AAI INTERNATIONAL

2320 Scientific Park Drive
Wilmington, NC 28405

Phone: 1.910.254.7000
Fax: 1.910.815.2300
1.800.575.4224

August 29, 2001

Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

RE: SUITABILITY PETITION

Dear Sirs;

The undersigned submits this petition, pursuant to 21 CFR 10.20 (and in the format specified in 21 CFR 10.30), in accordance with the regulations at 21 CFR 314.93(b), to obtain permission from the Commissioner of Food and Drugs to submit an abbreviated new drug application for a drug product which is not identical in strength to the listed drug.

A. Action Requested

The petitioner requests that the Commissioner take into consideration the evidence presented here and grant permission to submit an abbreviated new drug application for a drug product higher in strength than the reference listed drug.

B. Statement of Grounds

NDA 016-324 for the reference listed drug (Imuran®) currently lists only 50 mg strength oral tablets. In the Dosage and Administration section of the current package insert the maximum recommended dose for patients diagnosed with Rheumatoid Arthritis is 125 mg to 250 mg per day. For those patients who have had Renal Homotransplantation, the other approved indication for this drug, the initial dose can vary between 150 mg and 500 mg per day. In concurrence with the labeled dosing regimen and as a convenience to the patient, we wish to propose tablets of the additional strengths of 75 mg and 100 mg.

Although the requested strengths for the proposed product are higher than the currently approved strength for oral administration they are significantly lower than the dosing recommendations in the approved labeling.

OIP-0379

CP 1

In support of this petition, the following information is provided for consideration:

- A Summary of Product Information for our approved ANDA (75-252) for Azathioprine Tablets USP, 50 mg. This information highlights significant areas and changes made for the purpose of developing the proposed 75 mg and 100 mg products. In accordance with 21 CFR 314.93(d)(1) information is also included to demonstrate that the active ingredient, Azathioprine, meets cUSP specifications and therefore is of the same pharmacological and therapeutic class as that of the reference listed drug. (See Attachment I).

- In accordance with 21 CFR 314.93(d) the listed drug has been identified as Imuran® (NDA 16-034) and a copy of the proposed labeling for the subject drug product and a copy of the approved labeling for the listed drug are included. (See Attachment II).

- In accordance with 21 CFR 314.93(d)(2), information is included to show that the drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use in the reference listed drug's labeling. A summary of an Open-Label Randomized Single-Dose Bioequivalence Study of 100 mg Azathioprine Tablets and Imuran 50 mg Tablets under Fasting Conditions is provided for consideration. (See Attachment III).

- A dissolution study was performed on the proposed drug products and on Imuran 50 mg Tablets. The comparative results are presented here. (See Attachment IV)

- Stability data is being provided to demonstrate that the product is expected to be stable over the proposed shelf-life. (See Attachment V).

C. Environmental Impact

A claim for categorical exclusion of the requirements for an environmental impact assessment is made pursuant to 21 CFR 25.31.

D. Economic Impact

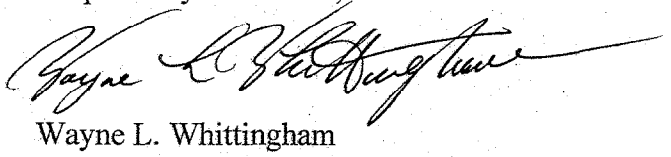
Pursuant to 21 CFR 10.30(b), economic impact information is submitted only when requested by the Commissioner. This information will be provided if so requested.

E. Certification

The undersigned certifies, that, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Pursuant to the regulations in 21 CFR 10.20, this petition is being provided to the Dockets Management Branch in Quadruplicate. If you have any questions, please feel free to contact me at the above address or by telephone at (910) 254-7027, by facsimile at (910) 815-2337 or by internet e-mail at Wayne.Whittingham@aaiintl.com.

Respectfully Submitted,



Wayne L. Whittingham
Regulatory Affairs Professional

Enclosures

Table of Contents

TABLE OF CONTENTS

Summary of Product Information

Drug Substance

Source

Responsibility	Name & Address	DMF #
Manufacturer	Fine Chemicals Corporation P.O. Box 253 Eppindust 7475 Cape Province South Africa	10119
U.S. Agent	Ceres Chemical Company Inc. 3 Gannett Drive White Plains, New York 10604	N/A

Specifications

Raw Material Specification **RM-00932**

SUBJECT:	Azathioprine (Micronized) USP+	
MANUFACTURER:	Fine Chemicals Corporation	
TEST	**METHOD**	**SPECIFICATION**
Appearance	25481	Pale yellow powder
Identification		
IR:	cUSP	The infrared absorption spectrum of the test preparation exhibits maxima only at the same wavelengths as that of a similar preparation of the corresponding USP Reference Standard.
TLC:	cUSP	The principal spot in the test preparation chromatogram in the test for *Limit of Mercaptopurine* shows the same Rf value as that obtained with the solution of Azathioprine reference standard
Acidity or Alkalinity	cUSP	20.0 mL of the filtrate requires for neutralization NMT 0.10 mL of 0.20 *N* hydrochloric acid or NMT 0.10 mL of 0.20 *N* sodium hydroxide
Loss on Drying	cUSP	NMT 1.0%
Residue on Ignition	cUSP	NMT 0.1%
Organic Volatile Impurities, *Method IV*	cUSP	Chloroform: NMT 60 µg/g 1,4-Dioxane: NMT 380 µg/g Methylene Chloride: NMT 600 µg/g Trichloroethylene: NMT 80 µg/g
Residual Solvent (OVI, Method IV)	cUSP	Chloroform: NMT 60µg/g
Related Substances		
TLC:	19838	5-Chloro-1-methyl-4-nitroimidazole (CMN): NMT 0.5% 6-Mercaptopurine: NMT 1.0% 5-Amino-1-methyl-4-nitroimidazole (AMN): NMT 0.5%
HPLC	54393	N,N'-dimethyloxamide (DMO): NMT 0.5% Hypoxanthine NMT 0.5% S-(6'-Purinyl)-6-mercaptopurine: NMT 1.0% Each unknown impurity: NMT 0.1%
TOTAL (TLC+HPLC)		NMT 2.0%
Assay	cUSP	98.0% - 101.5% of $C_9H_7N_7O_2S$, calculated on the dried basis
Particle Size	19867	90% ≤ 25 µm

The information provided in the table above demonstrates that the active ingredient, Azathioprine, is of the same pharmacological and therapeutic class as that of the reference listed drug. We therefore believe that we are in compliance with the requirements of 21 CFR 314.93(d)(1).

Drug Product

Manufacturer

Responsibility	Name & Address
Manufacturing, in-process testing, packaging and labeling	AAI International Manufacturing Services Division 1726 North 23rd Street Wilmington, North Carolina 28405
Release testing of active and inactive ingredients, in-process testing, packaging component testing, finished product testing, and stability evaluations	AAI International Manufacturing Services Division 1726 North 23rd street Wilmington, North Carolina 28405 **and/or** AAI International Lab A Route 6, Hall Drive Wilmington, North Carolina 28405 AAI International Lab B 1206 N 23rd Street Wilmington, North Carolina 28405 AAI International Lab C 6101 Quadrangle Drive Durham, North Carolina 27514 AAI International 3 Silverline Drive, Route One North Brunswick, New Jersey 08902
Stability samples storage	AAI International Stability Services 3101 N. Kerr Avenue Wilmington, North Carolina 28405

Master Manufacturing Formulae

Strength	50 mg			75 mg			100 mg		
Batch Size	180,000 tablets			110,000 tablets			110,000 tablets		
Ingredient and Test Standard	**Qty. per unit (mg)**	**Qty. per batch (g)**	**%**	**Qty. per unit (mg)**	**Qty. per batch (g)**	**%**	**Qty. per unit (mg)**	**Qty. per batch (g)**	**%**
Azathioprine (Micronized), USP	50.00	9,000	20.00	75.00	8,250	20.00	100.00	11,000	20.00
Lactose Monohydrate, NF	140.00	25,200	56.00	210.00	23,100	56.00	280.00	30,800	56.00
Starch 1500® LM (Low Moisture, Pregelatinized)	25.00	4,500	10.00	37.50	4,125	10.00	50.00	5,500	10.00
Povidone, USP	6.25	1,125	2.50	9.38	1,031.25	2.50	12.50	1,375	2.50
Corn Starch, NF (Sta-Rx®)	26.88	4,837.5	10.75	40.32	4,434.38	10.75	53.76	5,912.5	10.75
Magnesium Stearate, NF (Impalpable Powder) FCC	1.25	225	0.50	1.87	206.25	0.50	2.50	275	0.50
Stearic Acid, NF	0.62	112.5	0.25	0.93	103.12	0.25	1.24	137.5	0.25
Total	**250.00**	**45,000**	**100.00**	**375.00**	**41,250**	**100.00**	**500.00**	**55,000**	**100.00**

Manufacturing Process

The manufacture involves a wet granulation and is performed exactly as described in our approved ANDA with the following exceptions:

75 mg Tablets

Tooling 0.3750" x 0.3993" triangle shaped tooling, 75 mg embossed on the upper punch with a bisect between 75 and mg, lower punch embossed with "N"

In-Process Controls

Limits	Target	Specifications
Individual Weight (mg)	375	360 – 390
Individual Hardness (kp)	9.0	6.0 – 12.0
Individual Thickness (in.)	0.210	0.200 – 0.220

100 mg Tablets

Tooling 0.3750" x 0.5625" diamond shaped tooling, 100 mg embossed on the upper punch with a bisect between 100 and mg, lower punch embossed with "N"

In-Process Controls

Limits	Target	Specifications
Individual Weight (mg)	500	480 - 520
Individual Hardness (kp)	11.0	7.5 – 14.5
Individual Thickness (in.)	0.210	0.200 – 0.220

Specification

Test	Method	Acceptance Limit
Appearance	25481	50 mg: Yellow, capsule-shape tablet with debossed "GG 210" and central score between the "GG" and "210" on one face. 75 mg: Yellow, triangle-shaped tablet with debossed "75 mg" and central score between the "75" and "mg" on one face. Debossed "N" on other face. 100 mg: Yellow, diamond-shaped tablet with debossed "100 mg" and central score between the "100" and "mg" on one face. Debossed "N" on other face.
Identification (TLC)	17029	The R_f value of the principal spot obtained from the test solution corresponds to that obtained from the Standard solution.
Dissolution	23735	NLT 75% (Q) in 30 minutes
Content Uniformity	18987	Meets cUSP requirements
Assay	19149	93.0% - 107.0% Label Claim
Related Substances	19149	Known Impurity: NMT 1.0% Unknown Impurity: NMT 0.1% Total (known + unknown): NMT 2.0%

Container/Closure

Quantity/Strength	Component Description		
	Bottle	Cap	Coil
15 Tablets (75 mg and 100 mg) 100 Tablets (50 mg)	50 cc HDPE Round, White (33/400)	33/400 CR Cap with Foam Seal and PS-22 Liner	Low Moisture Polyester Coil, 12 g/yard
100 Tablets (75 mg and 100 mg)	120 cc HDPE White Wide Mouth Round (38/400)	38/400 CR Cap with Foam Seal and PS-22 Liner	
1000 Tablets (75 mg and 100 mg)	750 cc HDPE, White Wide Mouth Round (53/400)	53/400 CT Cap with Foam Seal and PS-22 Liner	

Labeling

Labeling

Introduction

In accordance with 21 CFR 314.93(d) the listed drug has been identified as Imuran. A copy of the proposed labeling for the subject drug product and a copy of the approved labeling for the innovator product are included here.

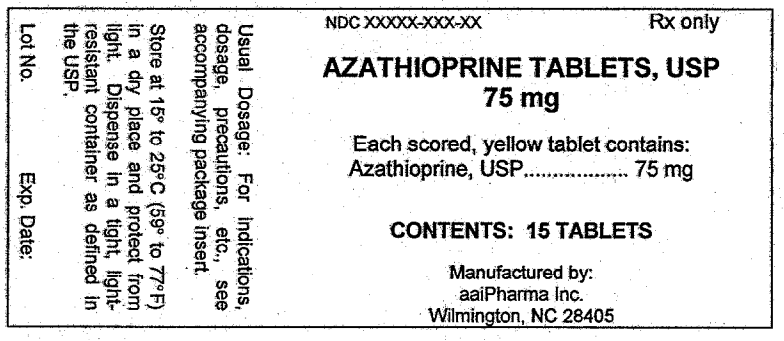
The proposed drug products will be packaged in the following packaging sizes:

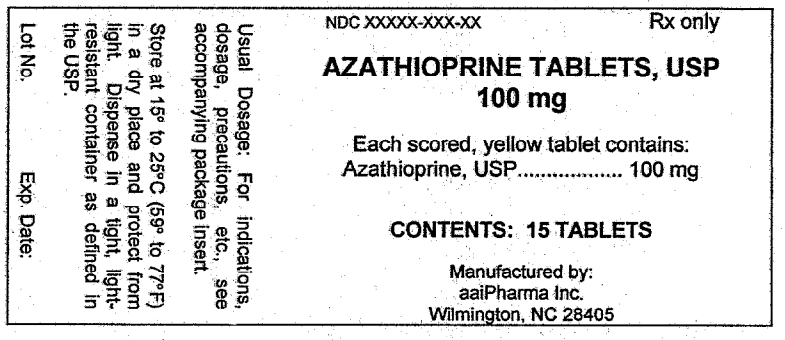
15 count bottles
100 count bottles
1000 count bottles

The proposed labeling is the same as currently approved for IMURAN® Tablets, except for the differences noted, specifically with regard to the manufacturer name, inactive ingredients, product strength, and tablet count. The lot number and expiration date will be stamped on the container labels at the time of packaging.

