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August 31, 2001

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

RE: CITIZEN PETITION

Dear Sirs;

The undersigned submits this petition pursuant to 21 CFR 10.30 and in accordance with the regulations at 21 CFR 314.161, to request the Commissioner of Food and Drugs to provide a determination whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or efficacy reasons.

A. Action Requested

The petitioner requests that the Commissioner determine whether Imuran® (Azathioprine) Tablets, 25 mg, (NDA 016-324), by Prometheus Labs, have been voluntarily withdrawn or withheld from sale for safety or efficacy reasons.

B. Statement of Grounds

The Food and Drug Administration maintains a list of drug products which are eligible for submission as abbreviated new drug applications. That list, commonly referred to as the "Orange Book", contains all *FDA Approved Drug Products with Therapeutic Equivalence Evaluations*. The List is composed of four parts, one of which is the Discontinued Drug Product List. By definition:

> *The Discontinued Drug Product List contains approved products that have never been marketed, have been discontinued from marketing, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing.*

NDA 016-324 for the reference listed drug (Imuran) was approved in 25 mg and 50 mg strengths for the oral tablets. According to the current labeling information, the initial dose for Rheumatoid Arthritis is 50 to 100 mg per day and for Renal Homotransplantation is 200 mg to 350 mg per day. For both indications the recommendation is for the dosage to be adjusted incrementally, as necessary, by 25 mg/day. Additionally, for use in patients with Renal Dysfunction or those receiving concomitant therapy with allopurinol (Zyloprim) a dose reduction of Imuran is recommended.

After an extensive search of the literature and other public data sources we were unable to locate any direct information regarding the reason for withdrawal. A review of the unit sales data from 1991 through 2001 seems to indicate that there may have been commercial reasons for discontinuing the product. There is no data available from 1994 onward for the 25 mg strength implying that this was the year the product was withdrawn. This would be consistent with the information available on the CDER Labeling Review Branch Homepage, which indicated that the latest approved labeling revision (SLR 011) was approved on 30-AUG-94.

In accordance with 21 CFR 314.122 we have attempted to compile all evidence available concerning the reasons for the withdrawal from sale. The table below lists the information referenced above which is also included for your review and consideration:

Item	Title	No. of Pages
1.	*Electronic Orange Book* information 25 mg product on Discontinued List 50 mg product on current Rx List	7
2.	Current approved package insert for Imuran®	6
3.	Sales & Marketing Data (Dollars and Units) 1991 – 2001 Scott-Levin 1994 – 1998 IMS	1
4.	Most Recently Approved labeling Supplements for Currently Marketed NDAs (ordered by active ingredients)	1

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.

Respectfully Submitted,

Wayne L. Whittingham
Regulatory Affairs Professional

Enclosures

Electronic Orange Book

Approved Drug Products
with
Therapeutic Equivalence Evaluations

Current through May 2001

Preface

FAQ

Search by Active Ingredient Search by Applicant Holder

Search by Proprietary Name Search by Application Number

The products in this list have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Drug questions email: DRUGINFO@CDER.FDA.GOV

U.S Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Information Technology
Division of Data Management and Services

Updated: August 08, 2001

Application Number Search Results from "Disc" table for query on "016324."

Appl No	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
016324	AZATHIOPRINE	Tablet; Oral	25MG	IMURAN	PROMETHEUS LABS

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Search results from the "Disc" table for query on "016324."

Active Ingredient:	AZATHIOPRINE
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	IMURAN
Applicant:	PROMETHEUS LABS
Strength:	25MG
Application Number:	016324
Product Number:	002
Approval Date:	Approved prior to Jan 1, 1982
RX/OTC/DISCN:	DISCN
Patent and Exclusivity Info for this product:	Click Here

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Patent and Exclusivity Search Results from query on 016324 002.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

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Patent and Exclusivity Terms

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Application Number Search Results from "Rx" table for query on "016324."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
016324	AB	Yes	AZATHIOPRINE	Tablet; Oral	50MG	IMURAN	PROMETHEUS LABS

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Search results from the "Rx" table for query on "016324."

