

PRODUCT MONOGRAPH

 AZATHIOPRINE

Azathioprine Tablets USP

50 mg

IMMUNOSUPPRESSIVE AGENT

**SANIS HEALTH INC.
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Dieppe, New Brunswick
E1A 1P2
Control #: 184965**

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 **AZATHIOPRINE**

Azathioprine Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	Tablet / 50 mg	Lactose <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Renal Homotransplantation

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

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).

Geriatrics (>65 years of age)

No data are available.

Pediatrics (<18 years of age)

No data are available.

CONTRAINDICATIONS

- AZATHIOPRINE (Azathioprine Tablets USP) should not be given to patients who have shown hypersensitivity to the drug.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **AZATHIOPRINE (Azathioprine Tablets USP) is mutagenic and carcinogenic and may increase the patients' risk of neoplasia, in particular lymphoma and skin cancer (see *Carcinogenesis and Mutagenesis* section).**
- **Severe leukopenia and/or thrombocytopenia may occur in patients on AZATHIOPRINE (see *Hematologic* section).**
- **Increased susceptibility to infection. (See *Warnings and Precautions*).**
- **AZATHIOPRINE can cause fetal harm when administered to a pregnant woman (see *Pregnant Women* section).**
- **Transplantation**
Only physicians experienced in immunosuppressive therapy and management of organ transplant should prescribe 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 AZATHIOPRINE-treated patients is mandatory. AZATHIOPRINE 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 (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 is mutagenic in animals and humans, carcinogenic in animals, and may increase the patient's risk of neoplasia. Patients receiving immunosuppressive drugs, particularly transplant patients receiving aggressive therapy, are known to have an increased risk of developing non-Hodgkin's lymphomas (***including the rare, very aggressive and usually fatal hepatosplenic Tcell lymphoma [HSTCL]***) and other malignancies, notably skin cancer (melanoma and nonmelanoma, sarcomas (Kaposi's and non-Kaposi's), uterine cervical cancer *in situ*, and reticulum cell or lymphomatous tumors.

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.

Azathioprine is mutagenic in animals and humans, carcinogenic in animals, and may increase the patient's risk of neoplasia. Patients receiving immunosuppressive drugs, particularly transplant patients receiving aggressive therapy, are known to have an increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's), uterine cervical cancer *in situ*, and reticulum cell or lymphomatous tumors. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. It has been reported that reduction or discontinuation of immunosuppression may be associated with partial or complete regression of non-Hodgkin's lymphomas and Kaposi's sarcomas. 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.

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 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.

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 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	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 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 homograft transplantation 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 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.

There have been rare reports of neoplasms including non-Hodgkins lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's), uterine cervical cancer *in situ*, acute myeloid leukaemia and myelodysplasia (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.

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

Allopurinol: The principal pathway for detoxification of azathioprine is inhibited by allopurinol. In patients receiving azathioprine, the concomitant administration of Zyloprim® (allopurinol) will require a reduction in dose to approximately 1/3 to 1/4 of the usual dose of azathioprine. Subsequent adjustment of doses of azathioprine should be made on the basis of therapeutic response and any toxic effects.

Other Agents Affecting Myelopoiesis: Drugs which may affect leukocyte production, including co-trimoxazole, 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.

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 (Azathioprine Tablets USP) required to prevent rejection and minimize toxicity will vary with individual patients; this necessitates careful management. The initial dose is usually 3-5 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 1-3 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 (50-100 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 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 can be discontinued abruptly, but delayed effects are possible.

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.

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, administer gastric lavage and fluids; blood transfusions may be needed due to suppression of the proliferation of granulocytes.

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, SGOT, 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

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 µg/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.

STORAGE AND STABILITY

Store at room temperature (15-30°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 Tablet contains the non-medicinal ingredients lactose, magnesium stearate, microcrystalline cellulose and starch.

Packaging

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

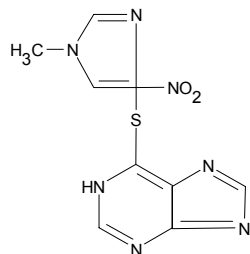
Proper Name: Azathioprine

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: C₉H₇N₇O₂S

Molecular Weight: 277.27

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 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	IMURAN^{®†}	
AUC _{0-T} (ng·hr/mL)	27.88 31.59 (52.42)	28.96 30.86 (34.64)	96.3
AUC _{0-∞} (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	IMURAN^{®†}	
AUC _{0-T} (ng·hr/mL)	16.1078 17.737 (44.9)	17.6405 18.998 (39.0)	91.31
AUC _{0-∞} (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 LD₅₀ dose in mice is 650 mg/kg, intraperitoneally, and about 2500 mg/kg, orally. In rats, the single LD₅₀ is 310 mg/kg, intraperitoneally, and 400 mg/kg, orally. Death after an LD₅₀ dose, and even after an LD₁₀₀ 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 LD₅₀ 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.

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 ($p < 0.01$) in lymphosarcomas. This increased incidence of lymphosarcoma in azathioprine-dose females was also responsible for a significant ($p < 0.01$) 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.

Teratology Studies

Reproductive studies have been performed in a variety of species. 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.

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PART III: CONSUMER INFORMATION

Ⓜ AZATHIOPRINE
Azathioprine Tablets USP

This leaflet is part III of a three-part "Product Monograph" published when AZATHIOPRINE (Azathioprine Tablets USP) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AZATHIOPRINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

AZATHIOPRINE (Azathioprine Tablets USP), an immunosuppressant agent is used in the following conditions:

- Renal Homotransplantations: as an adjunct (with other medications) in the prevention of rejection of kidney transplants.
- Rheumatoid Arthritis in adult patients who cannot be treated with other medications and treatments.