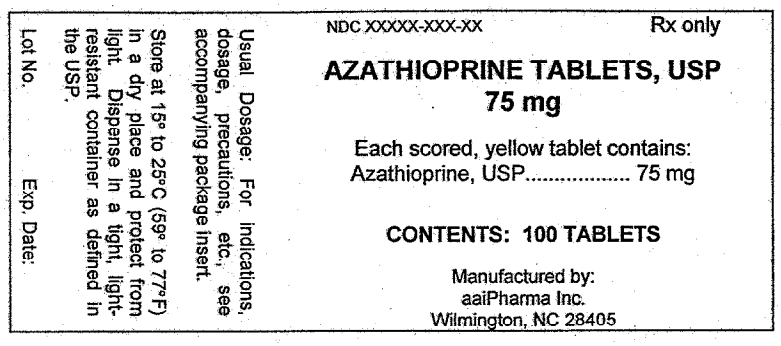
Proposed Labeling

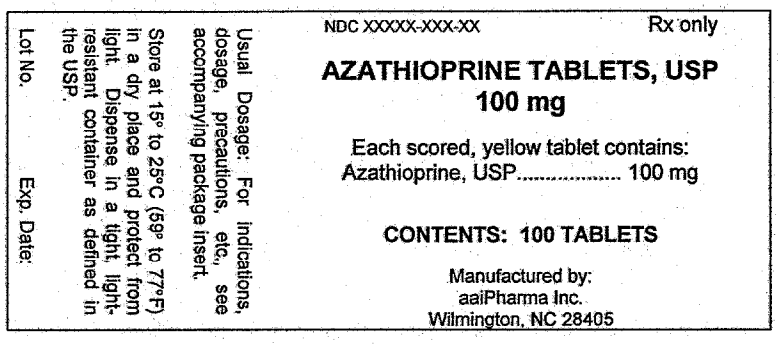
15 Count Bottle Label



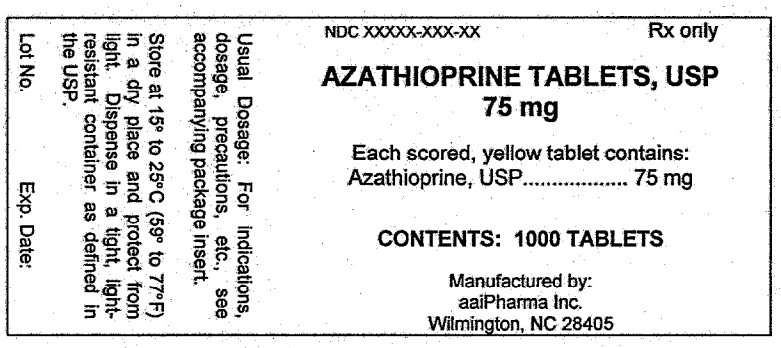


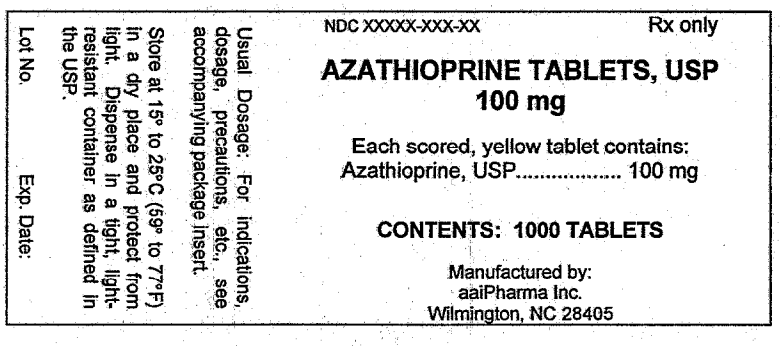
100 Count Bottle Label





1000 Count Bottle Label





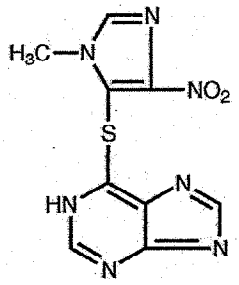
Proposed Package Insert

AZATHIOPRINE TABLETS, USP
75 mg Scored Tablets
100 mg Scored Tablets

WARNING: Chronic immunosuppression with this purine antimetabolite increases *risk of neoplasia* in humans. Physicians using this drug should be very familiar with this risk as well as with the mutagenic potential to both men and women and with possible hematologic toxicities. See WARNINGS.

DESCRIPTION: Azathioprine, an immunosuppressive antimetabolite, is available in tablet form for oral administration. Each scored tablet contains 50 mg azathioprine and the inactive ingredients lactose monohydrate, pregelatinized starch, povidone, corn starch, magnesium stearate, and stearic acid.

Azathioprine is chemically 1*H*-purine, 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-. The structural formula of azathioprine is:



$C_9H_7N_7O_2S$ M.W. 277.27

It is an imidazolyl derivative of 6-mercaptopurine (PURINETHOL®) and many of its biological effects are similar to those of the parent compound.

Azathioprine is insoluble in water, but may be dissolved with addition of one molar equivalent of alkali. The sodium salt of azathioprine is sufficiently soluble to make a 10 mg/mL water solution which is stable for 24 hours at 59° to 77°F (15° to 25°C). Azathioprine is stable in solution at neutral or acid pH but hydrolysis to mercaptopurine occurs in excess sodium hydroxide (0.1N), especially on warming. Conversion to mercaptopurine also occurs in the presence of sulfhydryl compounds such as cysteine, glutathione, and hydrogen sulfide.

CLINICAL PHARMACOLOGY:
Metabolism[1]: Azathioprine is well absorbed following oral administration. Maximum serum radioactivity occurs at 1 to 2 hours after oral ^{35}S-azathioprine and decays with a half-life of 5 hours. This is not an estimate of the half-life of azathioprine itself but is the decay rate for all ^{35}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 8 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 PRECAUTIONS: 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.

Homograft Survival[1,2]: Summary information from transplant centers and registries indicates relatively universal use of azathioprine with or without other immunosuppressive agents.[3,4,5] 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 autoimmune disease. For example, the severity of adjuvant arthritis is reduced by azathioprine.

The mechanisms whereby azathioprine affects autoimmune 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.

INDICATIONS AND USAGE: Azathioprine tablets are indicated as an adjunct for the prevention of rejection in renal homotransplantation. It is also indicated for the management of severe, active rheumatoid arthritis unresponsive to rest, aspirin, or other nonsteroidal anti-inflammatory drugs, or to agents in the class of which gold is an example.

Renal Homotransplantation: Azathioprine tablets are indicated as an adjunct for the prevention of rejection in renal homotransplantation. Experience with over 16,000 transplants shows a 5-year patient survival of 35% to 55%, but this is dependent on donor, match for HLA antigens, anti-donor and anti B-cell alloantigen antibody, and other variables. The effect of azathioprine on these variables has not been tested in controlled trials.

Rheumatoid Arthritis[6,7]**:** Azathioprine tablets are indicated only in adult patients meeting criteria for classic or definite rheumatoid arthritis as specified by the American Rheumatism Association.[8] Azathioprine should be restricted to patients with severe, active and erosive disease not responsive to conventional management including rest, aspirin, or other nonsteroidal drugs or to agents in the class of which gold is an example. 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 gold, antimalarials, or penicillamine has not been studied for either added benefit or unexpected adverse effects. The use of azathioprine with these agents cannot be recommended.

CONTRAINDICATIONS: Azathioprine should not be given to patients who have shown hypersensitivity to the drug.

Azathioprine should not be used for treating rheumatoid arthritis in pregnant women.

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.[9]

WARNINGS: 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 hemotologic 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.

Serious infections are a constant hazard for patients receiving chronic immunosuppression, especially for homograft recipients. 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.

Azathioprine is mutagenic in animals and humans, carcinogenic in animals, and may increase the patient's *risk of neoplasis*. Renal transplant patients are known to have an increased risk of malignancy, predominantly skin cancer and reticulum cell or lymphomatous tumors.[10] The risk of post-transplant lymphomas may be increased in patients who receive aggressive treatment with immunosuppressive drugs.[11] 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 post-transplant lymphomas. However, transplant 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. Information is available on the spontaneous neoplasia risk in rheumatoid arthritis,[12,13] and on neoplasia following immunosuppressive therapy of other autoimmune disease.[14,15] It has not been possible to define the precise risk of neoplasia due to azathioprine.[16] The data suggest the risk may be elevated in patients with rheumatoid arthritis, though lower than for renal transplant patients.[11,13] However, acute meylogenous 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.
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[17]; a reduced percentage of fertile matings occurred when animals received 5 mg/kg.[18]

Pregnancy: Pregnancy Category D. Azathioprine can cause fetal harm when administered to a pregnant woman. Azathioprine should not be given during pregnancy without careful weighing of risk versus benefit. Whenever possible, use of azathioprine in pregnant patients should be avoided. This drug should not be used for treating rheumatoid arthritis in pregnant women.[19]

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.[18]

Limited immunologic and other abnormalities have occurred in a few infants born of renal allograft recipients on azathioprine. In a detailed case report,[20] 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. DeWitte et al[21] reported pancytopenia and severe immune deficiency 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. Williamson and Karp[22] described an infant born with preaxial polydactyly whose mother received azathioprine 200 mg daily and prednisone 20 mg every other day during pregnancy. Tallent et al[23] 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.

Benefit versus risk must be weighed carefully before use of azathioprine in patients of reproductive potential. There are no adequate and well-controlled studies in pregnant women. 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.

PRECAUTIONS:
General: A gastrointestinal hypersensitivity reaction characterized be severe nausea and vomiting has been reported.[24,25,26] These symptoms may also be accompanied by diarrhea, rash, fever, malaise, myalgias, elevations in liver enzymes, and occasionally, hypotension. Symptoms of gastrointestinal toxicity most 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.

Information for Patients: Patients being started on azathioprine should be informed of the necessity of periodic blood counts while they are receiving the drug and should be encouraged to report any unusual bleeding or bruising to their physician. They should be informed of the danger of infection while receiving azathioprine and asked to report signs and symptoms of infection to their physician. Careful dosage instructions should be given to the patient, especially when azathioprine is being administered in the presence of impaired renal function or concomitantly with allopurinol (see PRECAUTIONS - Drug Interactions subsection and DOSAGE AND ADMINISTRATION). Patients should be advised of the potential risks of the use of azathioprine during pregnancy and during the nursing period. The increased risk of neoplasia following therapy with azathioprine should be explained to the patient.

Laboratory Tests: See WARNINGS and ADVERSE REACTIONS sections.

Drug Interactions:
Use with Allopurinol: The principal pathway for detoxification of azathioprine is inhibited by allopurinol. Patients receiving azathioprine and allopurinol concomitantly should have a dose reduction of azathioprine, to approximately 1/3 to 1/4 the usual dose.

Use with Other Agents Affecting Myelopoesis: Drugs which may affect leukocyte production, including co-trimoxazole, may lead to exaggerated leukopenia, especially in renal transplant recipients.[27]

Use with Angiotensin-Converting Enzyme Inhibitors: The use of angiotensin-converting enzyme inhibitors to control hypertension in patients on azathioprine has been reported to induce severe leukopenia.[28]

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS section.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category D. See WARNINGS section.

Nursing Mothers: 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.[29,30,31] Because of the potential for tumorgenicity shown for azathioprine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and efficacy of azathioprine in pediatric patients have not been established.

ADVERSE REACTIONS: 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). 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. 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.[12] 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.[13] 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 are dose dependent and may occur late in the course of therapy with azathioprine. Dose reduction or temporary withdrawal allows reversal of these toxicities. Infection may occur as a secondary manifestation of bone marrow suppression or leukopenia, but the incidence of infection in renal homotransplantation is 30 to 60 times that in rheumatoid arthritis. Macrocytic anemia and/or bleeding have been reported in two 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 often can 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, and myalgias (see PRECAUTIONS). Vomiting with abdominal pain may occur rarely with a hypersensitivity pancreatitis. Hepatotoxicity manifest by elevation of serum alkaline phosphatase, bilirubin, and/or serum transaminases is known to occur following azathioprine use, primarily in allograft recipients. Hepatotoxicity has been uncommon (less than 1%) in rheumatoid arthritis patients. Hepatotoxicity following transplantation most often occurs within 6 months of transplantation and is generally reversible after interruption of azathioprine. A rare, but life-threatening hepatic veno-occlusive disease associated with chronic administration of azathioprine has been described in transplant patients and in one patient receiving azathioprine for panuveitis.[32,33,34] Periodic measurement of serum transminases, alkaline phosphatase, and bilirubin is indicated for early detection of hepatotoxicity. If hepatic veno-occlusive disease is clinically suspected, azathioprine should be permanently withdrawn.

Others: Additionally side effects of low frequency have been reported. These include skin rashes, alopecia, fever, arthralgias, diarrhea, steatorrhea and negative nitrogen balance (all less than 1%).

OVERDOSAGE: The oral LD_{50}s for single doses of azathioprine in mice and rats are 2500 mg/kg and 400 mg/kg, respectively. Very large doses of this antimetabolite may lead to marrow hypoplasia, bleeding, infection, and death. About 30% of azathioprine is bound to serum proteins, but approximately 45% is removed during an 8-hour hemodialysis.[35] 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.

DOSAGE AND ADMINISTRATION:
Renal Homotransplantation: The dose of 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. Azathioprine is usually given as a single daily dose on the day of, and in a minority of cases 1 to 3 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 postoperative period. Intravenous administration of the sodium salt is indicated only in patients unable to tolerate oral medications. Dose reduction to maintenance levels of 1 to 3 mg/kg daily is usually possible. The dose of azathioprine should not be increased to toxic levels because of threatened rejection.

Discontinuation may be necessary for severe hematologic or other toxicity, even if rejection of the homograft may be a consequence of drug withdrawal.

Rheumatoid Arthritis: Azathioprine is usually given on a daily basis. The initial dose should be approximately 1 mg/kg (50 to 100 mg) given as a single dose or on a twice daily schedule. The dose may be increased, beginning at 6 to 8 weeks and thereafter by steps at 4-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 6 to 8; an adequate trial should be a minimum of 12 weeks. Patients not improved after 12 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 decrementally with changes of 0.5 mg/kg or approximately 25 mg daily every 4 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.

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, may be particularly sensitive to this drug, and are usually given lower doses.

Procedures for proper handling and disposal of this immunosuppressive antimetabolite drug should be considered. Several guidelines on this subject have been published.[36-42] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED:

Azathioprine Tablets, USP, 75 mg are triangular-shaped, yellow, scored tablets;
Bottles of 15 (NDC XXXXX-XXX-XX)
Bottles of 100 (NDC XXXXX-XXX-XX)
Bottles of 1000 (NDC XXXXX-XXX-XX).

Azathioprine Tablets, USP, 100 mg are diamond-shaped, yellow, scored tablets;
Bottles of 15 (NDC XXXXX-XXX-XX)
Bottles of 100 (NDC XXXXX-XXX-XX)
Bottles of 1000 (NDC XXXXX-XXX-XX).

Rx only.

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

Dispense in a tight, light-resistant container as defined in the USP.

REFERENCES:

1. Elion GB, Hitchings GH. Azathioprine. In: Sartorelli AC, Johns DG, eds. *Antineoplastic and Immunosuppressive Agents Pt II.* New York, NY:Springer Verlag; 1975:chap 48.
2. McIntosh J, Hansen P, Ziegler J, et al. Defective immune and phagocytic functions in uraemia and renal transplantation. *Int Arch Allergy Appl Immunol.* 1976;15:544-549.
3. Renal Transplant Registry Advisory Committee. The 12th report of the Human Renal Transplant Registry. *JAMA.* 1975;233:787-796.

