

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**Pr APO-AZATHIOPRINE**

Azathioprine Tablets

Tablets, 50 mg, Oral

USP

Immunosuppressive Agent

APOTEX INC.  
150 Signet Drive  
Toronto, Ontario  
M9L 1T9

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## RECENT MAJOR LABEL CHANGES

<a href="#">7 WARNINGS AND PRECAUTIONS</a>	05/2024
<a href="#">7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women</a>	05/2024

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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

APO-AZATHIOPRINE (azathioprine tablets) is indicated for:

- **Renal Homotransplantation**  
APO-AZATHIOPRINE is indicated as an adjunct for the prevention of rejection in renal homotransplantation.
- **Rheumatoid Arthritis**  
APO-AZATHIOPRINE is indicated only in adult patients meeting criteria for classic or definite rheumatoid arthritis as specified by the American Rheumatism Association. APO-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).

#### **1.1 Pediatrics**

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### **1.2 Geriatrics**

**Geriatrics (> 65 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

### **2 CONTRAINDICATIONS**

APO-AZATHIOPRINE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

### 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

#### Serious Warnings and Precautions

- APO-AZATHIOPRINE 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 [7 WARNINGS AND PRECAUTIONS, General](#) and [Carcinogenesis and Mutagenesis](#)).
- Severe leukopenia and/or thrombocytopenia may occur in patients on APO-AZATHIOPRINE (see [7 WARNINGS AND PRECAUTIONS, General](#) and [Hematologic](#)).
- Macrophage activation syndrome (see [7 WARNINGS AND PRECAUTIONS](#))
- Increased susceptibility to infection. (see [7 WARNINGS AND PRECAUTIONS, Immune](#)).
- APO-AZATHIOPRINE can cause fetal harm when administered to a pregnant woman (see [7.1.1 Pregnant Women](#)).
- **Transplantation**  
Only physicians experienced in immunosuppressive therapy and management of organ transplant should prescribe APO-AZATHIOPRINE. 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 APO-AZATHIOPRINE treated patients is mandatory. APO-AZATHIOPRINE should only be prescribed for rheumatoid arthritis by physicians experienced with the use of immunosuppressants.

### 4 DOSAGE AND ADMINISTRATION

#### 4.2 Recommended Dose and Dosage Adjustment

##### Renal Homotransplantation

The dose of APO-AZATHIOPRINE 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. APO-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. APO-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 APO-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**

APO-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. APO-AZATHIOPRINE 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 APO-AZATHIOPRINE has not been determined. APO-AZATHIOPRINE can be discontinued abruptly, but delayed effects are possible.

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

### **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.

### **Patients with NUDT15 variant**

Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-mercaptopurine toxicity (See [7 WARNINGS AND PRECAUTIONS, Patients with NUDT15 variant](#)). These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes (See [7 WARNINGS AND PRECAUTIONS, Patients with NUDT15 variant](#)). Genotypic testing of NUDT15 variants may be considered before initiating 6-mercaptopurine therapy. In any case, close monitoring of blood counts is necessary.

## **5 OVERDOSAGE**

Initial symptoms are nausea and vomiting; and symptoms appearing later are leukopenia, thrombocytopenia, hepatic necrosis and anorexia. If overdose occurs, the patient must be monitored for toxicity. Treatment of overdose with azathioprine consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

There is no specific antidote for overdose with azathioprine. 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.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

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

### Description

APO-AZATHIOPRINE 50 mg tablets are pale yellow, peanut-shaped, flat-faced, bevelled-edge tablet, scored and engraved "AZ 50" on one side, "APO" on the other side. APO-AZATHIOPRINE is available in bottles of 100 tablets.

## 7 WARNINGS AND PRECAUTIONS

Please see [3 SERIOUS WARNINGS AND PRECAUTIONS BOX](#) at the beginning of Part I: Health Professional Information.

### 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 APO-AZATHIOPRINE (see [7 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 APO-AZATHIOPRINE with these agents cannot be recommended.

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 (see [9 DRUG INTERACTIONS](#)).

### **Carcinogenesis and Mutagenesis**

Azathioprine is carcinogenic and mutagenic in human and animal (see [16 NON-CLINICAL TOXICOLOGY](#)).