Active Ingredient:	AZATHIOPRINE
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	IMURAN
Applicant:	PROMETHEUS LABS
Strength:	50MG
Application Number:	016324
Product Number:	001
Approval Date:	Approved prior to Jan 1, 1982
Reference Listed Drug:	Yes
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	Click Here

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Patent and Exclusivity Search Results from query on 016324 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

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Patent and Exclusivity Terms

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PRODUCT INFORMATION

IMURAN® (azathioprine)

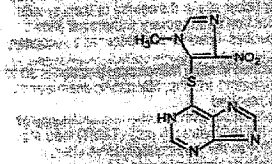
4098541
517101

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:[1-6] Summary information from transplant centers and registries indicates relatively universal use of IMURAN with or without other immunosuppressive agents.[7-14] 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.[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 diseases.[14,15] It has not been possible to define the precise risk of neoplasia due to IMURAN.[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 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;[17] a reduced percentage of fertile matings occurred when animals received 5 mg/kg.[18]

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.[19]

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.[18]

Limited immunologic and other abnormalities have occurred in a few infants born of renal allograft recipients on IMURAN. 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 Kam[22] described an infant born with preaxial polydactyly whose mother received azathioprine 200 mg daily and prednisone 20 mg every other day during pregnancy. Talbert 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 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.[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 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 ¼ to ⅓ 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

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.[32,33,34] 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.[35] 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[1-4]. 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).

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GlaxoWellcome

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Research Triangle Park, NC 27709

November 1997 RL-500 517101 4098641

Scott-Levin Data	1991 TRX Retail Dol.(000)	1991 TRX Ext. Units(000)	1992 TRX Retail Dol.(000)	1992 TRX Ext. Units(000)	1993 TRX Retail Dol.(000)	1993 TRX Ext. Units(000)	1994 TRX Retail Dol.(000)	1994 TRX Ext. Units(000)	1995 TRX Retail Dol.(000)	1995 TRX Ext. Units(000)
TOTAL MARKET	36495	36674	43265	40622	48633	43286	57366	49167	66962	54730
Imuran	36495	36674	43265	40622	48633	43286	57366	49167	66962	54730
Regular Tab	36495	36674	43265	40622	48603	43283	57335	49166	66939	54730
50MG	36495	36674	43265	40621	48603	43283	57335	49166	66939	54730
25MG	0	0	0	1	0	0	--	--	--	--
Vial, IV	--	--	--	--	30	3	31	1	23	0
100MG	--	--	--	--	30	3	31	1	23	0

Scott-Levin Data	1996 TRX Retail Dol.(000)	1996 TRX Ext. Units(000)	1997 TRX Retail Dol.(000)	1997 TRX Ext. Units(000)	1998 TRX Retail Dol.(000)	1998 TRX Ext. Units(000)	1999 TRX Retail Dol.(000)	1999 TRX Ext. Units(000)	2000 TRX Retail Dol.(000)	2000 TRX Ext. Units(000)	SIX/JUN/01 TRX Retail Dol.(000)	SIX/JUN/01 TRX Ext. Units(000)
TOTAL MARKET	60418	47314	40257	30414	28515	21683	21793	15644	18081	12582	7699	5050
Imuran	60418	47314	40257	30414	28515	21683	21793	15644	18081	12582	7699	5050
Regular Tab	60389	47313	40252	30414	28509	21683	21773	15643	18076	12582	7681	5050
50MG	60389	47313	40252	30414	28509	21683	21773	15643	18076	12582	7681	5050
25MG	--	--	--	--	--	--	--	--	--	--	--	--
Vial, IV	29	0	5	0	6	0	20	0	5	0	18	0
100MG	29	0	5	0	6	0	20	0	5	0	18	0

IMS Data	YEAR/DEC/94 Tot Dollars (Thousands)	YEAR/DEC/94 Tot Ex Units (Thousands)	YEAR/DEC/95 Tot Dollars (Thousands)	YEAR/DEC/95 Tot Ex Units (Thousands)	YEAR/DEC/96 Tot Dollars (Thousands)	YEAR/DEC/96 Tot Ex Units (Thousands)	YEAR/DEC/97 Tot Dollars (Thousands)	YEAR/DEC/97 Tot Ex Units (Thousands)	YEAR/DEC/98 Tot Dollars (Thousands)	YEAR/DEC/98 Tot Ex Units (Thousands)
IMURAN GWC 68/04	77933	74668	82122	78230	68628	65031	44469	40283	32620	28862
OSR ORALS,SOL,TAB/CAP RE	70225	74660	76406	78151	66479	65001	43424	40269	31835	28852
TABS 50MG 100 0597-55	68826	73096	75479	77196	66463	64985	43424	40269	31835	28852
TABS 50MG 100UD 0597-56	1399	1465	927	955	16	17	0	0	0	0
IAA INJECT,IM REG	7707	107	5716	79	2149	29	1045	14	785	10
VIAL 100MG 1 0598-71	7707	107	5716	79	2149	29	1045	14	785	10