4. McGeown M. Immunosuppression for kidney transplantation. *Lancet*. 1973;2:310-312.
5. Simmons RL, Thompson EJ, Yunis EJ, et al. 115 patients with first cadaver kidney transplants followed two to seven and a half years: a multifactorial analysis. *Am J Med*. 1977;62:234-242.
6. Fye K, Talal N. Cytotoxic drugs in the treatment of rheumatoid arthritis. *Ration Drug Ther*. 1975;9:1-5.
7. Davis JD, Muss HB, Turner RA. Cytotoxic agents in the treatment of rheumatoid arthritis. *South Med J*. 1978;71:58-64.
8. McEwen C. The diagnosis and differential diagnosis of rheumatoid arthritis. In: Hollander JL, ed. *Arthritis and Allied Conditions: A Textbook of Rheumatology*. 8th ed. Philadelphia, PA: Lea and Febiger;1972:403-418.
9. Hoover R, Fraumeni JF. Drug-induced cancer. *Cancer*.1981;47:1071-1080.
10. Hoover R, Fraumeni JF Jr. Risk of cancer in renal transplant recipients. *Lancet*.1973;2:55-57.
11. Wilkinson AH, Smith JL, Hunsiker LG, et al. Increased frequency of post-transplant lymphomas in patients treated with cyclosporine, azathioprine, and prednisone. *Tranplantation*. 1989;47:293-296.
12. Prior P, Symmons DPM, Hawkins CF, et al. Cancer morbidity in rheumatoid arthritis. *Ann Rheum Dis*. 1984;43:128-131.
13. Silman AJ, Petrie J, Hazelman B, et al. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. *Ann Rheum Dis*. 1988;47:988-992.
14. Louie S, Schwartz RS. Immunodeficiency and pathogenesis of lymphoma and leukemia. *Semin Hematol*. 1978;15:117-138.
15. Wang KK, Czaja AJ, Beaver SJ, et al. Extra hepatic malignancy following long-term immunosuppressive therapy of severe hepatitis B surface antigen-negative chronic active hepatitis. *Hepatology*. 1989;10:39-43.
16. Sieber SM, Adamson RH. Toxicity of antineoplastic agents in man: chromosomal aberrations, antifertility effects, congenital malformations, and carcinogenic potential. In: Klein G, Weinhouse S, eds. *Advances in Cancer Research*. New York, NY: Academic Press; 1975;22:57-155.
17. Clark JM. The mutagenicity of azathioprine in mice, *Drosophila Melanogaster and Neurospora Crassa. Mut Res*. 1975;28:87-99.
18. Data on file, Glaxo Wellcome Inc.
19. Tagatz GE, Simmons RL. Pregnancy after renal transplantation. *Ann Intern Med*. 1975;82:113-114. Editorial Notes.
20. Coté CJ, Meuwissen HJ, Pickering RJ. Effects on the neonate of prednisone and azathioprine administered to the mother during pregnancy. *J. Pediatr*. 1974;85:324-328.
21. DeWitte DB, Buick MK, Stephen EC, et al. Neonatal pancytopenia and severe combined immunodeficiency associated with antenatal administration of azathioprine and prednisone. *J. Pediatr*. 1984;105:625-628.
22. Williamson RA, Karp LE. Azathioprine teratogenicity; review of the literature and case report. *Obstet Gynecol*. 1981;58:247-250.
23. Tallent MB, Simmons RL, Najarian JS. Birth defects in child of male recipient of kidney transplant. *JAMA*. 1970;211:1854-1855.
24. Assini JF, Hamilton R, Strosberg JM. Adverse reactions to azathioprine mimicking gastroenteritis. *J Rheumatol*. 1986;13:1117-1118.
25. Cochrane D, Adamson AR, Halsey JP. Adverse reactions to azathioprine mimicking gastroenteritis. *J Rheumatol*. 1987;14:1075.
26. Cox J, Daneshmend JK, Hawkey CJ, et al. Devastating diarrhoea caused by azathioprine: management difficulty in inflammatory bowel disease. *Gut*. 1988;29:686-688.

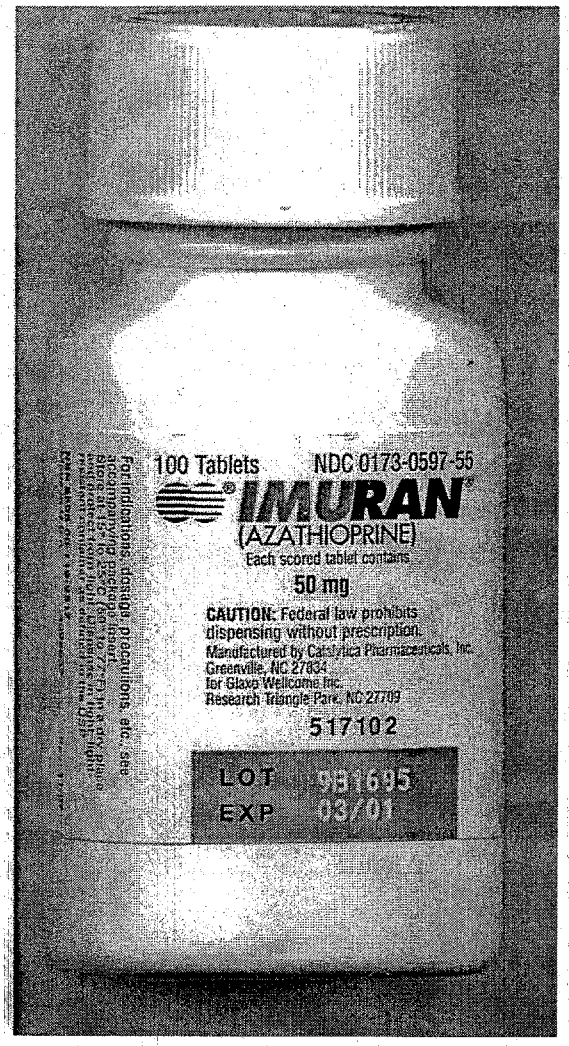
27. Bradley PP, Warden GD, Maxwell JG, et al. Neutropenia and thrombocytopenia in renal allograft recipients treated with trimethoprim-sulfamethoxazole. *Ann Int Med.* 1980;93:560-562.
28. Kirchertz EJ, Grone HJ, Rieger J, et al. Successful low dose captopril rechallenge following drug-induced leucopenia. *Lancet.* 1981;1:1362-1363.
29. Nelson D, Bugge C. Data on file, Glaxo Wellcome Inc.
30. Saarikoski S, Seppälä M. Immunosuppression during pregancy: transmission of azathioprine and its metabolites from the mother to the fetus. *Am J. Obstet Gynecol.* 1973;115:1100-1106.
31. Coulam CB, Moyer TP, Jiang NS, et al. Breast-feeding after renal transplantation. *Transplant Proc.* 1982;14:605-609.
32. Read AE, Wiesner RH, LaBrecque DR, et al. Hepatic venoocclusive disease associated with renal transplantation and azathioprine therapy. *Ann Intern Med.* 1986;104:651-655.
33. Katzka DA, Saul SH, Jorkasky D, et al. Azathioprine and hepatic venoocclusive disease in renal transplant patients. *Gastroenterology.* 1986;90:446-454.
34. Weitz H, Gokel JM, Loeschke K, et al. Veno-occlusive disease of the liver in patients receiving immunosuppressive therapy. *Virchows Arch A.* 1982;395:245-256.
35. Schusziarra V, Ziekursch V, Schlamp R, et al. Pharmacokinetics of azathioprine under haemodialysis. *Int J Clin Pharacol Biopharm.* 1976;14:298-302.
36. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, . Washington DC 20402.
37. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. *JAMA,* 1985;253(11):1590-1592.
38. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciencies, 179 Longwood Avenue, Boston, Massachusetts 02115.
39. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia,* 1983; 1:426-428.
40. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians,* 1983; (Sept/Oct) 258-263.
41. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm,* 1990; 47:1033-1049.
42. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm,* 1986; 43:1193-1204.

Manufactured by:
aaiPharma Inc.
Wilmington, NC 28405

August 2001

Approved Labeling for Listed Drug

This section contains a copy of the container label and package insert for the reference listed drug, IMURAN (azathioprine) Tablets. To the best of our knowledge, the package insert is the current prescribing information at the time of filing this petition.



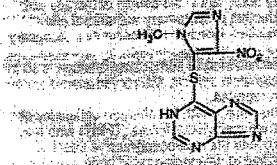
PRODUCT INFORMATION
4098641
517101

IMURAN® (azathioprine)
50-mg Scored Tablets
100 mg (as the sodium salt)
for I.V. injection, equivalent to 100 mg azathioprine sterile lyophilized material.

WARNING: Chronic immunosuppression with this purine antimetabolite increases *risk of neoplasia* in humans. Physicians using this drug should be very familiar with this risk as well as with the mutagenic potential to both men and women and with possible hematologic toxicities. See WARNINGS.

DESCRIPTION: IMURAN (azathioprine), an immunosuppressive antimetabolite, is available in tablet form for oral administration and 100-mg vials for intravenous injection. Each scored tablet contains 50 mg azathioprine and the inactive ingredients lactose, magnesium stearate, potato starch, povidone, and stearic acid. Each 100-mg vial contains azathioprine, as the sodium salt, equivalent to 100 mg azathioprine sterile lyophilized material and sodium hydroxide to adjust pH.

Azathioprine is chemically 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-1*H*-purine. The structural formula of azathioprine is:



It is an imidazolyl derivative of 6-mercaptopurine (PURINETHOL®) and many of its biological effects are similar to those of the parent compound.

Azathioprine is insoluble in water, but may be dissolved with addition of one molar equivalent of alkali. The sodium salt of azathioprine is sufficiently soluble to make a 10 mg/mL water solution which is stable for 24 hours at 59° to 77°F (15° to 25°C). Azathioprine is stable in solution at neutral or acid pH but hydrolysis to mercaptopurine occurs in excess sodium hydroxide (0.1N), especially on warming. Conversion to mercaptopurine also occurs in the presence of sulfhydryl compounds such as cysteine, glutathione, and hydrogen sulfide.

cysteine, glutathione, and hydrogen sulfide.

CLINICAL PHARMACOLOGY:

Metabolism: Azathioprine is well absorbed following oral administration. Maximum serum radioactivity occurs at 1 to 2 hours after oral ^{35}S-azathioprine and decays with a half-life of 5 hours. This is not an estimate of the half-life of azathioprine itself, but is the decay rate for all ^{35}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 8 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 (ZYLOPRIM®) is the basis for the azathioprine dosage reduction required in these patients (see PRECAUTIONS, 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.

Homograft Survival:[1-4] Summary information from transplant centers and registries indicates relatively universal use of IMURAN with or without other immunosuppressive agents.[1-4] 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 autoimmune disease. For example, the severity of adjuvant arthritis is reduced by azathioprine.

The mechanisms whereby azathioprine affects autoimmune 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.

INDICATIONS AND USAGE: IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. It is also indicated for the management of severe, active rheumatoid arthritis unresponsive to rest, aspirin, or other nonsteroidal anti-inflammatory drugs, or to agents in the class of which gold is an example.

Renal Homotransplantation: IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. Experience with over 16,000 transplants shows a 5-year patient survival of 35% to 55%, but this is dependent on donor, match for HLA antigens, anti-donor or anti-B-cell alloantigen antibody, and other variables. The effect of IMURAN on these variables has not been tested in controlled trials.

Rheumatoid Arthritis:[6,7] IMURAN is indicated only in adult patients meeting criteria for classic or definite rheumatoid arthritis as specified by the American Rheumatism Association.[8] IMURAN should be restricted to patients with severe, active and erosive disease not responsive to conventional management including rest, aspirin, or other nonsteroidal drugs, or to agents in the class of which gold is an example. Rest, physiotherapy, and salicylates should be continued while IMURAN is given, but it may be possible to reduce the dose of corticosteroids in patients on IMURAN. The combined use of IMURAN with gold, antimalarials, or penicillamine has not been studied for either added benefit or unexpected adverse effects. The use of IMURAN with these agents cannot be recommended.

CONTRAINDICATIONS: IMURAN should not be given to patients who have shown hypersensitivity to the drug.

IMURAN should not be used for treating rheumatoid arthritis in pregnant women.

Patients with rheumatoid arthritis previously treated with alkylating agents (cyclophosphamide, chlorambucil, melphalan, or others) may have a prohibitive risk of neoplasia if treated with IMURAN.[9]

WARNINGS: Severe *leukopenia and/or thrombocytopenia* may occur in patients on IMURAN. 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 IMURAN 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.

Serious infections are a constant hazard for patients receiving chronic immunosuppression, especially for homograft recipients. 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.

IMURAN is mutagenic in animals and humans, carcinogenic in animals, and may increase the patient's *risk of neoplasia*. Renal transplant patients are known to have an increased risk of malignancy, predominantly skin cancer and reticulum cell or lymphomatous tumors.[12] The risk of post-transplant lymphomas may be increased in patients who receive aggressive treatment with immunosuppressive drugs.[13] 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 post-transplant lymphomas. However, transplant 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. Information is available on the spontaneous neoplasia risk in rheumatoid arthritis,[12,13] and on neoplasia following immunosuppressive therapy of other autoimmune diseases.[11,12] *It has not been possible to* define the precise risk of neoplasia due to IMURAN.[12] The data suggest the risk may be elevated in patients with rheumatoid arthritis, though lower than for renal transplant patients.[11,12] 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 IMURAN can be found under ADVERSE REACTIONS.

IMURAN 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;[14] a reduced percentage of fertile matings occurred when animals received 5 mg/kg.[15]

Pregnancy: Pregnancy Category D. IMURAN can cause fetal harm when administered to a pregnant woman. IMURAN should not be given during pregnancy without careful weighing of risk versus benefit. Whenever possible, use of IMURAN in pregnant patients should be avoided. This drug should not be used for treating rheumatoid arthritis in pregnant women.[16]

IMURAN 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.[15]

Limited immunologic and other abnormalities have occurred in a few infants born of renal allograft recipients on IMURAN. In a detailed case report,[16] 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. DeWitte et al[17] reported pancytopenia and severe immune deficiency *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. Williamson and Karp[18] described an infant born with preaxial polydactyly whose mother received azathioprine 200 mg daily and prednisone 20 mg every other day during pregnancy. Tallent et al[19] described an infant with a large myelomeningocoele in the upper lumbar region, bilateral dislocated hips, and bilateral talipes equinovarus. The father was on long-term azathioprine therapy.

Benefit versus risk must be weighed carefully before use of IMURAN in patients of reproductive potential. There are no adequate and well-controlled studies in pregnant women. 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.

PRECAUTIONS:

General: A gastrointestinal hypersensitivity reaction characterized by severe nausea and vomiting has been reported.[23,25,26] These symptoms may also be accompanied by diarrhea, rash, fever, malaise, myalgias, elevations in liver enzymes, and occasionally, hypotension. Symptoms of gastrointestinal toxicity most often develop within the first several weeks of therapy with IMURAN and are reversible upon discontinuation of the drug. The reaction can recur within hours after rechallenge with a single dose of IMURAN.

Information for Patients: Patients being started on IMURAN should be informed of the necessity of periodic blood counts while they are receiving the drug and should be encouraged to report any unusual bleeding or bruising to their physician. They should be informed of the danger of infection while receiving IMURAN and asked to report signs and symptoms of infection to their physician. Careful dosage instructions should be given to the patient, especially when IMURAN is being administered in the presence of impaired renal function or concomitantly with allopurinol (see Drug Interactions subsection and DOSAGE AND ADMINISTRATION). Patients should be advised of the potential risks of the use of IMURAN during pregnancy and during the nursing period. The increased risk of neoplasia following therapy with IMURAN should be explained to the patient.

Laboratory Tests: See WARNINGS and ADVERSE REACTIONS sections.

Drug Interactions: ***Use with Allopurinol:*** The principal pathway for detoxification of IMURAN is inhibited by allopurinol. Patients receiving IMURAN and allopurinol concomitantly should have a dose reduction of IMURAN, to approximately ⅓ to ¼ the usual dose.

Use with Other Agents Affecting Myelopoesis: Drugs which may affect leukocyte production, including co-trimoxazole, may lead to exaggerated leukopenia, especially in renal transplant recipients.[27]

Use with 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.[28]

Use with Warfarin: IMURAN may inhibit the anticoagulant effect of warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS section.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category D. See WARNINGS section.

Nursing Mothers: The use of IMURAN in nursing mothers is not recommended. Azathioprine or its metabolites are transferred at low levels, both transplacentally and in breast milk.[29,30,31] Because of the potential for tumorigenicity shown for azathioprine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and efficacy of azathioprine in pediatric patients have not been established.

ADVERSE REACTIONS: The principal and potentially serious toxic effects of IMURAN are hematologic and gastrointestinal. The risks of secondary infection and neoplasia are also significant (see WARNINGS). The frequency and severity of adverse reactions depend on the dose and duration of IMURAN 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

IMURAN® (azathioprine)

higher than that in studies employing IMURAN for rheumatoid arthritis. The relative incidences in clinical studies are summarized below:

Toxicity	Renal Homograft	Rheumatoid Arthritis
Leukopenia (any degree)	>50%	28%
<2,500 cells/mm³	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.[12] In one completed study, the rate of lymphoproliferative disease in RA patients receiving higher than recommended doses of azathioprine (5 mg/kg per day) was 1.8 cases per 1,000 patient-years of follow-up, compared with 0.8 cases per 1,000 patient-years of follow-up in those not receiving azathioprine.[13] 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 are dose-dependent and may occur late in the course of therapy with IMURAN. Dose reduction or temporary withdrawal allows reversal of these toxicities. Infection may occur as a secondary manifestation of bone marrow suppression or leukopenia; but the incidence of infection in renal homotransplantation is 30 to 60 times that in rheumatoid arthritis. Macrocytic anemia and/or bleeding have been reported.