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 rarer, 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 autoimmune 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 [8 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 APO-AZATHIOPRINE.

### **Driving and Operating Machinery**

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

### **Endocrine and Metabolism**

Administration of purine analogues (azathioprine and mercaptopurine) may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency/pellagra. Few cases have been reported with the use of azathioprine, especially in patients with IBD (Crohn's disease, colitis ulcerative). Diagnosis of pellagra should be considered in a patient presenting with localised pigmented rash (dermatitis); gastroenteritis (diarrhoea); and widespread neurologic deficits, including cognitive decline (dementia). Dose reduction or discontinuation of azathioprine treatment should be considered based on careful benefit-risk assessment and appropriate medical care with niacin/nicotinamide supplementation should be initiated.

### **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, cholestasis and occasionally, hypotension. Symptoms of gastrointestinal toxicity may often develop within the first several weeks of APO-AZATHIOPRINE therapy and are reversible upon discontinuation of the drug. The reaction can recur within hours after rechallenge with a single dose of APO-AZATHIOPRINE.

### **Hematologic**

Severe leukopenia and/or thrombocytopenia may occur in patients on APO-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 APO-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 methyl-transferase (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 APO-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.

### **Hepatic/Biliary/Pancreatic**

Cholestasis of pregnancy, including foetal death, has been reported in association with azathioprine therapy. If cholestasis of pregnancy occurs, dose reduction or discontinuation should be considered based on case by case risk-benefit profile assessment.

### **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 [8 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.

### **Hypersensitivity**

Patients with a history of hypersensitivity reaction to 6-mercaptopurine should not be prescribed azathioprine.

### **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 [9 DRUG INTERACTIONS](#)). It can also potentiate the neuromuscular block that is produced by depolarising agents such as succinylcholine (see [9 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 [9 DRUG INTERACTIONS](#)).

### **Reproductive Health: Female and Male Potential**

The specific effect of azathioprine therapy on human fertility is unknown. In animal studies, 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 mating occurred when animals received 5 mg/kg<sup>2</sup>.

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 (see [16 NON-CLINICAL TOXICOLOGY](#)).

### **Infections**

Patients treated with 6-mercaptopurine alone or in combination with other immunosuppressive agents, including corticosteroids, have shown increased susceptibility to

viral, fungal and bacterial infections, including severe or atypical infection, and viral reactivation. The infectious disease and complications may be more severe in these patients than in non-treated patients.

Prior exposure including serological testing should be considered for conditions like varicella zoster and hepatitis B.

### **Patients with NUDT15 variant**

Patients with inherited mutated NUDT15 gene are at increased risk for severe 6-mercaptopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy. They generally, require dose reduction, particularly those being NUDT15 variant homozygotes (see [4.2 Recommended Dose and Dosage Adjustment](#)).

The frequency of NUDT15 c.415C>T has an ethnic variability of approximately 10 % in East Asians, 4 % in Hispanics, 0.2 % in Europeans and 0 % in Africans. In any case, close monitoring of blood count is necessary.

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

There are no adequate and well-controlled studies in pregnant women therefore APO-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.

APO-AZATHIOPRINE can cause fetal harm when administered to a pregnant woman.

APO-AZATHIOPRINE should not be given during pregnancy or in patients of reproductive potential without careful weighing of risk versus benefit. Use of APO-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 (see [16 NON-CLINICAL TOXICOLOGY](#)).

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.

Cholestasis of pregnancy, including foetal deaths, has been reported in association with azathioprine therapy. Monitoring of 6-methyl mercaptopurine (6-MMP) should be considered in the presence of pruritus with elevated maternal total serum bile acids levels in second trimester of pregnancy to establish early diagnosis and minimise impact on the foetus. If cholestasis of pregnancy occurs, dose reduction or discontinuation should be considered based on case by case risk-benefit profile assessment (see [7 Hepatic/Biliary/Pancreatic](#)).

### **7.1.2 Breast-feeding**

The use of APO-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.

### **7.1.3 Pediatrics**

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### **7.1.4 Geriatrics**

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

## 8 ADVERSE REACTIONS

### 8.1 Adverse 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 [7 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.

