanut-shaped tablets, scored and engraved "AZ 50" on one side and plain on the other. AZATHIOPRINE-50 Tablets are available in bottles of 100, 250, 500 and 1000 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

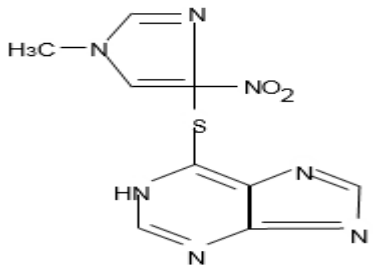
Proper Name: Azathioprine

Chemical Name(s): 1) 1*H*-Purine,6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)-thio]-;
2) 6-[(1-Methyl-4-nitro-1*H*-imidazol-5-yl)thio]-1*H*-purine

Molecular Formula: $C_9H_7N_7O_2S$

Molecular Weight: 277.27 g/mol

Structural Formula:



Physicochemical Properties:

pKa: 8.2 (25°C)

Description: Azathioprine is a pale yellow, odourless powder. It is insoluble in water, soluble in dilute solutions of alkali hydroxides, sparingly soluble in dilute mineral acids and very slightly soluble in alcohol and in chloroform.

CLINICAL TRIALS

Renal Homotransplantation

Azathioprine is indicated as an adjunct for the prevention of rejection in renal homotransplantation. Experience with over 16,000 transplants shows a five-year patient survival of 35% to 55%, but this is dependent on donor, match for HLA antigens, antidonor or anti B-cell alloantigen antibody and other variables. The effect of azathioprine on these variables has not been tested in controlled trials.

Rheumatoid Arthritis

Azathioprine is indicated only in adult patients meeting criteria for classic or definite rheumatoid arthritis as specified by the American Rheumatism Association. Azathioprine should be restricted to patients with severe, active and erosive disease not responsive to conventional management including rest, acetylsalicylic acid or other non-steroidal drugs, or with disease- modifying antirheumatic drugs (DMARD's). Rest, physiotherapy and salicylates should be continued while azathioprine is given, but it may be possible to reduce the dose of corticosteroids in patients on azathioprine. The combined use of azathioprine with DMARD's have not been studied for either added benefit or unexpected adverse effects. The use of azathioprine with these agents cannot be recommended.

Comparative Bioavailability

Two comparative bioavailability studies were performed on healthy human volunteers - one fasted and one fed study. The rate and extent of absorption of 6-mercaptopurine were measured and compared following oral administration of 50 mg of either AZATHIOPRINE - 50 50 mg tablets or IMURAN 50 mg tablets. The results from measured data are summarized as follows.

FASTED STUDY:

Summary Table of the 6-Mercaptopurine Comparative Bioavailability Data (1 x 50 mg) from Measured Data			
Parameter	**Geometric Mean Arithmetic Mean (C.V.)**		**Ratio of Geometric Means (%)**
	AZATHIOPRINE-50	**IMURAN†**	
AUC_{0-T} (ng·hr/mL)	27.88 31.59 (52.42)	28.96 30.86 (34.64)	96.3
$AUC_{0-\infty}$ (ng·hr/mL)	33.95 37.31 (45.10)	34.61 36.45 (31.33)	98.1
C_{max} (ng/mL)	15.3 18.10 (63.20)	16.9 18.75 (42.09)	90.5
T_{max} (hours)*	1.33 (71.41)	1.25 (66.65)	--
$T_{1/2}$ (hours)*	1.51 (35.22)	1.52 (31.50)	--

*Arithmetic means only (CV%).
†IMURAN is manufactured by Glaxo Wellcome Inc., and was purchased in Canada.