There are rare 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 suppression following the initiation of treatment with IMURAN.

Gastrointestinal: Nausea and vomiting may occur within the first few months of therapy with IMURAN, and occurred in approximately 12% of 676 rheumatoid arthritis patients. The frequency of gastric disturbance often can 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, and myalgias (see PRECAUTIONS). Vomiting with abdominal pain may occur rarely with a hypersensitivity pancreatitis. Hepatotoxicity manifest by elevation of serum alkaline phosphatase, bilirubin, and/or serum transaminases is known to occur following azathioprine use, primarily in allograft recipients. Hepatotoxicity has been uncommon (less than 1%) in rheumatoid arthritis patients. Hepatotoxicity following transplantation most often occurs within 6 months of transplantation and is generally reversible after interruption of IMURAN. A rare, but life-threatening hepatic veno-occlusive disease associated with chronic administration of azathioprine has been described in transplant patients and in one patient receiving IMURAN for panuveitis.[22,23,24] Periodic measurement of serum transaminases, alkaline phosphatase, and bilirubin is indicated for early detection of hepatotoxicity. If hepatic veno-occlusive disease is clinically suspected, IMURAN should be permanently withdrawn.

Others: 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.

OVERDOSAGE: The oral LD_{50}s for single doses of IMURAN in mice and rats are 2,500 mg/kg and 400 mg/kg, respectively. Very large doses of this antimetabolite may lead to marrow hypoplasia, bleeding, infection, and death. About 30% of IMURAN is bound to serum proteins, but approximately 45% is removed during an 8-hour hemodialysis.[25] A single case has been reported of a renal transplant patient who ingested a single dose of 7,500 mg IMURAN. 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.

DOSAGE AND ADMINISTRATION:

Renal Homotransplantation: The dose of IMURAN 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. IMURAN is usually given as a single daily dose on the day of, and in a minority of cases 1 to 3 days before, transplantation. IMURAN is often initiated with the intravenous administration of the sodium salt, with subsequent use of tablets (at the same dose level) after the postoperative 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 IMURAN 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: IMURAN 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 6 to 8 weeks and thereafter by steps at 4-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 per day. Therapeutic response occurs after several weeks of treatment, usually 6 to 8; an adequate trial should be a minimum of 12 weeks. Patients not improved after 12 weeks can be considered refractory. IMURAN 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 decrementally with changes of 0.5 mg/kg or approximately 25 mg daily every 4 weeks while other therapy is kept constant. The optimum duration of maintenance IMURAN has not been determined. IMURAN can be discontinued abruptly, but delayed effects are possible.

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

Parenteral Administration: Add 10 mL of Sterile Water for Injection, and swirl until a clear solution results. This solution, equivalent to 100 mg azathioprine, is for intravenous use only; it has a pH of approximately 9.6, and it should be used within 24 hours. Further dilution into sterile saline or dextrose is usually made for infusion; the final volume depends on time for the infusion, usually 30 to 60 minutes, but as short as 5 minutes and as long as 8 hours for the daily dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Procedures for proper handling and disposal of this immunosuppressive antimetabolite drug should be considered. Several guidelines on this subject have been published.[5-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED: 50 mg overlapping circle-shaped, yellow to off-white, scored tablets imprinted with "IMURAN" and "50" on each tablet, bottle of 100 (NDC 0173-0597-55).

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

20-mL vial, each containing the equivalent of 100 mg azathioprine (as the sodium salt) (NDC 0173-0598-71).

Store at 15° to 25°C (59° to 77°F) and protect from light.

The sterile, lyophilized sodium salt is yellow, and should be dissolved in Sterile Water for Injection (see DOSAGE AND ADMINISTRATION: Parenteral Administration).

REFERENCES:

1. Elion GB, Hitchings GH. Azathioprine. In: Sartorelli AC, Johns DG, eds. *Antineoplastic and Immunosuppressive Agents Pt II*. New York, NY: Springer Verlag; 1975:chap 48.
2. McIntosh J, Hansen P, Ziegler J, et al. Defective immune and phagocytic functions in uraemia and renal transplantation. *Int Arch Allergy Appl Immunol*. 1976;15:544-549.
3. Renal Transplant Registry Advisory Committee. The 12th report of the human Renal Transplant Registry. *JAMA*. 1975;233:787-796.
4. McGeown M. Immunosuppression for kidney transplantation. *Lancet*. 1973;2:310-312.
5. Simmons RL, Thompson EJ, Yunis EJ, et al. 115 patients with first cadaver kidney transplants followed two to seven and a half years: a multifactorial analysis. *Am J Med*. 1977; 62:234-242.
6. Fye K, Talal N. Cytotoxic drugs in the treatment of rheumatoid arthritis. *Ration Drug Ther*. 1975;9:1-5.
7. Davis JD, Muss HB, Turner RA. Cytotoxic agents in the treatment of rheumatoid arthritis. *South Med J*. 1978;71: 58-64.
8. McEwen C. The diagnosis and differential diagnosis of rheumatoid arthritis. In: Hollander JL, ed. *Arthritis and Allied Conditions: A Textbook of Rheumatology*. 8th ed. Philadelphia, PA: Lea and Febiger; 1972:403-418.
9. Hoover R, Fraumeni JF. Drug-induced cancer. *Cancer*. 1981;47:1071-1080.
10. Hoover R, Fraumeni JF Jr. Risk of cancer in renal transplant recipients. *Lancet*. 1973;2:55-57.
11. Wilkinson AH, Smith JL, Hunsicker LG, et al. Increased frequency of post-transplant lymphomas in patients treated with cyclosporine, azathioprine, and prednisone. *Transplantation*. 1989;47:293-295.
12. Prior P, Symmons DPM, Hawkins CF, et al. Cancer morbidity in rheumatoid arthritis. *Ann Rheum Dis*. 1984; 43:128-131.
13. Silman AJ, Petrie J, Hazelman B, et al. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. *Ann Rheum Dis*. 1988;47:988-992.
14. Louie S, Schwartz RS. Immunodeficiency and pathogenesis of lymphoma and leukemia. *Semin Hematol*. 1976;13: 117-138.
15. Wang KK, Czaja AJ, Beaver SJ, et al. Extra hepatic malignancy following long-term immunosuppressive therapy of severe hepatitis B surface antigen-negative chronic active hepatitis. *Hepatology*. 1989;10:39-43.
16. Sieber SM, Adamson RH. Toxicity of antineoplastic agents in man: chromosomal aberrations, antifertility effects, congenital malformations, and carcinogenic potential. In: Klein G, Weinhouse S, eds. *Advances in Cancer Research*. New York, NY: Academic Press; 1975;22:57-155.
17. Clark JM. The mutagenicity of azathioprine in mice, *Drosophila Melanogaster and Neurospora Crassa*. *Mut Res*. 1975;28:87-99.
18. Data on file, Glaxo Wellcome Inc.
19. Tagatz GE, Simmons RL. Pregnancy after renal transplantation. *Ann Intern Med*. 1975;82:113-114. Editorial Notes.
20. Coté CJ, Meuwissen HJ, Pickering RJ. Effects on the neonate of prednisone and azathioprine administered to the mother during pregnancy. *J Pediatr*. 1974;85: 324-328.
21. DeWitte DB, Buick MK, Stephen EC, et al. Neonatal pancytopenia and severe combined immunodeficiency associated with antenatal administration of azathioprine and prednisone. *J Pediatr*. 1984;105:625-628.
22. Williamson RA, Karp LE. Azathioprine teratogenicity: review of the literature and case report. *Obstet Gynecol*. 1981;58:247-250.
23. Tallent MB, Simmons RL, Najarian JS. Birth defects in child of male recipient of kidney transplant. *JAMA*. 1970;211:1854-1855.
24. Assini JF, Hamilton R, Strosberg JM. Adverse reactions to azathioprine mimicking gastroenteritis. *J Rheumatol*. 1986;13:1117-1118.

25. Cochrane D, Adamson AR, Halsey JP. Adverse reactions to azathioprine mimicking gastroenteritis. *J Rheumatol.* 1987;14:1075.
26. Cox J, Daneshmend JK, Hawkey CJ, et al. Devastating diarrhoea caused by azathioprine: management difficulty in inflammatory bowel disease. *Gut.* 1988;29:686-688.
27. Bradley PP, Warden GD, Maxwell JG, et al. Neutropenia and thrombocytopenia in renal allograft recipients treated with trimethoprim-Sulfamethoxazole. *Ann Int Med.* 1980; 93:560-562.
28. Kirchertz EJ, Grone HJ, Rieger J, et al. Successful low-dose captopril rechallenge following drug-induced leucopenia. *Lancet.* 1981;1:1362-1363.
29. Nelson D, Bugge C. Data on file, Glaxo Wellcome Inc.
30. Saarikoski S, Seppälä M. Immunosuppression during pregnancy: transmission of azathioprine and its metabolites from the mother to the fetus. *Am J Obstet Gynecol.* 1973;115:1100-1106.
31. Coulam CB, Moyer TP, Jiang NS, et al. Breast-feeding after renal transplantation. *Transplant Proc.* 1982;14: 605-609.
32. Read AE, Wiesner RH, LaBrecque DR, et al. Hepatic veno-occlusive disease associated with renal transplantation and azathioprine therapy. *Ann Intern Med.* 1986;104:651-655.
33. Katzka DA, Saul SH, Jorkasky D, et al. Azathioprine and hepatic venoocclusive disease in renal transplant patients. *Gastroenterology.* 1986;90:446-454.
34. Weitz H, Gokel JM, Loeschke K, et al. Veno-occlusive disease of the liver in patients receiving immunosuppressive therapy. *Virchows Arch A.* 1982;395:245-256.
35. Schuszlarra V, Ziekursch V, Schlamp R, et al. Pharmacokinetics of azathioprine under haemodialysis. *Int J Clin Pharmacol Biopharm.* 1976;14:298-302.
36. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC: Division of Safety, National Institutes of Health; 1983. US Dept of Health and Human Services, Public Health Service publication NIH 83-2621.
37. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA.* 1985;253:1590-1591.
38. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. 1987. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
39. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia.* 1983;1:426-428.
40. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. *CA-A Cancer J for Clin.* 1983;33:258-263.
41. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm.* 1990;47:1033-1049.
42. Yodaiken RE, Bennett D. OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. *Am J Hosp Pharm.* 1986;43:1193-1204.

GlaxoWellcome

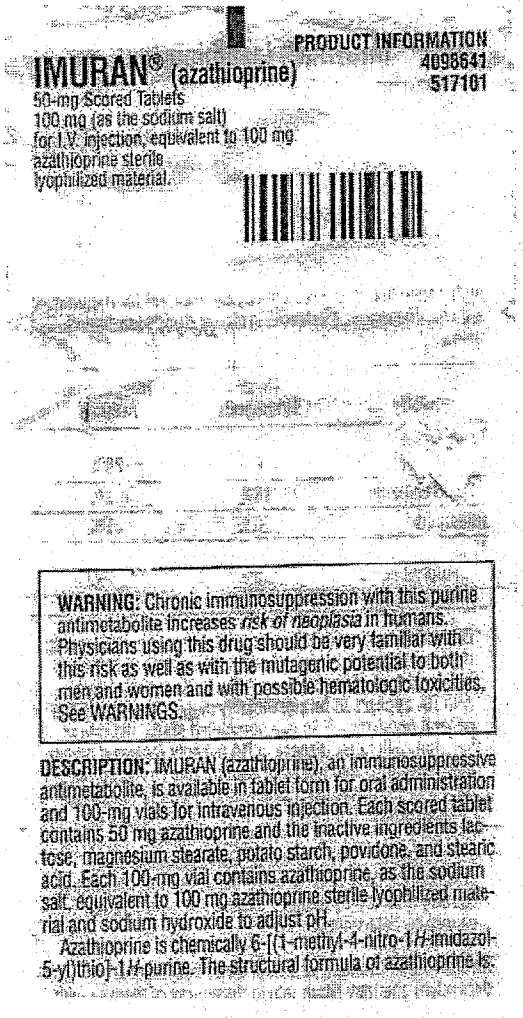
Manufactured by
Catalytica Pharmaceuticals, Inc.
Greenville, NC 27834
for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

November 1997 RL-500 517101 4098641

Highlights of Labeling Differences

To facilitate the review of the package insert information a side-by-side comparison of areas where there are differences between Imuran and the proposed products are included here.

Innovator PI



PRODUCT INFORMATION
4098641
517101

IMURAN® (azathioprine)
50-mg Scored Tablets
100 mg (as the sodium salt)
for I.V. injection, equivalent to 100 mg
azathioprine sterile
lyophilized material.

WARNING: Chronic immunosuppression with this purine antimetabolite increases *risk of neoplasia* in humans. Physicians using this drug should be very familiar with this risk as well as with the mutagenic potential to both men and women and with possible hematologic toxicities. See WARNINGS.

DESCRIPTION: IMURAN (azathioprine), an immunosuppressive antimetabolite, is available in tablet form for oral administration and 100-mg vials for intravenous injection. Each scored tablet contains 50 mg azathioprine and the inactive ingredients lactose, magnesium stearate, potato starch, povidone, and stearic acid. Each 100-mg vial contains azathioprine, as the sodium salt, equivalent to 100 mg azathioprine sterile lyophilized material and sodium hydroxide to adjust pH.

Azathioprine is chemically 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-1*H*-purine. The structural formula of azathioprine is:

Proposed PI
(differences highlighted)

AZATHIOPRINE TABLETS, USP
75 mg Scored Tablets
100 mg Scored Tablets

WARNING: Chronic immunosuppression with this purine antimetabolite increases *risk of neoplasia* in humans. Physicians using this drug should be very familiar with this risk as well as with the mutagenic potential to both men and women and with possible hematologic toxicities. See WARNINGS.

DESCRIPTION: Azathioprine, an immunosuppressive antimetabolite, is available in tablet form for oral administration. Each scored tablet contains 50 mg azathioprine and the inactive ingredients lactose monohydrate, pregelatinized starch, povidone, corn starch, magnesium stearate, and stearic acid.

Azathioprine is chemically 1*H*-purine, 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-. The structural formula of azathioprine is:

HOW SUPPLIED: 50 mg overlapping circle-shaped, yellow to off-white, scored tablets imprinted with "IMURAN" and "50" on each tablet; bottle of 100 (NDC 0173-0597-55).
Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

20-mL vial, each containing the equivalent of 100 mg azathioprine (as the sodium salt) (NDC 0173-0598-71).
Store at 15° to 25°C (59° to 77°F) and protect from light.
The sterile, lyophilized sodium salt is yellow, and should be dissolved in Sterile Water for Injection (see DOSAGE AND ADMINISTRATION: Parenteral Administration).

HOW SUPPLIED:

Azathioprine Tablets, USP, 75 mg are triangular-shaped, yellow, scored tablets:

Bottles of 15	(NDC XXXXX-XXX-XX)
Bottles of 100	(NDC XXXXX-XXX-XX)
Bottles of 1000	(NDC XXXXX-XXX-XX)

Azathioprine Tablets, USP, 100 mg are diamond-shaped, yellow, scored tablets:

Bottles of 15	(NDC XXXXX-XXX-XX)
Bottles of 100	(NDC XXXXX-XXX-XX)
Bottles of 1000	(NDC XXXXX-XXX-XX)

Rx only.

Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.

Comparison of Therapeutic Effect

21 CFR 314.93(d)(2) requires that information be included to show that the drug product can be expected to have the same therapeutic effect as the reference listed drug when administered to patients for each condition of use in the reference listed drug's labeling. The proposed drug products have the same active ingredient and similar formulation to the reference listed drug. The therapeutic effect can therefore be expected to be the same if they are shown to be bioequivalent.

A study was performed to determine the bioequivalence of azathioprine formulations after administration of single doses to normal healthy males under fasting conditions. The data were to be evaluated statistically to determine if the products meet the criteria for bioequivalence.

Regarding safety and tolerability, the treatments were reasonably well tolerated.

The 90% confidence intervals for the geometric mean test-to-reference area and peak concentration ratios, for both azathioprine and 6-mercaptopurine, were within the bioequivalence interval 0.80-1.25. aaiPharma's 100 mg azathioprine tablets are bioequivalent to 50 mg Imuran® tablets when each is administered as a single 300 mg dose after an overnight fast.

A summary of the study is included for consideration immediately following this page.

1) Investigator and Study Site

Title of Study:	An Open-Label Randomized Single-Dose Bioequivalence Study Of 100 mg Azathioprine Tablets And Imuran® 50 mg Tablets Under Fasting Conditions
Sponsor:	aaiResearch, Inc. 2320 Scientific Park Drive Wilmington, NC 28405
Clinical Facility:	AAI Clinic 6101 Quadrangle Drive Chapel Hill, NC 27514 919-493-9404
Principal Investigator:	Ralph Scallion, EE, MD AAI 6101 Quadrangle Drive Chapel Hill, NC 27514 919-493-9404
Clinical Study Period 1:	1/13/01
Clinical Study Period 2:	1/20/01
AAI Study Number:	AAI-US-89

2) Objective

The purpose of this study was to determine the bioequivalence of azathioprine formulations after administration of single doses to normal healthy males under fasting conditions. These data were to be evaluated statistically to determine if the products meet bioequivalence criteria.

3) Subjects

Before entering the study, all volunteers had to undergo a physical examination, including clinical laboratory screening and electrocardiogram, to verify inclusion criteria. Prior to study start, all volunteers were informed about the aim, design, risks and preparations of the study in writing, and were offered the opportunity to ask any questions. All subjects declared their consent and the voluntary nature of participation by signing the informed consent form. A total of 48 non-smoking subjects were included in this study, of which 46 finished the study according to the protocol. The mean age was 27.1 years with a range of 18 to 45. The mean height was 69.8 inches and the mean weight was 170.7 pounds. Detailed demographic data are listed in **Table 1: Subject Characteristics** located in Section III.

4) Study Design

The study was performed as a single-dose two-way crossover bioequivalence study with an adequate washout period (7 days) between the two phases of the study and with an equal number of subjects randomly assigned to receive the study test (Treatment A) and reference (Treatment B).

The study conduct was consistent with Good Clinical Practice (GCP) and regulatory requirements of the U.S. Food and Drug Administration. Venous blood samples were collected over a 8-hour period of time post drug administration. Medical care of the volunteers was assured by the presence of a physician for at least 4 hours post dose and the physician was on-call throughout the blood-sampling period. Professional medical personnel were on site during the entire study confinement period. Subjects were confined in the clinical facility for at least 10 hours before dosing and for 8 hours after dosing. Subjects were discharged after the 8-hour blood sample. Standardized meals were served and no caffeine, alcohol, or grapefruit-containing foods or beverages were allowed to be consumed 24 hours before dosing or throughout study confinement.

5) Ethics

Essex Institutional Review Board, Inc. of Lebanon, New Jersey, USA, approved the study protocol on 11/13/00 and approved the informed consent form on 11/20/00.

6) Study Preparations and Treatments

Clinical supplies were received at the AAI Clinic on 1/12/01.

Test Preparation:	Treatment A
Name:	Azathioprine
Supplier:	aaiResearch, Inc.
Dosage Form/Strength:	100 mg tablet
Appearance:	yellow-colored, diamond-shaped, biconvex, scored tablets with "N" on one side and "100 mg" on the other side
Batch/Lot no.:	00322D
Exp Date:	To Be Determined

The Clinic received from aaiResearch, Inc. 500 tablets of test product, Azathioprine. For Period 1, 72 tablets were dispensed. For Period 2, 69 tablets were dispensed. The remaining 359 tablets are retained at the Clinic.

Reference Preparation:	Treatment B
Name:	Imuran®
Supplier:	Faro Pharmaceuticals
Dosage Form/Strength:	50 mg tablet
Appearance:	yellow-colored, overlapping circle-shaped, scored tablets with "Imuran" and "50" on the scored side and raised striations on the other side of the tablet
Batch/Lot no.:	9K2238
Expiration Date:	02/02

The Clinic received from aaiResearch, Inc. 500 tablets of reference product, Imuran®. For Period 1, 144 tablets were dispensed. For Period 2, 138 tablets were dispensed. The remaining 218 tablets are retained at the Clinic.

Final drug accountability was performed on 01/29/01 and all tablets have been reconciled. Remaining tablets will be kept as retention samples in accordance with 21 CFR 320.38 and 320.63.

7) Mode of Administration

All subjects fasted for at least 10 hours before dosing. All subjects remained fasted for 4 hours post drug administration with the exception of water. From 1 hour before, through 1 hour after drug administration, only the water supplied with the drug was permitted. After this time, water was permitted ad lib. Four hours after drug administration, a standardized boxed lunch was served. The menu used during the study is included in **Table 6: Menu** located in Section III.

A single, 300-mg dose of the study drugs was administered per randomization code together with 240 ml of tepid water and a mouth check was performed. **Table 2: Treatment Schedule** can be found in Section III. The time of drug administration was defined as study time 0 in each period. All further study times indicated refer to this time. **Table 3: Study Schedule** includes details of activities during the confinement period.

8) Adverse Events

No serious adverse events were reported during the entire course of the study. A total of 23 adverse events were reported by 12 subjects, including urinary discoloration (5), headache(4), nausea(1), diarrhea (1), fever(2), muscle soreness(1), sore throat(1), cold sore(1), tight joint(1), rectal bleeding(1), tongue coating(1), hematoma, left anticubital(1), runny nose(1), fatigue(1) and productive cough(1). A summary of Adverse Events observed during the study is summarized in Section III labeled **Table 4: Summary of Adverse Events**

9) Blood Sampling

Blood samples (1 x 10 ml) were drawn from an antecubital or forearm vein into EDTA vacuum tubes and were obtained according to the following table:

Day	Procedure	Collection	Time (relative)	Hours
- 1	Confinement		1900	
	Snack		2100	
	Fasting Begins		2200	-10
1	Vital Signs		0600 – 0730	
		1	0730	Pre Dose
	Dosing		0800	0
		2	0815	0.25
		3	0830	0.5
		4	0845	0.75
		5	0900	1
		6	0920	1.33
		7	0940	1.67
		8	1000	2
		9	1030	2.5
		10	1100	3
	Lunch (after sample)	11	1200	4
		12	1400	6
	Discharge (after sample)	13	1600	8
	Safety Labs (1-2 weeks later)			

Approximately 260 mL of blood was needed for the pharmacokinetic samples. Blood samples were centrifuged until separation of red cells from plasma occurred. Plasma was transferred split into two polypropylene tubes and placed into a freezer within one hour of sample collection. Plasma samples were stored at a temperature at or below -20° ± 5°C until transferred to the analytical laboratory for analysis.

10) Deviations from Study Protocol

The study was performed in accordance with the protocol for all essential parts except as outlined below. None of the subjects violated inclusion/exclusion criteria. Due to an error in processing, there are no plasma samples for Subject #16, Period 2 (01/20/01), 2.5 hours post dose.

There were 5 significant deviations to the blood draw schedule, as noted on Section III, **Table 5: Significant Deviations to Blood Draw Schedule.** These were reported to the study Biostatistician.

On several occasions, the sample storage freezer temperature rose beyond -15° C for a short period of time. These deviations were caused by frequent placement of samples into the freezer or by sample preparation for shipment. None of the frozen samples thawed during these times.

11) Sample Analyses

Samples were analyzed for the content of azathioprine and 6-mercaptopurine by HPLC/UV assay. Analyses were begun on February 9, 2001 and were completed on March 24, 2001.

Calibration standards and controls were prepared by spiking human, interference-free, plasma with drug reference materials. Calibration standards were prepared to contain azathioprine concentrations of 2.50, 5.00, 10.0, 25.0, 50.0, 75.0, and 100 ng/ml, and 6-mercaptopurine concentrations of 5.00, 10.0, 20.0, 50.0, 100, 150, and 200 ng/ml. Quality control samples were prepared to contain azathioprine concentrations of 12.0, 60.0, and 180 ng/ml, and 6-mercaptopurine concentrations of 6.00, 30.0, and 90.0 ng/ml.

The assay for azathioprine involved liquid-liquid extraction of the drug and its internal standard, pentoxifylline, with ethylacetate. The organic phase was removed and evaporated to dryness and then reconstituted with mobile phase. After a diethylether wash, an aliquot was injected onto an HPLC system equipped with a Zorbax SB CN, 5-µ column. The system was run as a gradient under isocratic conditions with peak detection and quantification by UV absorbance at 278 nm.

The assay for 6-mercaptopurine involved washing of the plasma sample with ethylacetate. The drug and its internal standard, 2-amino-6-mercaptopurine, were then precipitated with $Al(ClO_4)_3$. After mixing the precipitate with $HClO_4$ and $N_2S_2O_4$, and centrifuging, an aliquot of the clear aqueous layer was injected onto the HPLC system. Chromatographic separation was on a Lichrosphere 100, RP-8, 5-µ column using a gradient under isocratic conditions. Peak detection and quantification were based on UV absorbance at 353/323 nm.

Samples were analyzed in runs that consisted of a control sample, a plasma blank, a set of calibration standards, a duplicate set of quality control samples (3 concentrations in duplicate) and the samples from two subjects, both periods.

The calibrator peak height response ratios (analyte-to-internal) for azathioprine and 6-mercaptopurine were plotted as a function of concentration to obtain calibration response lines. A linear regression for each analyte was calculated by the method of weighted least-squares using the inverse of concentration (1/x) as a weighting factor.

A calculated concentration was determined for each calibrator standard from the corresponding calibration line. The azathioprine and 6-mercaptopurine concentrations in samples and controls were estimated from the calibration lines by use of the equation:

(Ratio – Intercept) / Slope.

The coefficient of variation for the calculated concentrations for the quality control samples for azathioprine ranged from 5.0% to 6.6%. The apparent bias (% deviation of the mean from known concentration) ranged from +1.5 to +1.9%. The coefficient of variation for the back-calculated concentrations of the azathioprine calibration standards ranged from 4.4% to 6.2 and the bias ranged from –2.2% to +1.7%. The lower limit of quantification of the azathioprine assay was established at 2.50 ng/ml. Any sample whose calculated concentration was below this limit was reported as less than this lower limit. The assay was linear over the azathioprine concentration range of 2.50 ng/ml to 100 ng/ml.

The coefficient of variation for the calculated concentrations for the quality control samples for 6-mercaptopurine ranged from 7.6% to 9.6%, with an apparent bias ranging from –5.9 to –4.4%. The coefficient of variation for the back-calculated 6-mercaptopurine concentrations for the calibration standards ranged from 2.8% to 7.5%, with bias ranging from –2.5% to +1.4%. The lower limit of quantification of the assay was established at 5.00 ng/ml 6-mercaptopurine. Any sample whose calculated concentration was below this limit was reported as less than this lower limit. The assay was linear over the 6-mercaptopurine concentration range of 5.00 ng/ml to 200 ng/ml.

12) Pharmacokinetic Procedures and Statistical Analyses

Pharmacokinetic Procedures

All the available data from the 46 subjects who completed the study were used in the pharmacokinetic analyses. All pharmacokinetic calculations were performed using SAS (PC version 6.12). Any sample concentration reported less than the assay limit of quantitation was set to zero for use in the pharmacokinetic and statistical analyses. Pharmacokinetic and statistical analyses were conducted on reported values. No concentration estimates were calculated for missing values.

Pharmacokinetic parameters (areas, times to peak and elimination rates) were calculated using the actual rather than the scheduled times of sample collection. Graphical presentations of individual subject results also used the exact times of sample collection. Graphical presentations of mean results used the scheduled times of sample collection.

Peak concentration (Cmax) was the observed maximum value during the collection period of 0 to 8 hours. The time to peak concentration (Tmax) was the time at which Cmax was observed (or first observed, if the peak value occurred at more than one time).

The apparent first-order elimination rate constant (Ke) was estimated as the negative value of the slope of the regression line for the terminal log-linear concentration-time values. A minimum of three terminal values was used to obtain an estimate. The values included in the regression analyses were determined by examination of the individual subject plots of natural logarithm of concentration against time. Whenever the terminal concentration-time values were not log-linear or the estimated rate would have been physiologically implausible (Ke<0.01), no elimination rate was estimated. Elimination half-life (T½) was estimated as $\log_e(2)/Ke$.

Area under the curve (AUC 0-t) to the last measured concentration (C_t) was calculated by the linear trapezoidal method. Area to infinite time (AUCinf) was calculated by extrapolating AUC 0-t, by the addition of the quantity: C_t / Ke. Area to infinity could only be calculated when an elimination rate constant had been estimated.

Statistical Analyses

Statistical analyses were performed using the General Linear Models (GLM) procedure of the SAS statistical program (PC version 6.12). The pharmacokinetic parameter estimates, as well as the concentrations at each scheduled sample time were evaluated by analysis of variance. Hypothesis testing for treatment effects in the analysis was conducted at α=0.05.

The statistical model contained main effects of sequence, subject nested within sequence, treatment, and period. F-ratios for testing main effects were constructed using the mean square error term for the effect as the numerator and the mean square error term from the ANOVA as the denominator. The F-ratio to test for sequence effects was constructed using the type III mean square term for sequence as the numerator and type III mean square for subjects nested within sequence as the denominator.

Power for the test-to-reference comparisons of the pharmacokinetic parameters was calculated as the probability ($\alpha = 0.05$) of detecting a difference equal to 20% of the reference mean (or detecting a ratio of 1.25 for log-transformed results). [Winer, BJ. *Statistical Principles in Experimental Design.* New York: McGraw-Hill Book Company (1962) 21-26.]

Confidence Intervals (90%) for the area and peak concentration comparisons were calculated by the t-test approach (2,1-sided) at $\alpha = 0.10$ overall, $\alpha = 0.05$ each side:

$$\text{Interval Lower Limit} = (X_T - X_R) - Se * t_{\alpha/2}$$
$$\text{Interval Upper Limit} = (X_T - X_R) + Se * t_{\alpha/2}$$

Where X_T, X_R are the test treatment and reference treatment least-squares means, respectively.

Se is the standard error of the estimated difference between means from the SAS estimate statement.

$t_{\alpha/2}$ is the critical value from the t-distribution with degrees of freedom that of the error term and $\alpha = 0.10$.

For log-transformed data the interval was calculated from the ANOVA results on the transformed values and then exponentiated to convert to the non-transformed scale:

$$\text{Interval Limit} = e^{(\text{log-transformed interval limit})}$$

The intervals were computed for the "true" mean treatment differences, expressed as a percent of the reference mean, and true geometric mean ratios (from logarithmic transformation).

13) Results

There were no serious adverse events observed or reported during the study.