### 8.2 Clinical Trial Adverse 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 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 <sup>3</sup>	16%	5.3%
Infections	20%	<1%
Neoplasia		
Lymphoma	0.5%	*
Others	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 APO-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 [7 WARNINGS AND PRECAUTIONS](#)) and renal or hepatic insufficiency and in patients failing to reduce the dose of azathioprine when receiving concurrent allopurinol therapy (see [7 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, cholestasis and myalgias (see [7 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 [7 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 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 liver injury 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, APO-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.

## **8.3 Less Common Clinical Trial Adverse Reactions**

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

interstitial pneumonitis, bacterial and viral infections, and infections associated with neutropenia.

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

There have been reports of neoplasms (frequency rare  $\geq 1/10,000$  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).

## **8.5 Post-Market Adverse Reactions**

In addition to the adverse reaction reports from clinical trials, the following possible adverse reactions have been identified during post-approval use of azathioprine. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been considered possible adverse reactions due to a combination of their seriousness, frequency of reporting or potential causal relationship with treatment.

Skin and subcutaneous tissue disorders: Sweet's syndrome (acute febrile neutrophilic dermatosis); Stevens-Johnson syndrome; toxic epidermal necrolysis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported.

Infections and infestations: Cases of progressive multifocal leukoencephalopathy (PML) have been reported with the use of azathioprine.

Immune system disorders: hypersensitivity, erythema nodosum

Investigations: liver function test abnormal

Nicotinic acid deficiency/pellagra and cholestasis of pregnancy.

## **9 DRUG INTERACTIONS**

### **9.4 Drug-Drug Interactions**

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).



**Vaccines:** The immunosuppressive activity of azathioprine could result in an atypical and potentially deleterious response to live vaccines. It is therefore recommended that patients do not receive live vaccines at least 3 months after the end of their treatment with azathioprine (see [7 WARNINGS AND PRECAUTIONS](#)).

**Allopurinol/oxipurinol/thiopurinol and other 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 xanthine oxidase inhibitors, such as febuxostat may decrease the metabolism of azathioprine. Concomitant administration is not recommended as data are insufficient to determine an adequate dose reduction.

**Other agents affecting myelopoiesis:** 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:** APO-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 [7 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 [7 WARNINGS AND PRECAUTIONS](#)).

**Infliximab:** An interaction has been observed between azathioprine and infliximab. Patients receiving ongoing azathioprine experienced transient increases in 6-TGN (6-thioguanine nucleotide, an active metabolite of azathioprine) levels and a decrease in the mean leukocyte count in the initial weeks following infliximab infusion, which returned to previous levels after 3 months.

## 9.5 Drug-Food Interactions

Interactions of azathioprine with food have not been established.

## 9.6 Drug-Herb Interactions

Interactions of azathioprine with herbal products have not been established.

## 9.7 Drug-Laboratory Test Interactions

Interactions of azathioprine with laboratory tests have not been established.

# 10 CLINICAL PHARMACOLOGY

## 10.1 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.

## 10.2 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 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.

### 10.3 Pharmacokinetics

#### **Distribution:**

The volume of distribution at steady state ( $V_{dss}$ ) of azathioprine is unknown. The mean ( $\pm$  SD) apparent  $V_{dss}$  of 6-MP is 0.9 ( $\pm$ 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  $^{35}\text{S}$ -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  $^{35}\text{S}$ -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 allopurinol is the basis for the azathioprine dosage reduction required in these patients (see [7 WARNINGS AND PRECAUTIONS, Xanthine oxidase inhibitors](#) and [9 DRUG INTERACTIONS](#)). 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.

#### **NUDT15 R139C (NUDT15 c.415C>T) Variant**

Recent studies indicate that a strong association exists between the NUDT15 variant NUDT15 c.415C>T [p.Arg139Cys] (also known as NUDT15 R139C [rs116855232]), which is thought to lead to a loss of function of the NUDT15 enzyme, and thiopurine-mediated toxicity such as leukopenia and alopecia. The frequency of NUDT15 c.415C>T has an ethnic variability of 9.8 % in East Asians, 3.9 % in Hispanics, 0.2 % in Europeans and 0.0 % in Africans, indicating an increased risk for the Asian population. Patients who are NUDT15 variant homozygotes (NUDT15 T risk alleles) are at an excessive risk of thiopurine toxicity compared with the C homozygotes.