MOST RECENTLY APPROVED LABELING SUPPLEMENTS FOR CURRENTLY MARKETED NDAs ORDERED BY ACTIVE INGREDIENT(S)

NDA No.	Supp No.	Trade Name	Active Ingredient	Approval Date
19-058	SLR 012	TENORMIN	ATENOLOL	4-Apr-00
18-760	SLR 022	TENORETIC 100	ATENOLOL/CHLORTHALIDONE	4-Apr-00
20-702	SLR 014	LIPITOR	ATORVASTATIN CALCIUM	28-Aug-98
20-500	SLR 002	MEPRON	ATOVAQUONE	2-May-97
18-831	SLR 021	TRACRIUM	ATRACURIUM BESYLATE	3-Oct-00
18-831	SLR 022	TRACRIUM	ATRACURIUM BESYLATE	3-Oct-00
18-831	SLR 021	TRACRIUM PRESERVATIVE FREE	ATRACURIUM BESYLATE	3-Oct-00
18-831	SLR 022	TRACRIUM PRESERVATIVE FREE	ATRACURIUM BESYLATE	3-Oct-00
17-106	SLR 014	ATROPEN	ATROPINE	21-Apr-98
18-689	SLR 015	RIDAURA	AURANOFIN	22-Dec-99
17-601	SLR 003	OPTIMINE	AZATADINE MALEATE	8-Jan-80
17-391	SLR 002	IMURAN	AZATHIOPRINE	23-Apr-82
16-324	SLR 011	IMURAN	AZATHIOPRINE	30-Aug-94
20-428	SLR 013	AZELEX	AZELAIC ACID	27-Apr-01
20-114	SLR 002	ASTELIN	AZELASTINE HYDROCHLORIDE	16-Feb-99
50-670	SLR 014	ZITHROMAX	AZITHROMYCIN	11-Nov-00
50-693	SLR 002	ZITHROMAX	AZITHROMYCIN	11-Nov-00
50-710	SLR 006	ZITHROMAX	AZITHROMYCIN	11-Nov-00
50-730	SLR 004	ZITHROMAX	AZITHROMYCIN	11-Nov-00
50-733	SLR 005	ZITHROMAX	AZITHROMYCIN	28-Feb-01
50-580	SLR 028	AZACTAM	AZTREONAM	16-Feb-99
50-580	SLR 031	AZACTAM	AZTREONAM	16-Feb-99
50-632	SLR 009	AZACTAM	AZTREONAM	16-Feb-99
50-520	SLR 003	SPECTROBID	BACAMPICILLIN HYDROCHLORIDE	2-Feb-83
50-168	SLR 073	CORTISPORIN	BACITRACIN/HYDROCORT/NEOMYCIN/POLYMYXIN	19-Jul-99
17-851	SLR 034	LIORESAL	BACLOFEN	17-Nov-89
18-584	SLR 025	BECONASE	BECLOMETHASONE DIPROPIONATE	4-Apr-96
17-573	SLR 040	VANCERIL	BECLOMETHASONE DIPROPIONATE	8-Feb-99
19-589	SLR 001	VANCENASE AQ	BECLOMETHASONE DIPROPIONATE MONOHYDRATE	15-Dec-88
20-469	SLR 002	VANCENASE AQ	BECLOMETHASONE DIPROPIONATE MONOHYDRATE	13-Feb-97
20-469	SLR 003	VANCENASE AQ	BECLOMETHASONE DIPROPIONATE MONOHYDRATE	13-Feb-97
19-389	SLR 017	BECONASE AQ	BECLOMETHASONE DIPROPIONATE MONOHYDRATE	30-May-97
20-033	SLR 013	LOTENSIN HCT	BENAZEPRIL HCL/HYDROCHLOROTHIAZIDE	29-Jul-98
19-851	SLR 016	LOTENSIN	BENAZEPRIL HYDROCHLORIDE	29-Jul-98
12-164	SLR 019	NATURETIN-10	BENDROFLUMETHIAZIDE	4-May-79
11-210	SLR 031	TESSALON	BENZONATATE	4-Sep-92
50-557	SLR 018	BENZAMYCIN	BENZOYL PEROXIDE/ERYTHROMYCIN	5-Mar-96
12-427	SLR 021	DIDREX	BENZPHETAMINE HYDROCHLORIDE	28-Jul-00

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