FED STUDY:

Summary Table of the 6-Mercaptopurine Comparative Bioavailability Data (1 x 50 mg) from Measured Data			
Parameter	**Geometric Mean Arithmetic Mean (C.V.)**		**Ratio of Geometric Means (%)**
	AZATHIOPRINE-50	**IMURAN®†**	
AUC_{0-T} (ng·hr/mL)	16.1078 17.737 (44.9)	17.6405 18.998 (39.0)	91.31
$AUC_{0-\infty}$ (ng·hr/mL)	23.6023 24.763 (31.8)	22.7782 24.102 (34.5)	103.62
C_{max} (ng/mL)	6.9298 8.299 (69.8)	7.8071 8.868 (54.4)	88.76
T_{max} (hours)*	1.847 (59.6)	1.791 (54.0)	--
$T_{1/2}$ (hours)*	2.216 (31.2)	2.075 (43.2)	--

*Arithmetic means only (CV%).
†IMURAN is manufactured by Glaxo Wellcome Inc., and was purchased in Canada.

TOXICOLOGY

Acute toxicity studies in mice and rats showed a species variation and a somewhat lower toxicity when azathioprine was administered orally than when it was given intraperitoneally. The single LD_{50} dose in mice is 650 mg/kg, intraperitoneally, and about 2500 mg/kg, orally. In rats, the single LD_{50} is 310 mg/kg, intraperitoneally, and 400 mg/kg, orally. Death after an LD_{50} dose, and even after an LD_{100} dose, was delayed two to seven days. Subacute toxicity studies also demonstrated the cumulative toxicity.

When the drug was given to mice for five successive days, the maximum tolerated daily dose was 100 mg/kg intraperitoneally and 200 mg/kg orally. In rats given five consecutive daily doses, the LD_{50} was 100 mg/kg whether the drug was given intraperitoneally or orally, and in these animals death occurred within a day or two of the last dose.

Chronic toxicity studies in rats revealed that all the animals that died of drug toxicity at the two highest dosage levels (60 mg/kg body weight/day and 180 mg/kg body weight/day incorporated in the diet) showed agranulocytic spleens and bone marrows and hemorrhagic lungs.

There was also some colloid depletion of the thyroid and failure of spermatogenesis. None of the animals that survived the six-month period showed blood dyscrasias or histological abnormalities.

Dogs receiving 1 or 2 mg/kg body weight/day orally for 18 weeks showed a normal weight gain and no hematologic changes. Of four dogs receiving 4 mg/kg/day orally for 18 weeks, two had episodes of fever during the last six weeks and one of these died of pneumonia and had evidence of bone marrow depression. The other two dogs maintained a normal hematologic picture. Two dogs (including the one that died) showed reduced weight gain; the other two dogs that survived the dosage of 4 mg/kg/day showed at autopsy discolored and mottled lungs but no histological abnormalities in the liver, spleen, kidneys, testes, adrenals, pancreas or myocardium. Bone marrows showed normal cellularity.

A dog given ten doses of 10 mg/kg, orally, over a 12-day period became moribund four days after the last dose and had agranulocytosis and acute ulcers of the anal and rectal region with tissue necrosis. At a dose of 7.5 mg/kg given orally for ten doses, a dog maintained its weight and showed a normal white blood cell count for several months after the study; the red blood cell count was slightly depressed to 3.7 million two weeks after the final dose, but the count gradually returned to normal. At a dose of 5 mg/kg for ten doses, a dog maintained its weight and continued to show a normal blood picture for several months. Dogs with kidney homografts generally tolerated doses of 10 mg/kg/day, orally, for two days followed by maintenance doses of 2.5 mg to 4 mg/kg/day.

The hepatotoxic potential of azathioprine was studied by Starzl *et al.* in 18 normal dogs. Azathioprine alone was administered for 40 days in the same dosage as used for prevention of homograft rejection. There were declines in hematocrit, weight loss and elevations of SGOT, SGPT and alkaline phosphatase.

These changes tended to occur early suggesting that the liver injury was due to direct hepatotoxicity. Although there was usually a partial recovery from these biochemical abnormalities, 13 of the 18 dogs had histologic evidence of liver injury at the end of 40 days. The principal histologic alterations were usually in the centrilobular area. As Starzl pointed out, the hepatotoxicity of azathioprine is greater in dogs than in man. This is borne out by the 3% incidence of hepatitis in the cases reported in the Registry.