What it does:

AZATHIOPRINE belongs to a group of medicines called immunosuppressants. This means that it reduces the strength of your immune system.

Immunosuppressant medicines are sometimes necessary to help your body accept an organ transplant, such as a new kidney or to treat rheumatoid arthritis where your immune system is reacting against your own body (autoimmune diseases).

When it should not be used:

You should NOT take AZATHIOPRINE if you:

- are allergic to azathioprine or any of the other ingredients of AZATHIOPRINE (see What the non-medicinal ingredients are).

What the medicinal ingredient is:

Azathioprine

What the important non-medicinal ingredients are:

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

What dosage forms it comes in:

The AZATHIOPRINE 50 mg tablet is a pale yellow, peanut-shaped tablet, scored and engraved "AZ 50" on one side and "APO" on the other.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

Patients taking immunosuppressive medicines may have an increased risk of developing tumours including skin cancer. Therefore while taking AZATHIOPRINE tablets you should avoid too much exposure to sunlight. You are advised to wear protective clothing and to use a sunscreen with a high protection factor.

Patients receiving AZATHIOPRINE alone or in combination with other immunosuppressants, particularly corticosteroids, have shown increased susceptibility to infections.

Infection with chickenpox or shingles can become severe in patients taking immunosuppressive medicine. Therefore you should avoid contact with anyone suffering from chickenpox or shingles.

Patients receiving AZATHIOPRINE have experienced gastrointestinal hypersensitivity reactions including severe nausea and vomiting.

BEFORE you use AZATHIOPRINE talk to your doctor or pharmacist if:

- you have rheumatoid arthritis and have been previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan or others)
- you are under 18 years of age
- you are pregnant or breast feeding
- you are planning to have a baby - discuss this with your doctor whether you are male or female
- 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 suffered from chickenpox or shingles

INTERACTIONS WITH THIS MEDICATION

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those that you have bought yourself without a doctor's prescription.

Certain medicines can interact with AZATHIOPRINE (Azathioprine Tablets USP) such as those listed below:

- angiotensin-converting enzyme inhibitors such as captopril (used mainly to treat high blood pressure and heart failure)
- co-trimoxazole also known as SEPTRA® (used to treat infections).
- allopurinol (used mainly to treat gout)
- curare, d-tubocurarine, tubocurarine, succinylcholine (used during anaesthesia and as muscle relaxants)
- warfarin (used to prevent blood clots)
- mesalazine, olsalazine or sulphasalazine (used mainly to treat ulcerative colitis).

PROPER USE OF THIS MEDICATION

It is important to take your medicine at the right times. You must take it in the way your doctor has told you to. Swallow the tablet whole, do not break the tablet.

It is important that you and/or your caregivers are aware of the need for safe handling of this medicine. Please consult your pharmacist or doctor for advice.

The amount of azathioprine people take can be very different. Your dose will depend on the condition your doctor is treating.

Your doctor will tell you how long your treatment will last. Do not stop treatment early.

From time to time, while you are taking AZATHIOPRINE (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 Dose for Adults for Renal Homotransplantation:

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. This is likely to be between 1 to 3 mg/kg bodyweight per day.

Usual Dose for Adults for Rheumatoid Arthritis:

If you are receiving 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:

In case of overdose, contact a healthcare professional, hospital emergency department or regional poison control centre, 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. Speak to your doctor as soon as you can about the doses you may have missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, AZATHIOPRINE (Azathioprine Tablets USP) can cause side effects.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking AZATHIOPRINE STOP taking this medicine and tell your doctor immediately or go to the nearest hospital emergency department:

- you develop muscle or bone pain
- you develop kidney problems
- you start feeling faint especially on standing up
- you develop bad diarrhoea and/or abdominal pain
- you develop a serious skin reaction (e.g. blistering and/or peeling)

Tell your doctor immediately if any of the following happen to you while you are taking AZATHIOPRINE:

- you start to notice any signs of a fever or an infection
- you have any unexpected bruising or bleeding
- you develop any new marks on your skin or any change to marks that you may have had previously
- you develop a cough or difficulty breathing similar to a chest infection
- you have nausea and vomiting
- you feel tired, dizzy or generally unwell
- you come into contact with anyone who is suffering from chickenpox or shingles.

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

Cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported.

You may notice some hair loss while taking AZATHIOPRINE. Often hair does grow again, even if you carry on taking AZATHIOPRINE. If you are worried ask

IMPORTANT: PLEASE READ

your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Common	signs of fever or infection (in the non-transplant population infection is uncommon)		√
	unexpected bruising or bleeding		√
	nausea		√
Un-common	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		√
	serious skin reaction (e.g. blistering and/or peeling)		√

If you notice any side effects not mentioned in this leaflet, tell your doctor or pharmacist.

HOW TO STORE IT

Store between 15°C and 30°C. Protect from light.

Do not take the medicine after the expiry date shown on the tablet pack.

If your doctor tells you to stop taking the tablets, please return any which are left over to your pharmacist. Only keep them if your doctor tells you to.

As with all medicines, keep AZATHIOPRINE (Azathioprine Tablets USP) tablets out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
 By toll-free fax: 866-678-6789
 Online: www.healthcanada.gc.ca/medeffect
 By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
 Canada Vigilance National Office
 Marketed Health Products Safety and Effectiveness Information Bureau
 Marketed Health Products Directorate
 Health Products and Food Branch
 Health Canada
 Tunney's Pasture, AL 0701E
 Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Sanis Health Inc. at:

1-866-236-4076 or
quality@sanis.com

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