Clinical Laboratory Results

Clinical laboratory parameters (clinical chemistry and hematology) were obtained at the end of the final period of subject confinement and 1-2 weeks after the final dose of study medication. No clinically significant laboratory abnormalities were observed.

Pharmacokinetic Results

Statistical analyses were performed on the results in order to compare AAI's 100 mg azathioprine tablets to 50 mg Imuran® tablets when each was administered as a single 300-mg dose after an overnight fast. Tables 1.1 and 1.2, which follow, summarize the results of the statistical analyses of the pharmacokinetic parameters. Comparisons of the azathioprine and 6-mercaptopurine levels at each sampling time are summarized in Tables 2.1 and 2.2, and the accompanying graphs.

14) Conclusions

Clinical

Regarding safety and tolerability, the treatments were reasonably well tolerated. The clinical portion of the study was completed per protocol with a total of 46 subjects completing both periods of the study.

Pharmacokinetic

The 90% confidence intervals for the geometric mean test-to-reference area and peak concentration ratios, for both azathioprine and 6-mercaptopurine, were within the bioequivalence interval 0.80-1.25. AAI's 100 mg azathioprine tablets are bioequivalent to 50 mg Imuran® tablets when each is administered as a single 300 mg dose after an overnight fast.

AZATHIOPRINE STUDY AAI-US-89

SUMMARY TABLES

Table 1.1: Summary of statistical comparisons of azathioprine results for AAI's 100 mg azathioprine tablets (Test) and 50 mg Imuran® tablets (Reference) when each was administered as a single 300 mg dose immediately after an overnight fast to 46 subjects.

Parameter	Least-Squares Means [1]		Ratio [2]	Power [3]	90% Confidence Interval [4]	
	Test	Reference			Lower	Upper
AUC 0-t (ng-hr/ml)	87.5	93.2	0.938	>0.99	0.885	0.992
AUCinf (ng-hr/ml)	100	105	0.955	0.97	0.869	1.040
Cmax (ng/ml)	53.2	53.5	0.995	0.99	0.917	1.072
Tmax (hour)	0.87	0.95	0.909	0.35	-	-
Ke (1/hour)	0.7997	0.6625	1.207	0.31	-	-
T½ (hour)	1.22	1.63	0.751	0.21	-	-
Log-Transformed:						
AUC 0-t (ng-hr/ml)	83.4	88.2	0.946	>0.99	0.895	1.000
AUCinf (ng-hr/ml)	94.2	100	0.942	>0.99	0.870	1.019
Cmax (ng/ml)	50.5	51.3	0.984	>0.99	0.912	1.062

1. Least-squares geometric means for log-transformed data.
2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean. None of the comparisons was detected as statistically significant by ANOVA (α=0.05).
3. Power to detect a difference of 20% of the Reference mean or a ratio of 1.25 (log-transformed results).
4. Confidence interval on the ratio.

AZATHIOPRINE STUDY AAI-US-89

SUMMARY TABLES

Table 1.2: Summary of statistical comparisons of 6-mercaptopurine results for AAI's 100 mg azathioprine tablets (Test) and 50 mg Imuran® tablets (Reference) when each was administered as a single 300 mg dose immediately after an overnight fast to 46 subjects.

Parameter	Least-Squares Means [1]		Ratio [2]	Power [3]	90% Confidence Interval [4]	
	Test	Reference			Lower	Upper
AUC 0-t (ng-hr/ml)	207	195	1.065	0.53	0.904	1.227
AUCinf (ng-hr/ml)	264	264	0.999	0.77	0.877	1.121
Cmax (ng/ml)	78.8	80.3	0.982	0.67	0.845	1.118
Tmax (hour)	1.49	1.59	0.939	0.55	-	-
Ke (1/hour)	0.4941	0.4687	1.054	0.56	-	-
T½ (hour)	1.72	1.77	0.972	0.75	-	-
Log-Transformed:						
AUC 0-t (ng-hr/ml)	158	164	0.965	0.82	0.849	1.097
AUCinf (ng-hr/ml)	224	228	0.983	0.90	0.878	1.100
Cmax (ng/ml)	66.4	67.6	0.981	0.79	0.859	1.121

1. Least-squares geometric means for log-transformed data.
2. Ratio calculated as Test least-squares mean divided by the Reference least-squares mean. None of the comparisons was detected as statistically significant by ANOVA (α=0.05).
3. Power to detect a difference of 20% of the Reference mean or a ratio of 1.25 (log-transformed results).
4. Confidence interval on the ratio.

AZATHIOPRINE STUDY AAI-US-89

SUMMARY TABLES

Table 2.1: Summary of plasma azathioprine concentrations at each sampling time comparing AAI's 100 mg azathioprine tablets (Test) and 50 mg Imuran® tablets (Reference) when each was administered as a single 300 mg dose immediately after an overnight fast to 46 subjects.

Collection (Hour)	Least-Squares Means (ng/ml) Test	Reference	Significance * ($p<0.05$)
0.000	0.000	0.000	None
0.250	20.3	22.8	None
0.500	43.6	41.4	None
0.750	36.6	35.7	None
1.00	28.3	32.4	None
1.33	27.5	30.7	None
1.67	25.3	28.5	None
2.00	21.6	26.3	0.0343
2.50	17.2	18.3	None
3.00	12.1	12.5	None
4.00	6.96	6.41	None
6.00	1.55	1.61	None
8.00	0.848	0.846	None

* Results of the statistical evaluation by ANOVA ($\alpha=0.05$) for the hypothesis of equal treatment effects. None indicates that no difference was detected between treatment means ($p>0.05$) at the sampling time evaluated.

SUMMARY TABLES

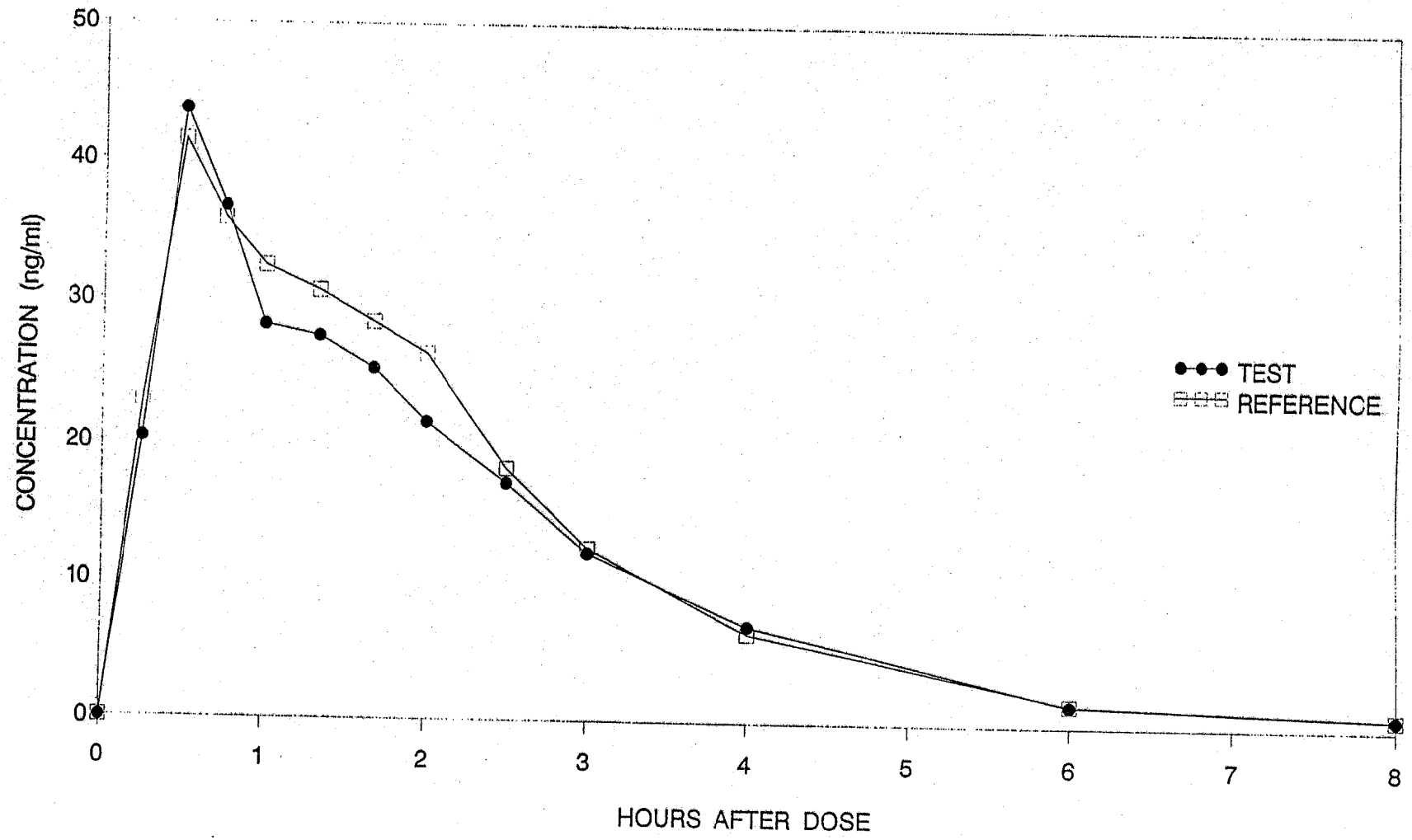
Table 2.2: Summary of plasma 6-mercaptopurine concentrations at each sampling time comparing AAI's 100 mg azathioprine tablets (Test) and 50 mg Imuran® tablets (Reference) when each was administered as a single 300 mg dose immediately after an overnight fast to 46 subjects.

Collection (Hour)	Least-Squares Means (ng/ml) Test	Reference	Significance * ($p<0.05$)
0.000	0.000	0.000	None
0.250	4.08	5.81	None
0.500	39.2	42.4	None
0.750	53.4	48.1	None
1.00	52.2	52.5	None
1.33	55.7	54.3	None
1.67	49.7	48.9	None
2.00	52.9	54.4	None
2.50	45.4	45.8	None
3.00	44.0	41.7	None
4.00	31.3	29.8	None
6.00	8.99	6.82	None
8.00	2.15	1.52	None

* Results of the statistical evaluation by ANOVA ($\alpha=0.05$) for the hypothesis of equal treatment effects. None indicates that no difference was detected between treatment means ($p>0.05$) at the sampling time evaluated.

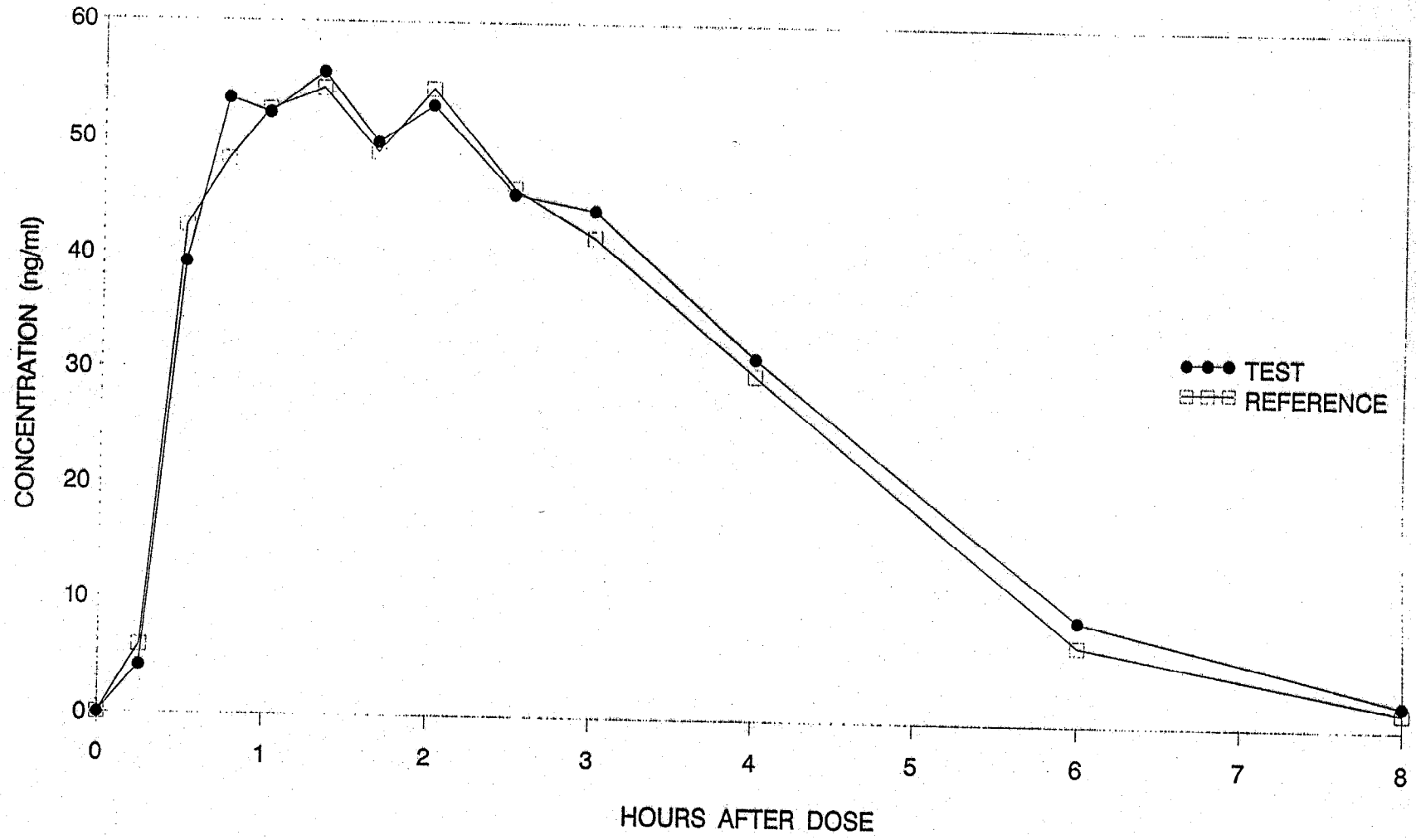
STUDY AAI – US – 89

LEAST – SQUARES MEAN AZATHIOPRINE PLASMA CONCENTRATIONS (N = 46)



STUDY AAI – US – 89

LEAST – SQUARES MEAN 6 – MERCAPTOPURINE PLASMA CONCENTRATIONS (N = 46)



Dissolution Profiles

As further evidence of the pharmaco-equivalence of the proposed drug products to the reference listed drug, a dissolution study was performed. The method is based on the procedure from USP 23 and adapted for the dissolution profile of the tablets. The procedure uses USP dissolution apparatus II (paddles) at 50 rpm and a dissolution medium of deionized, degassed water. The samples are analyzed for azathioprine by measuring and comparing the absorbance responses of the sample solution to a standard solution at 280 nm. This method is the same as in our approved ANDA (75-252) for Azathioprine Tablets USP, 50 mg.

The comparative results are presented for consideration immediately following this page.