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

Carcinogenicity Studies

Rats: Azathioprine was administered orally in the diet at doses of 0, 3 or 10 mg/kg/day to groups of 70 male and 70 female Sprague-Dawley rats for 90 and 97 consecutive weeks, respectively.

A life-table analysis indicated comparable cumulative survival of the control and 3 mg/kg/day female group. Survival of the male 3 mg/kg/day group began to diverge from the control group by day 600. Reduced cumulative survival of the male and female 10 mg/kg/day groups compared to the controls began by 450 and 350 days respectively.

There were no effects on food consumption. The mean weight of the 10 mg/kg group was lower than the untreated control group mean.

There was a marked depletion of body fat in the 10 mg/kg/day rats.

An increased incidence of neoplasms of the skin, ear canal (including the auditory sebaceous or Zymbal's gland) and preputial gland was associated with azathioprine administration. The presence of a few neoplasms of the nonglandular stomach in the treated males was considered potentially significant due to their rare spontaneous occurrence. Two mucinous adenocarcinomas of the duodenum, which were noted in the male 3 mg/kg/day group, were considered possibly significant.

Mice: A study was carried out to determine the carcinogenic effects of azathioprine when given orally in the diet to mice during an 18-month period. Six hundred (300 males and 300 females) clinically healthy 21-day-old mice were used in this study. Mice were randomly assigned to 1 of the 3 following dose groups of 100 males and 100 females: 0 mg/kg/day, 3 mg/kg/day and 10 mg/kg/day.

Mice in the high dose group (10 mg/kg/day) were fed a drug-free diet during dose weeks 21 through 38 because high mortality due to drug toxicity was observed. Otherwise the drug-diet mixture was fed until there was 10 to 20% survival of that sex in any treatment groups. Surviving females were sacrificed after 524 to 530 days on study and surviving males after 600 to 602 days on study.

Mice were observed daily and palpated weekly for tumors. Complete necropsies were performed

on each mouse after death or sacrifice. Representative sections of all major organs and all tumors were fixed, prepared, and examined histologically from high dose (10 mg/kg/day) and control mice. Target organs and all tumors were examined from low dose (3 mg/kg/day) mice.

Azathioprine in the diet significantly reduced the survival of 3 mg/kg/ day females and 10 mg/kg/day males and females. Paleness of the mucous membranes, probably due to anemia, was observed. Significant differences in food consumption and body weights were periodically observed, but they were not consistently present throughout the study.

The number of clinically palpable nodules was similar in control and treated mice. At necropsy enlarged thymuses, lymph nodes, and spleens were observed, especially in the high dose group. Cystic endometrial hyperplasia was present in the majority of control and treated females.

Histologically, both male and female mice had a dose-related increase ($p<.01$) in lymphosarcomas. This increased incidence of lymphosarcoma in azathioprine-dose females was also responsible for a significant ($p<.01$) increase in total malignant and/or malignant plus benign tumors. In treated male mice, the incidence of malignant or malignant plus benign tumors was not significantly increased.

Synergistic immunosuppression with N-nitrosobutylurea and azathioprine induced leukemia, mean latent period of 189 days, in 14 of 24 (58%) C57BL mice. Immunosuppression with azathioprine of NZB X NZW mice that had lupus nephritis also increased the incidence of lymphosarcoma. In view of the above, lymphosarcoma as observed in this current study in treated mice may have been secondary to azathioprine immunosuppression.

An increased number of squamous cell carcinomas was observed in the preputial area of treated mice, and for purposes of statistical comparison were considered to be of preputial gland origin. Although the total number of these tumors in either treated group of male mice was not significantly greater than the number in controls, a positive dose response was detected statistically. The incidence of spontaneous preputial gland carcinomas reported in the literature is low; therefore, these tumors may have been induced by azathioprine.

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.