Reduced thiopurine doses for patients who carry the NUDT15 variants may decrease their risk of toxicity. Therefore, genotypic analysis determining NUDT15 genotype should be determined for all patients, including paediatric patients, prior to initiating thiopurine treatment (see [4.2 Recommended Dose and Dosage Adjustment, Patients with NUDT15 variant](#)). The prescribing physician is advised to establish whether dose reduction is required based on patient response to treatment as well as their genetic profile.

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

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

#### **Elimination**

After oral administration of 100 mg 35S-azathioprine, 50% of the radioactivity was excreted in the urine over 24 hours and 12% in the faeces after 24 hours. In the urine, the major compound was the inactive oxidised metabolite thiouric acid. Less than 2% was excreted in the urine as azathioprine or 6-MP. Azathioprine has a high extraction ratio with a total clearance greater than 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/m<sup>2</sup> and 0.9 hr respectively.

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

## **11 STORAGE, STABILITY AND DISPOSAL**

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

## **12 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.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

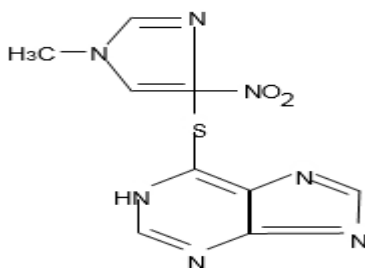
#### Drug Substance

Proper name: Azathioprine

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

Molecular formula and molecular mass:  $C_9H_7N_7O_2S$  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.

## 14 CLINICAL TRIALS

### 14.1 Clinical Trial by Indication

#### 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.

### 14.3 Comparative Bioavailability Studies

#### Fasting Study

A two treatment, two period, single dose, two way crossover comparative bioavailability study comparing APO-AZATHIOPRINE (Apotex Inc.) 50 mg tablets with IMURAN 50 mg tablets was conducted in 44 healthy adult subjects under fasting conditions. Comparative bioavailability data, based on the active metabolite of azathioprine (6-mercaptopurine), are summarized in the table below:

**SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA**

<b>6-mercaptopurine (1 x 50 mg azathioprine) Geometric Mean Arithmetic Mean (CV %)</b>				
<b>Pharmacokinetic Parameter</b>	<b>Test<sup>1</sup></b>	<b>Reference<sup>2</sup></b>	<b>% Ratio of Geometric Means</b>	<b>95% Confidence Interval</b>
AUC <sub>T</sub> (ng·h/mL)	27.75 31.59 (52.42)	28.98 30.86 (34.64)	95.8	84.5 – 180.5
AUC <sub>I</sub> (ng·h/mL)	33.56 37.31 (45.10)	34.78 36.45 (31.33)	96.5	86.8 – 107.3

6-mercaptopurine (1 x 50 mg azathioprine) Geometric Mean Arithmetic Mean (CV %)				
Pharmacokinetic Parameter	Test <sup>1</sup>	Reference <sup>2</sup>	% Ratio of Geometric Means	95% Confidence Interval
C <sub>max</sub> (ng/mL)	15.16 18.10 (63.20)	16.74 18.75 (42.09)	90.6	76.6 – 107.1
T <sub>max</sub> (h) <sup>3</sup>	1.33 (71.41)	1.25 (66.65)		
T <sub>1/2</sub> (h) <sup>3</sup>	1.51 (35.22)	1.52 (31.50)		

<sup>1</sup> APO-AZATHIOPRINE (azathioprine) tablets, 50 mg (Apotex Inc.)

<sup>2</sup> PrIMURAN® (azathioprine) tablets, 50 mg (Glaxo Wellcome Inc., Canada)

<sup>3</sup> Expressed as the arithmetic mean (CV%) only.