Comparative Results of Azathioprine Tablets
Vs.
IMURAN®

Azathioprine Tablets, 75 mg
Lot No. 00321

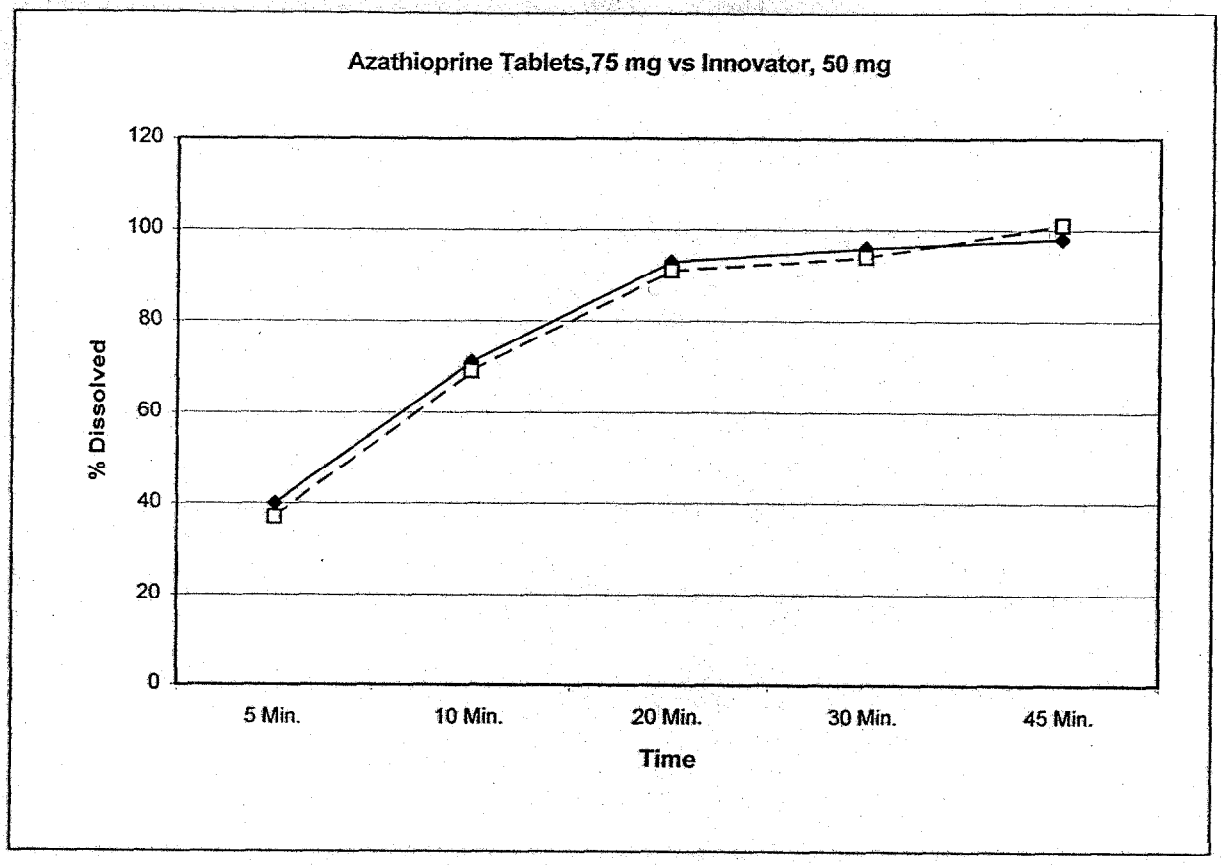
Unit	5 Min.	10 Min.	20 Min.	30 Min.	45 Min.
1	43	74	94	97	98
2	43	74	95	97	98
3	31	62	89	95	96
4	42	74	93	96	98
5	30	60	88	94	96
6	43	69	91	95	97
7	35	70	95	98	99
8	39	72	93	95	96
9	46	75	95	97	98
10	39	73	95	97	98
11	44	79	97	98	99
12	40	74	94	97	98
Mean (12)	40	71	93	96	98
%RSD	12.9	7.6	2.9	1.4	1.1

Date of Analysis: 10/26/2000

IMURAN® Tablets, 50 mg
Lot No. 6X1644

Unit	5 Min.	10 Min.	20 Min.	30 Min.	45 Min.
1	48	87	98	99	100
2	44	73	84	86	100
3	37	68	91	95	101
4	31	62	85	89	98
5	42	76	101	101	102
6	32	66	95	98	103
7	28	56	77	82	97
8	30	60	88	96	98
9	33	62	84	88	101
10	40	72	98	100	103
11	45	81	96	98	100
12	34	63	91	94	103
Mean(12)	37	69	91	94	101
%RSD	17.9	13.4	8	6.6	2.1

Date of Analysis: 7/7-10/97


Azathioprine Tablets,75 mg vs Innovator, 50 mg
120
100
80
60
40
20
0
% Dissolved
5 Min.
10 Min.
20 Min.
30 Min.
45 Min.
Time

Azathioprine Tablets, 100 mg
Lot No. 00322

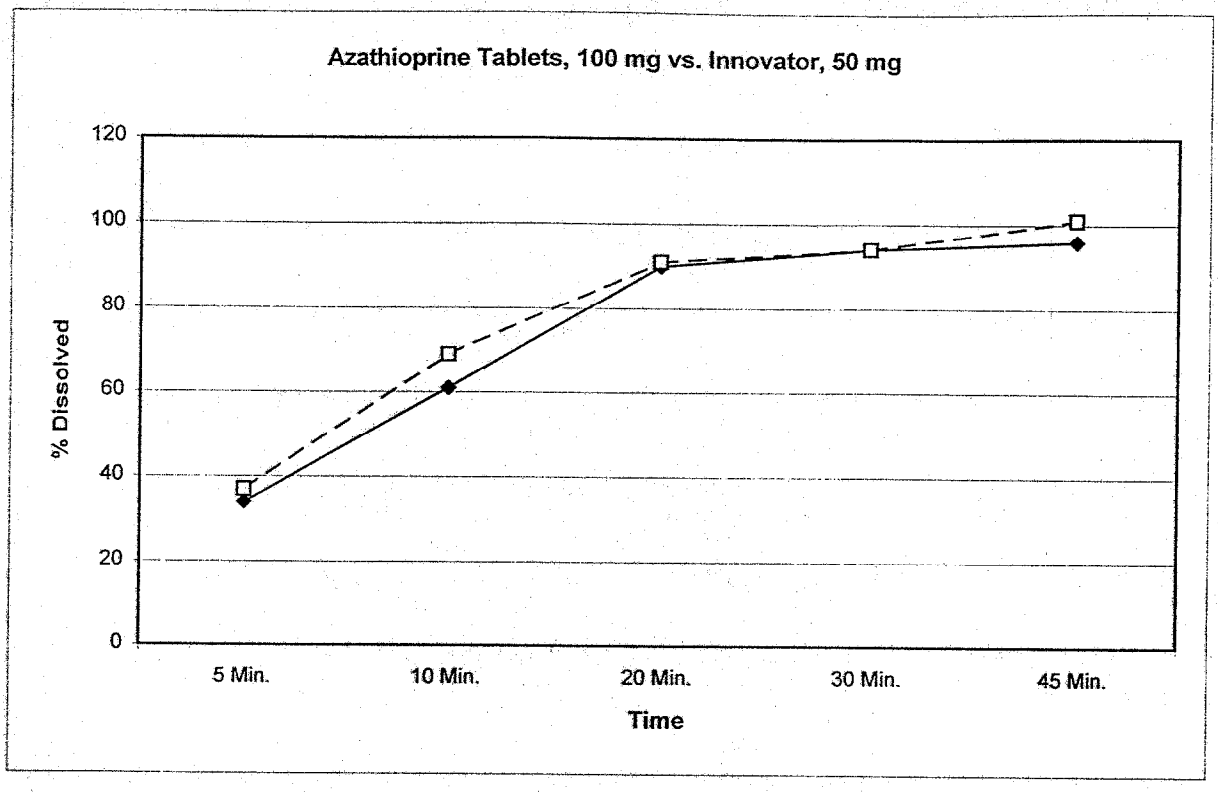
Unit	5 Min.	10 Min.	20 Min.	30 Min.	45 Min.
1	42	70	92	96	97
2	38	66	92	96	96
3	33	63	88	93	94
4	30	55	89	95	97
5	30	56	89	93	95
6	28	53	89	94	95
7	34	64	93	96	97
8	30	55	86	92	94
9	33	61	90	96	98
10	41	73	92	95	96
11	32	59	89	95	97
12	34	61	89	92	94
Mean (12)	34	61	90	94	96
%RSD	13.2	10.2	2.3	1.7	1.5

Date of Analysis: 10/26/2000

IMURAN® Tablets, 50 mg
Lot No. 6X1644

Unit	5 Min.	10 Min.	20 Min.	30 Min.	45 Min.
1	48	87	98	99	100
2	44	73	84	86	100
3	37	68	91	95	101
4	31	62	85	89	98
5	42	76	101	101	102
6	32	66	95	98	103
7	28	56	77	82	97
8	30	60	88	96	98
9	33	62	84	88	101
10	40	72	98	100	103
11	45	81	96	98	100
12	34	63	91	94	103
Mean(12)	37	69	91	94	101
%RSD	17.9	13.4	8	6.6	2.1

Date of Analysis: 7/7-10/97


Azathioprine Tablets, 100 mg vs. Innovator, 50 mg
120
100
80
60
40
20
0
% Dissolved
5 Min.
10 Min.
20 Min.
30 Min.
45 Min.
Time

Stability

The proposed products have been placed on a stability protocol to establish shelf-life. We fully expect them to be comparable to the 50 mg tablets in our approved ANDA (75-252). The cumulative data from six months on the protocol under ICH conditions is presented here for consideration.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321A
PACKAGING: WHITE HDPE BOTTLE OF 15 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Date(s) Tested	Appearance TP # 25481	Assay TP # 54672	Dissolution TP # 54673	
Limits		**See Below**	**93.0 - 107.0% LC**	NLT 75% (Q) in 30 minutes % Dissolved	
				n=6	Range
Initial (AFK16)	30NOV - 08DEC00	Conforms	97.3	96	93 - 98
25°C/60% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	96.7	97	96 - 99
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	97.8	94	92 - 96
3 Months (AFJ82)	09FEB - 28FEB01	Conforms - Unchanged from control	98.0	92	88 - 95
6 Months (AAII262-02-02)	09MAY - 04JUN01	Conforms - Unchanged from control	97.6	93	91 - 97
40°C/75% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	96.9	97	96 - 98
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	96.8	94	93 - 96
3 Months (AFJ82)	09FEB - 28FEB01	Conforms - Unchanged from control	96.7	93	90 - 95

Reference: SS-2567
Appearance Limits: Yellow, triangle-shape tablet with debossed "75 mg" and central score between the "75" and "mg" on one face and an "N" on the other face. Packaged in a white, round, plastic bottle with CR cap, foam seal liner, and pharmaceutical coil.
NOTE: Prior to the 6 month timepoint, assay was performed using TP # 54203, and dissolution performed using TP # 54204.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321A
PACKAGING: WHITE HDPE BOTTLE OF 15 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672			
Limits	Known Impurity: NMT 1.0%			
	Hypoxanthine	Mercaptopurine	5-Chloro-1-methyl-4-nitroimidazole	AMN + DMO
Initial (AFK16)	<0.1	0.1	<0.1	0.1
25°C/60% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1
6 Months (AAII262-02-02)	<0.1	0.1	<0.1	0.1
40°C/75% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321A
PACKAGING: WHITE HDPE BOTTLE OF 15 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672	
Limits	**Unknown Impurity: NMT 0.1% (RRT/% Area)**	Total Known and Unknown: NMT 2.0%
Initial (AFK16)	0.61/0.1	0.3
25°C/60% RH		
1 Month (AFJ80)	0.60/0.1	0.3
2 Months (AFJ81)	0.63/0.1	0.3
3 Months (AFJ82)	0.60/0.1	0.3
6 Months (AAII262-02-02)	0.61/0.1	0.3
40°C/75% RH		
1 Month (AFJ80)	0.60/0.1	0.3
2 Months (AFJ81)	0.63/0.1	0.3
3 Months (AFJ82)	0.47/0.1	0.4
	0.60/0.1	

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321A
PACKAGING: WHITE HDPE BOTTLE OF 15 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Hardness TP # 00086	Friability TP # 03384	Karl Fischer TP # 99719
Limits	**None specified kp (n=10)**	**None specified (%)**	None specified % Water (n=2)
Initial (AFK16)	8.0	0.4	4.6
25°C/60% RH			
1 Month (AFJ80)	7.3	0.2	4.6
2 Months (AFJ81)	6.9	0.0	5.4
3 Months (AFJ82)	6.8	0.3	5.2
6 Months (AAII262-02-02)	5.4	0.2	4.9
40°C/75% RH			
1 Month (AFJ80)	4.7	0.2	5.3
2 Months (AFJ81)	6.0	0.2	6.2
3 Months (AFJ82)	6.3	0.3	6.2

NOTE: TP # is as shown or is a current revision thereof.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321B
PACKAGING: WHITE HDPE BOTTLE OF 100 TABLETS WITH CRC
22JUN01

Cumulative

Condition/ Timepoint (Project)	Date(s) Tested	Appearance TP # 25481	Assay TP # 54672	Dissolution TP # 54673	
Limits		**See Below**	**93.0 - 107.0% LC**	NLT 75% (Q) in 30 minutes % Dissolved	
				n=6	Range
Initial (AFK16)	30NOV - 08DEC00	Conforms	97.3	98	96 - 100
25°C/60% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	97.3	99	97 - 100
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	95.9	94	92 - 96
3 Months (AFJ82)	09FEB - 28FEB01	Conforms - Unchanged from control	98.7	94	92 - 96
6 Months (AAII262-02-02)	09MAY - 04JUN01	Conforms - Unchanged from control	98.6	95	93 - 97
40°C/75% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	97.1	98	95 - 99
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	97.2	95	93 - 98
3 Months (AFJ82)	09FEB - 28FEB01	Conforms - Unchanged from control	99.4	95	92 - 97

Reference: SS-2568
Appearance Limits: Yellow, triangle-shape tablet with debossed "75 mg" and central score between the "75" and "mg" on one face and an "N" on the other face. Packaged in a white, round, plastic bottle with CR cap, foam seal liner, and pharmaceutical coil.
NOTE: Prior to the 6 month timepoint, assay was performed using TP # 54203, and dissolution performed using TP # 54204.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321B
PACKAGING: WHITE HDPE BOTTLE OF 100 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672			
Limits	Known Impurity: NMT 1.0%			
	Hypoxanthine	Mercaptopurine	5-Chloro-1-methyl-4-nitroimidazole	AMN + DMO
Initial (AFK16)	<0.1	0.1	<0.1	0.1
25°C/60% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1
6 Months (AAII262-02-02)	<0.1	0.1	<0.1	0.1
40°C/75% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321B
PACKAGING: WHITE HDPE BOTTLE OF 100 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672	
Limits	**Unknown Impurity: NMT 0.1% (RRT/% Area)**	Total Known and Unknown: NMT 2.0%
Initial (AFK16)	0.61/0.1	0.3
25°C/60% RH		
1 Month (AFJ80)	0.60/0.1	0.3
2 Months (AFJ81)	0.63/0.1	0.3
3 Months (AFJ82)	0.61/0.1	0.3
6 Months (AAII262-02-02)	0.61/0.1	0.3
40°C/75% RH		
1 Month (AFJ80)	0.60/0.1	0.3
2 Months (AFJ81)	0.63/0.1	0.3
3 Months (AFJ82)	0.61/0.1	0.3

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321B
PACKAGING: WHITE HDPE BOTTLE OF 100 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Hardness TP # 00086	Friability TP # 03384	Karl Fischer TP # 99719
Limits	**None specified kp (n=10)**	**None specified (%)**	None specified % Water (n=2)
Initial (AFK16)	8.6	0.2	3.3
25°C/60% RH			
1 Month (AFJ80)	7.3	0.1	4.7
2 Months (AFJ81)	7.1	0.1	5.1
3 Months (AFJ82)	8.2	0.2	4.8
6 Months (AAII262-02-02)	8.3	0.2	4.1
40°C/75% RH			
1 Month (AFJ80)	7.6	0.2	4.9
2 Months (AFJ81)	6.3	0.2	5.3
3 Months (AFJ82)	7.3	0.2	5.2