Teratology Studies

Reproductive studies have been performed in a variety of species. 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. The administration of azathioprine to pregnant rats and one strain of mice did not produce significant congenital anomalies. However, studies with pregnant rabbits and Swiss-Webster mice have shown that azathioprine has significant teratogenic potential producing resorptions and skeletal anomalies even when administered as late as the midpoint of gestation. Teratogenicity was evident in rabbits at 10 mg/kg bodyweight/day.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrAZATHIOPRINE-50
Azathioprine Tablets USP

Read this carefully before you start taking AZATHIOPRINE-50 and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about AZATHIOPRINE-50.

Serious Warnings and Precautions

AZATHIOPRINE-50:

- **may increase your risk of developing cancer, especially skin cancer and lymphoma**
- **can cause a severe decrease in the number of white blood cells and platelets thereby increasing your risk of having infection and unusual bleeding or bruising**
- **can cause harm to an unborn child when taken by a pregnant woman**
- **should be prescribed by doctors who are experienced in immunosuppressive therapy and management of organ transplant**

What is AZATHIOPRINE-50 used for?
AZATHIOPRINE-50 (Azathioprine Tablets USP), is used in adults:

- along with other medications to prevent kidney rejection after a transplant.
- with Rheumatoid Arthritis who cannot be treated with other medications and treatments.

How does AZATHIOPRINE-50 work?
AZATHIOPRINE-50 belongs to a group of medicines called immunosuppressants. It reduces the strength of your immune system. This helps your body accept an organ after a transplant. It also helps to treat rheumatoid arthritis a condition where your immune system is reacting against your own body (autoimmune diseases).

What are the *ingredients* in AZATHIOPRINE-50?
AZATHIOPRINE-50 tablets
Medicinal Ingredients: Azathioprine
Non-medicinal Ingredients: lactose, magnesium stearate, microcrystalline cellulose and starch

AZATHIOPRINE-50 comes in the following dosage forms:
The AZATHIOPRINE-50 50 mg tablet is a pale yellow, peanut-shaped tablet, scored and engraved "AZ 50" on one side and plain on the other.

Do not use AZATHIOPRINE-50 if:

- You are allergic to azathioprine or to any of the other ingredients in AZATHIOPRINE-50 (see "**What are the ingredients AZATHIOPRINE-50** above)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AZATHIOPRINE-50. Talk about any health conditions or problems you may have, including if:

- you have rheumatoid arthritis and have been previously treated with alkylating agents (such as cyclophosphamide, chlorambucil, melphalan or others)
- you suffer from liver or kidney disease
- you have been told you have any type of cancer
- you have a condition where your body produces too little of a natural chemical called thiopurine methyltransferase (TPMT)

- you have never had chickenpox or shingles
- you are going to have an operation. Medicines including tubocurarine, or succinylcholine that are used as muscle relaxants during surgery may interact with AZATHIOPRINE-50. You should tell your doctor you are taking AZATHIOPRINE-50 before your surgery.
- you are pregnant. You should not take AZATHIOPRINE-50 while pregnant. It can cause harm to your unborn baby.
- you are planning to have a baby - discuss this with your doctor whether you are male or female
- you are breast feeding. The ingredient in AZATHIOPRINE-50 can be transferred through your breast milk.
- you are under 18 years of age

Other warning you should know about:

General: If you are receiving immunosuppressive therapy, taking AZATHIOPRINE-50 could put you at a greater risk of developing certain types of cancers called lymphoproliferative disorders. These are cancers that affect the blood and immune system.

Exposure to Sunlight: Patients taking immunosuppressive medicines may have an increased risk for developing tumours, including skin cancer. While you are taking AZATHIOPRINE-50, you should avoid too much exposure to sunlight. You should wear sunscreen with a high protections factor and wear protective clothing.

Use with other immunosuppressant, particularly corticosteroids: Patients taking AZATHIOPRINE-50 alone or in combination with other immunosupressants, particularly corticosteroids are at a greater risk for infections.

Chickenpox or shingles: Infection with chickenpox or shingles can become severe in patients taking immunosuppressive medicines. You should therefore avoid contact with anyone who has chickenpox or shingles. Tell your doctor right away if you do come into contact with someone with chickenpox or shingles.