#### Fed Study

A two treatment, two period, single dose, two way crossover comparative bioavailability study comparing APO-AZATHIOPRINE (Apotex Inc.) 50 mg tablets with IMURAN 50 mg tablets was conducted in 47 healthy adult subjects under fed conditions. Comparative bioavailability data, based on the active metabolite of azathioprine (6-mercaptopurine), are summarized in the table below:

#### SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

6-mercaptopurine (1 x 50 mg azathioprine) Geometric Mean Arithmetic Mean (CV %)				
Pharmacokinetic Parameter	Test <sup>1</sup>	Reference <sup>2</sup>	% Ratio of Geometric Means	95% Confidence Interval
AUC <sub>T</sub> (ng·h/mL)	16.11 17.74 (44.9)	17.64 19.00 (39.0)	91.1	83.5 – 99.4
AUC <sub>I</sub> (ng·h/mL)	23.60 24.76 (31.8)	22.78 24.10 (34.5)	98.6	88.8 – 109.5
C <sub>max</sub> (ng/mL)	6.93 8.30 (69.8)	7.81 8.87 (54.4)	89.6	77.3 – 103.8
T <sub>max</sub> (h) <sup>3</sup>	1.85 (59.6)	1.79 (54.0)		
T <sub>1/2</sub> (h) <sup>3</sup>	2.22 (31.2)	2.07 (43.2)		

<sup>1</sup> APO-AZATHIOPRINE (azathioprine) tablets, 50 mg (Apotex Inc.)

<sup>2</sup> PrIMURAN® (azathioprine) tablets, 50 mg (Glaxo Wellcome Inc., Canada)

<sup>3</sup> Expressed as the arithmetic mean (CV%) only.



## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL 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<sub>50</sub> dose in mice is 650 mg/kg, intraperitoneally, and about 2500 mg/kg, orally. In rats, the single LD<sub>50</sub> is 310 mg/kg, intraperitoneally, and 400 mg/kg, orally. Death after an LD<sub>50</sub> dose, and even after an LD<sub>100</sub> 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<sub>50</sub> 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.

## **17 SUPPORTING PRODUCT MONOGRAPHS**

1. PRIMURAN<sup>®</sup>, Azathioprine Tablets, 50 mg, submission control 273848, Product Monograph, Aspen Pharmacare Canada Inc. (SEP 27, 2023).

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### PrAPO-AZATHIOPRINE

#### Azathioprine Tablets

Read this carefully before you start taking **APO-AZATHIOPRINE** 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 **APO-AZATHIOPRINE**.

#### Serious Warnings and Precautions

- 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 APO-AZATHIOPRINE used for?

APO-AZATHIOPRINE, 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 APO-AZATHIOPRINE work?

APO-AZATHIOPRINE 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 APO-AZATHIOPRINE?

Medicinal Ingredients: Azathioprine

Non-medicinal Ingredients: Lactose, magnesium stearate, microcrystalline cellulose and starch

#### APO-AZATHIOPRINE comes in the following dosage forms:

Tablets: 50 mg

#### Do not use APO-AZATHIOPRINE if:

- You are allergic to azathioprine or to any of the other ingredients in APO-AZATHIOPRINE (see "[What are the ingredients in APO-AZATHIOPRINE](#)" above)

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-AZATHIOPRINE. 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 been told you have an inherited mutation in the NUDT15 gene
- you have never had chickenpox or shingles
- you have had chickenpox or hepatitis B (a liver disease caused by a virus) in the past
- you are going to have an operation. Medicines including tubocurarine, or succinylcholine that are used as muscle relaxants during surgery may interact with APO-AZATHIOPRINE. You should tell your doctor you are taking APO-AZATHIOPRINE before your surgery.
- you are pregnant. You should not take APO-AZATHIOPRINE 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 APO-AZATHIOPRINE can be transferred through your breast milk.
- you are planning to get a vaccine. You should not receive live vaccines while taking APO-AZATHIOPRINE
- you have had an allergic reaction to a medicine used to treat certain cancers called mercaptopurine.

**Other warnings you should know about:**

**General:** If you are receiving immunosuppressive therapy, taking APO-AZATHIOPRINE 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 APO-AZATHIOPRINE, you should avoid too much exposure to sunlight. You should wear sunscreen with a high protection factor and wear protective clothing.

**Use with other immunosuppressant, particularly corticosteroids:** Patients taking APO-AZATHIOPRINE alone or in combination with other immunosuppressants, 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 APO-AZATHIOPRINE.

### **Infections**

You are more likely to get a viral, fungal, or bacterial infection while you are taking APO-AZATHIOPRINE. If you do get an infection, it may become more severe. Talk to your doctor if you have questions about infections while taking or receiving APO-AZATHIOPRINE.