NOTE: TP # is as shown or is a current revision thereof.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321C
PACKAGING: WHITE HDPE BOTTLE OF 1000 TABLETS WITH SCREW CAP
25JUN01

Cumulative

Condition/ Timepoint (Project)	Date(s) Tested	Appearance TP # 25481	Assay TP # 54672	Dissolution TP # 54673	
Limits		**See Below**	**93.0 - 107.0% LC**	**NLT 75% (Q) in 30 minutes % Dissolved**	
Initial (AFK16)	30NOV - 08DEC00	Conforms	98.7	n=6 97	Range 96 - 100
25°C/60% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	97.6	98	96 - 99
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	96.5	96	95 - 97
3 Months (AFJ82)	09FEB - 28FEB01	Conforms - Unchanged from control	98.5	95	93 - 97
6 Months (AAII262-02-02)	09MAY - 04JUN01	Conforms - Unchanged from control	98.3	94	93 - 96
40°C/75% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	97.4	99	96 - 102
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	98.4	96	95 - 97
3 Months (AFJ82)	09FEB - 28FEB01	Conforms - Unchanged from control	97.8	94	91 - 96

Reference: SS-2569
Appearance Limits: Yellow, triangle-shape tablet with debossed "75 mg" and central score between the "75" and "mg" on one face and an "N" on the other face. Packaged in a white, round, plastic bottle with white plastic cap, foam seal liner, and pharmaceutical coil.
NOTE: Prior to the 6 month timepoint, assay was performed using TP # 54203, and dissolution performed using TP # 54204.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321C
PACKAGING: WHITE HDPE BOTTLE OF 1000 TABLETS WITH SCREW CAP
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672			
Limits	Known Impurity: NMT 1.0%			
	Hypoxanthine	Mercaptopurine	5-Chloro-1-methyl-4-nitroimidazole	AMN + DMO
Initial (AFK16)	<0.1	0.1	<0.1	0.1
25°C/60% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1
6 Months (AAII262-02-02)	<0.1	0.1	<0.1	0.1
40°C/75% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321C
PACKAGING: WHITE HDPE BOTTLE OF 1000 TABLETS WITH SCREW CAP
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672	
Limits	**Unknown Impurity: NMT 0.1% (RRT/% Area)**	**Total Known and Unknown: NMT 2.0%**
Initial (AFK16)	0.51/0.1 0.61/0.1	0.4
25°C/60% RH		
1 Month (AFJ80)	0.60/0.1	0.3
2 Months (AFJ81)	0.62/0.1	0.3
3 Months (AFJ82)	0.61/0.1	0.3
6 Months (AAII262-02-02)	0.61/0.1	0.3
40°C/75% RH		
1 Month (AFJ80)	0.52/0.1 0.60/0.1	0.4
2 Months (AFJ81)	0.63/0.1	0.3
3 Months (AFJ82)	0.60/0.1	0.3

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 75 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00321C
PACKAGING: WHITE HDPE BOTTLE OF 1000 TABLETS WITH SCREW CAP
25JUN01

Condition/ Timepoint (Project)	Hardness TP # 00086	Friability TP # 03384	Karl Fischer TP # 99719
	Cumulative		
Limits	**None specified kp (n=10)**	**None specified (%)**	None specified % Water (n=2)
Initial (AFK16)	7.5	0.3	4.6
25°C/60% RH			
1 Month (AFJ80)	7.9	0.0	4.8
2 Months (AFJ81)	6.1	0.4	5.1
3 Months (AFJ82)	7.5	0.2	4.8
6 Months (AAII262-02-02)	8.0	0.2	2.9
40°C/75% RH			
1 Month (AFJ80)	6.8	0.0	4.9
2 Months (AFJ81)	6.8	0.2	5.0
3 Months (AFJ82)	7.2	0.2	5.1

NOTE: TP # is as shown or is a current revision thereof.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322A
PACKAGING: WHITE HDPE BOTTLE OF 15 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Date(s) Tested	Appearance TP # 25481	Assay TP # 54672	Dissolution TP # 54673	
Limits		**See Below**	**93.0 - 107.0% LC**	NLT 75% (Q) in 30 minutes % Dissolved	
				n=6	Range
Initial (AFK16)	30NOV - 08DEC00	Conforms	97.0	94	93 - 95
25°C/60% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	97.6	97	95 - 98
2 Months (AFJ81)	18JAN - 02FEB01	Conforms - Unchanged from control	97.6	95	93 - 96
3 Months (AFJ82)	12FEB - 28FEB01	Conforms - Unchanged from control	98.1	93	92 - 95
6 Months (AAII262-02-02)	09MAY - 04JUN01	Conforms - Unchanged from control	99.1	93	93 - 93
40°C/75% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	98.8	96	95 - 97
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	98.1	95	93 - 96
3 Months (AFJ82)	12FEB - 28FEB01	Conforms - Unchanged from control	98.5	96	95 - 98

Reference: SS-2570
Appearance Limits: Yellow, diamond-shape tablet with debossed "100 mg" and central score between the "100" and "mg" on one face and an "N" on the other face. Packaged in a white, round, plastic bottle with CR cap, foam seal liner, and pharmaceutical coil.
NOTE: Prior to the 6 month timepoint, assay was performed using TP # 54203, and dissolution performed using TP # 54204.

60

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322A
PACKAGING: WHITE HDPE BOTTLE OF 15 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672			
Limits	Known Impurity: NMT 1.0%			
	Hypoxanthine	Mercaptopurine	5-Chloro-1-methyl-4-nitroimidazole	AMN + DMO
Initial (AFK16)	<0.1	0.1	<0.1	0.1
25°C/60% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	<0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1
6 Months (AAII262-02-02)	<0.1	0.1	<0.1	0.1
40°C/75% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322A
PACKAGING: WHITE HDPE BOTTLE OF 15 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672	
Limits	**Unknown Impurity: NMT 0.1% (RRT/% Area)**	Total Known and Unknown: NMT 2.0%
Initial (AFK16)	0.51/0.1 0.60/0.1	0.4
25°C/60% RH		
1 Month (AFJ80)	0.61/0.1	0.3
2 Months (AFJ81)	0.65/0.1	0.2
3 Months (AFJ82)	0.61/0.1	0.3
6 Months (AAII262-02-02)	0.61/0.1	0.3
40°C/75% RH		
1 Month (AFJ80)	0.61/0.1	0.3
2 Months (AFJ81)	0.62/0.1	0.3
3 Months (AFJ82)	0.61/0.1	0.3

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322A
PACKAGING: WHITE HDPE BOTTLE OF 15 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Hardness TP # 00086	Friability TP # 03384	Karl Fischer TP # 99719
Limits	**None specified kp (n=10)**	**None specified (%)**	None specified % Water (n=2)
Initial (AFK16)	10.6	0.2	3.2
25°C/60% RH			
1 Month (AFJ80)	4.9	0.2	4.7
2 Months (AFJ81)	8.8	0.2	5.2
3 Months (AFJ82)	9.1	0.3	5.1
6 Months (AAII262-02-02)	6.5	0.3	3.5
40°C/75% RH			
1 Month (AFJ80)	7.0	0.3	5.1
2 Months (AFJ81)	6.6	0.3	6.3
3 Months (AFJ82)	8.1	0.3	5.9

NOTE: TP # is as shown or is a current revision thereof.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322B
PACKAGING: WHITE HDPE BOTTLE OF 100 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Date(s) Tested	Appearance TP # 25481	Assay TP # 54672	Dissolution TP # 54673	
Limits		**See Below**	**93.0 - 107.0% LC**	NLT 75% (Q) in 30 minutes % Dissolved	
Initial (AFK16)	30NOV - 08DEC00	Conforms	98.1	n=6 93	Range 92 - 95
25°C/60% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	98.3	97	94 - 99
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	98.0	95	93 - 96
3 Months (AFJ82)	12FEB - 28FEB01	Conforms - Unchanged from control	98.6	95	93 - 99
6 Months (AAII262-02-02)	09MAY - 04JUN01	Conforms - Unchanged from control	97.7	93	90 - 96
40°C/75% RH					
1 Month (AFJ80)	14DEC00 - 15JAN01	Conforms - Unchanged from control	97.6	97	95 - 99
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	98.8	94	93 - 95
3 Months (AFJ82)	12FEB - 28FEB01	Conforms - Unchanged from control	98.3	94	91 - 97

Reference: SS-2571
Appearance Limits: Yellow, diamond-shape tablet with debossed "100 mg" and central score between the "100" and "mg" on one face and an "N" on the other face. Packaged in a white, round, plastic bottle with CR cap, foam seal liner, and pharmaceutical coil.
NOTE: Prior to the 6 month timepoint, assay was performed using TP # 54203, and dissolution performed using TP # 54204.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322B
PACKAGING: WHITE HDPE BOTTLE OF 100 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672			
Limits	Known Impurity: NMT 1.0%			
	Hypoxanthine	Mercaptopurine	5-Chloro-1-methyl-4-nitroimidazole	AMN + DMO
Initial (AFK16)	<0.1	0.1	<0.1	0.1
25°C/60% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1
6 Months (AAII262-02-02)	<0.1	0.1	<0.1	0.1
40°C/75% RH				
1 Month (AFJ80)	<0.1	0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1

NOTE: Prior to the 6 month timepoint, related substanceswere performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322B
PACKAGING: WHITE HDPE BOTTLE OF 100 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672	
Limits	**Unknown Impurity: NMT 0.1% (RRT/% Area)**	**Total Known and Unknown: NMT 2.0%**
Initial (AFK16)	0.51/0.1 0.60/0.1	0.4
25°C/60% RH		
1 Month (AFJ80)	0.61/0.1	0.3
2 Months (AFJ81)	0.62/0.1	0.3
3 Months (AFJ82)	0.61/0.1	0.3
6 Months (AAII262-02-02)	0.61/0.1	0.3
40°C/75% RH		
1 Month (AFJ80)	0.52/0.1 0.61/0.1	0.4
2 Months (AFJ81)	0.62/0.1	0.3
3 Months (AFJ82)	0.47/0.1 0.61/0.1	0.4

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322B
PACKAGING: WHITE HDPE BOTTLE OF 100 TABLETS WITH CRC
25JUN01

Cumulative

Condition/ Timepoint (Project)	Hardness TP # 00086	Friability TP # 03384	Karl Fischer TP # 99719
Limits	**None specified kp (n=10)**	**None specified (%)**	None specified % Water (n=2)
Initial (AFK16)	10.4	0.2	3.3
25°C/60% RH			
1 Month (AFJ80)	6.9	0.1	4.8
2 Months (AFJ81)	8.3	0.2	5.0
3 Months (AFJ82)	9.6	0.2	4.2
6 Months (AAI1262-02-02)	7.8	0.2	4.1
40°C/75% RH			
1 Month (AFJ80)	6.8	0.3	4.9
2 Months (AFJ81)	7.8	0.2	4.6
3 Months (AFJ82)	8.6	0.3	5.1

NOTE: TP # is as shown or is a current revision thereof.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322C
PACKAGING: WHITE HDPE BOTTLE OF 1000 TABLETS WITH SCREW CAP
25JUN01

Cumulative

Condition/ Timepoint (Project)	Date(s) Tested	Appearance TP # 25481	Assay TP # 54672	Dissolution TP # 54673	
Limits		**See Below**	**93.0 - 107.0% LC**	NLT 75% (Q) in 30 minutes % Dissolved	
Initial (AFK16)	30NOV - 08DEC00	Conforms	97.4	n=6 93	Range 92 - 94
25°C/60% RH					
1 Month (AFJ80)	14DEC00 - 16JAN01	Conforms - Unchanged from control	97.4	95	93 - 98
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	96.9	94	91 - 95
3 Months (AFJ82)	12FEB - 28FEB01	Conforms - Unchanged from control	97.0	95	94 - 97
6 Months (AAII262-02-02)	09MAY - 04JUN01	Conforms - Unchanged from control	97.4	92	89 - 95
40°C/75% RH					
1 Month (AFJ80)	14DEC00 - 16JAN01	Conforms - Unchanged from control	95.1	95	93 - 97
2 Months (AFJ81)	17JAN - 02FEB01	Conforms - Unchanged from control	98.0	94	93 - 95
3 Months (AFJ82)	12FEB - 28FEB01	Conforms - Unchanged from control	98.6	94	93 - 94

Reference: SS-2572
Appearance Limits: Yellow, diamond-shape tablet with debossed "100 mg" and central score between the "100" and "mg" on one face and an "N" on the other face. Packaged in a white, round, plastic bottle with white plastic cap, foam seal liner, and pharmaceutical coil.
NOTE: Prior to the 6 month timepoint, assay was performed using TP # 54203, and dissolution performed using TP # 54204.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322C
PACKAGING: WHITE HDPE BOTTLE OF 1000 TABLETS WITH SCREW CAP
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672			
Limits	Known Impurity: NMT 1.0%			
	Hypoxanthine	Mercaptopurine	5-Chloro-1-methyl-4-nitroimidazole	AMN + DMO
Initial (AFK16)	<0.1	0.1	<0.1	0.1
25°C/60% RH				
1 Month (AFJ80)	<0.1	<0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1
6 Months (AAII262-02-02)	<0.1	0.1	<0.1	0.1
40°C/75% RH				
1 Month (AFJ80)	<0.1	<0.1	<0.1	0.1
2 Months (AFJ81)	<0.1	0.1	<0.1	0.1
3 Months (AFJ82)	<0.1	0.1	<0.1	0.1

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322C
PACKAGING: WHITE HDPE BOTTLE OF 1000 TABLETS WITH SCREW CAP
25JUN01

Cumulative

Condition/ Timepoint (Project)	Related Substances TP # 54672	
Limits	**Unknown Impurity: NMT 0.1% (RRT/% Area)**	**Total Known and Unknown: NMT 2.0%**
Initial (AFK16)	0.61/0.1	0.3
25°C/60% RH		
1 Month (AFJ80)	0.62/0.1	0.2
2 Months (AFJ81)	0.62/0.1	0.3
3 Months (AFJ82)	0.61/0.1	0.3
6 Months (AAII262-02-02)	0.61/0.1	0.3
40°C/75% RH		
1 Month (AFJ80)	0.62/0.1	0.2
2 Months (AFJ81)	0.63/0.1	0.3
3 Months (AFJ82)	0.47/0.1	0.4
	0.61/0.1	

NOTE: Prior to the 6 month timepoint, related substances were performed using TP # 54203.

STABILITY SUMMARY FOR AZATHIOPRINE 100 mg TABLETS FOR AAI - RESEARCH AND DEVELOPMENT
SET DATE: 09NOV00
LOT#: 00322C
PACKAGING: WHITE HDPE BOTTLE OF 1000 TABLETS WITH SCREW CAP
25JUN01

Condition/ Timepoint (Project)	Hardness TP # 00086	Friability TP # 03384	Karl Fischer TP # 99719
Limits	**None specified kp (n=10)**	**None specified (%)**	**None specified % Water (n=2)**
Initial (AFK16)	11.5	0.2	3.9
25°C/60% RH			
1 Month (AFJ80)	8.6	0.1	4.5
2 Months (AFJ81)	8.7	0.2	4.6
3 Months (AFJ82)	10.8	0.2	4.5
6 Months (AAII262-02-02)	8.6	0.1	3.3
40°C/75% RH			
1 Month (AFJ80)	8.6	0.2	4.8
2 Months (AFJ81)	9.2	0.2	4.9
3 Months (AFJ82)	10.1	0.2	4.8

Cumulative

NOTE: TP # is as shown or is a current revision thereof.