Gastrointestinal hypersensitivity: Severe nausea and vomiting have been reported in patients taking AZATHIOPRINE-50.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AZATHIOPRINE-50:
- angiotensin-converting enzyme inhibitors such as captopril (used to treat high blood pressure and heart failure)
- trimethoprim and sulfamethoxazole (used to treat bacterial infections). It is also known as SEPTRA®
- allopurinol, oxipurinol, thiopurinol (used to treat gout)
- curare, d-tubocurarine, tubocurarine, pancuronium and succinylcholine (used as a muscle relaxant during surgery)
- warfarin (used to prevent blood clots)
- mesalazine, olsalazine or sulphasalazine (used to treat ulcerative colitis)

How to take AZATHIOPRINE-50:
AZATHIOPRINE-50 tablets:
Important Information: The tablets require safe handling. Consult your doctor or pharmacist for instructions on how to safely handle this product.

- It is important you take the tablets at right times
- You must take it exactly the way your doctor has told you to
- Swallow the tablet **whole** with water. **Do NOT** break the tablet

Laboratory Tests: From time to time, while you are taking AZATHIOPRINE-50 (Azathioprine Tablets USP), your doctor will want you to have a blood test. This is to check your blood cell count and to change your dose if necessary.

Usual Adult dose:
Kidney Transplant: A starting dose of up to 5 mg/kg of your bodyweight is usually given on the first day of therapy. You will then be given a maintenance dose of AZATHIOPRINE-50. This is likely to be between 1 to 3 mg/kg bodyweight per day.

Rheumatoid Arthritis: If you are receiving AZATHIOPRINE-50 for rheumatoid arthritis the dose given is likely to start at approximately 1 mg/kg of your bodyweight. Depending on how your treatment is working, your dose may be adjusted, until an optimal maintenance dose is determined.

Overdose:

If you think you have taken too much AZATHIOPRINE-50, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take a dose, do not take extra tablets to make up for the dose or doses you have missed. When you remember, take your next dose at the usual time and continue as before. Talk to your doctor as soon as you can about the doses you may have missed.

What are possible side effects from using AZATHIOPRINE-50:

These are not all the possible side effects you may feel when taking AZATHIOPRINE-50. If you experience any side effects not listed here, contact your healthcare professional.

Side effects include:

- Hair loss. Often hair does grow again, even if you carry on taking AZATHIOPRINE-50. If you are worried ask your doctor.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Common fever or infection after transplant		✓	
unexpected bruising or bleeding		✓	
nausea		✓	
Rare new marks on skin or a change to marks		✓	
cough or difficulty breathing similar to a chest infection		✓	
tired, dizzy or generally unwell		✓	
muscle or bone pain			✓
kidney problems			✓
feeling faint especially on standing up			✓
bad diarrhea and/or abdominal pain			✓

fever and infection		✓	
Serious Skin Reaction **Serious Skin Reaction: Steven Johnson Syndrome (SJS):** flu-like symptoms, skin rash often with blisters or lesions and shedding of the skin within days of the formation of the blisters **Toxic Epidermal Necrolysis (TEN):** flu-like symptoms, redness of the skin, and the detachment of the skin (epidermal layer)			✓
Hepatosplenic T-cell lymphoma (enlargement of the liver)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store between 15°C and 30°C. Protect from light.
- Do not take the medicine after the expiry date shown on the package.
- If your doctor tells you to stop taking the tablets, return any left-overs to your pharmacy for proper disposal. Only keep them if your doctor tells you to.

Keep AZATHIOPRINE-50 out of reach and sight of children.

If you want more information about **AZATHIOPRINE-50**:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Patient Medication Information on (http:// www.prodoc.qc.ca) or by contacting Pro Doc Ltée at 1-800-361-8559 or info@prodoc.qc.ca.

This leaflet was prepared by
Pro Doc Ltée
Laval, Québec
H7L 3W9

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