### **NUDT15 gene mutation**

Tell your doctor before you start taking APO-AZATHIOPRINE if you have an inherited mutation in the NUDT15 gene. The NUDT15 gene is involved in the break-down of azathioprine in the body, you have a higher risk of getting infections and hair loss if you have this mutation. Your doctor may need to give you a lower dose of APO-AZATHIOPRINE.

**Fertility:** It is not known if APO-AZATHIOPRINE affects fertility in humans. When tested in animals, APO-AZATHIOPRINE decreased fertility in animals that mated. It also decreased sperm viability and count in male animals. Talk to your doctor if you have questions about your fertility while taking or receiving APO-AZATHIOPRINE.

**Vaccines:** You should not receive live vaccines while taking or receiving APO-AZATHIOPRINE. They can cause you get an infection. You should wait at least 3 months after you stop taking APO-AZATHIOPRINE before getting a live vaccine. Talk to your doctor if you have questions about receiving vaccines while taking APO-AZATHIOPRINE.

**Itching during pregnancy:** You need to inform your doctor immediately if you experience intense, excessive itching, but without a rash during your pregnancy, especially in the second trimester. You may also experience nausea, and loss of appetite together with itching, which indicates that you have a condition called cholestasis of pregnancy (condition affecting the liver during pregnancy). Your doctor may order blood tests, while you are taking azathioprine and based on the results of this tests, your doctor may change your dose of azathioprine or stop it completely.

**Vitamin B3 Deficiency:** Tell your doctor immediately if you experience diarrhea, localized pigmented rash (dermatitis), and decline in your memory, reasoning or other thinking skills (dementia) as these symptoms may suggest vitamin B3 deficiency (nicotinic acid deficiency/pellagra). Your doctor will likely prescribe vitamin supplements (niacin/nicotinamide) to help you improving the condition.

**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 APO-AZATHIOPRINE:**

- 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)
- live vaccines
- infliximab (used to treat autoimmune disease)

**How to take APO-AZATHIOPRINE:**

**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
- You may feel sick (have nausea) when you first start taking APO-AZATHIOPRINE. If this happens, your doctor may tell you to take the tablets after meals to relieve this.

**Laboratory Tests:** From time to time, while you are taking APO-AZATHIOPRINE, 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 APO-AZATHIOPRINE. This is likely to be between 1 to 3 mg/kg bodyweight per day.

**Rheumatoid Arthritis:** If you are receiving APO-AZATHIOPRINE 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, or a person you are caring for, have taken too much APO-AZATHIOPRINE, contact a 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 APO-AZATHIOPRINE:**

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

Side effects include:

- Tender red bumps on your shins
- hair loss. Often hair does grow again, even if you carry on taking APO-AZATHIOPRINE. If you are worried ask your doctor.

<b>Serious side effects and what to do about them</b>			
<b>Symptom / effect</b>	<b>Talk with your healthcare professional</b>		<b>Stop taking drug and get immediate medical help</b>
	<b>Only if severe</b>	<b>In all cases</b>	
<b>Common</b> fever or infection after transplant		✓	
unexpected bruising or bleeding		✓	
nausea		✓	
<b>Rare</b> 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 diarrhoea and/or abdominal pain any signs of fever and infection (sore throat and			✓

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	
sore mouth)			
<b>Urinary tract infection</b> (infection in urinary system including kidneys, ureters, bladder, and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine.			✓
<b>Serious Skin Reaction:</b>  Stevens-Johnson syndrome (SJS): flu-like symptoms, skin rash often with blister 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, detachment of the skin (epidermal layer)  Acute febrile neutrophilic dermatosis also known as Sweet's Syndrome (a serious inflammatory skin condition): fever, painful dark red bumps or small blisters on the face, neck, arms, legs or hands, skin and mouth lesions, skin discoloration, skin swelling, muscle or joint pain, fatigue.			✓
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-over tablets to your pharmacy for proper disposal. Only keep them if your doctor tells you to.

Keep out of reach and sight of children.

## If you want more information about APO-AZATHIOPRINE:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (<http://www.apotex.ca/products>), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario M9L 1T9.

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