

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 16-885/S022

Trade Name: Lysodren

Generic Name: (mitotane tablets)

Sponsor: Bristol-Myers Squibb Company

Approval Date: July 10, 2003

Indications: The treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types.

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APPLICATION NUMBER:
NDA 16-885/S022

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APPLICATION NUMBER:

NDA 16-885/S022

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 16-885/S-022

Bristol-Myers Squibb Company
Attention: Steven J. Knapp
Executive Director, Life Cycle Management
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Mr. Knapp:

Please refer to your supplemental new drug application dated January 9, 2003, received January 10, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LYSODREN[®] (mitotane tablets, USP).

This supplemental new drug application provides for revised labeling to comply with the Federal Register notice of August 27, 1997, entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling."

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 16-885/S-022." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

NDA 16-885/S-022

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If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 594-5779.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.

Director

Division of Oncology Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Richard Pazdur
7/10/03 01:41:47 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 16-885/S022

LABELING

LYSODREN[®]

(mitotane tablets, USP)

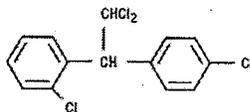
Rx only

WARNINGS

LYSODREN (mitotane tablets, USP) should be administered under the supervision of a qualified physician experienced in the uses of cancer chemotherapeutic agents. LYSODREN should be temporarily discontinued immediately following shock or severe trauma since adrenal suppression is its prime action. Exogenous steroids should be administered in such circumstances, since the depressed adrenal may not immediately start to secrete steroids.

DESCRIPTION

LYSODREN[®] (mitotane tablets, USP) is an oral chemotherapeutic agent. It is best known by its trivial name, o,p'-DDD, and is chemically, 1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl) ethane. The chemical structure is shown below.



LYSODREN is a white granular solid composed of clear colorless crystals. It is tasteless and has a slight pleasant aromatic odor. It is soluble in ethanol, isooctane and carbon tetrachloride. It has a molecular weight of 320.05.

Inactive ingredients in LYSODREN tablets are: avicel, Polyethylene Glycol 3350, silicon dioxide, and starch.

LYSODREN is available as 500 mg scored tablets for oral administration.

CLINICAL PHARMACOLOGY

LYSODREN can best be described as an adrenal cytotoxic agent, although it can cause adrenal inhibition, apparently without cellular destruction. Its biochemical mechanism of action is unknown. Data are available to suggest that the drug modifies the peripheral metabolism of steroids as well as directly suppressing the adrenal cortex. The administration of LYSODREN alters the extra-adrenal metabolism of cortisol in man; leading to a reduction in measurable 17-hydroxy corticosteroids, even

though plasma levels of corticosteroids do not fall. The drug apparently causes increased formation of 6-B-hydroxyl cortisol.

Data in adrenal carcinoma patients indicate that about 40% of oral LYSODREN is absorbed and approximately 10% of administered dose is recovered in the urine as a water-soluble metabolite. A variable amount of metabolite (1 to 17%) is excreted in the bile and the balance is apparently stored in the tissues.

Following discontinuation of LYSODREN, the plasma terminal half-life has ranged from 18 to 159 days. In most patients blood levels become undetectable after 6 to 9 weeks. Autopsy data have provided evidence that LYSODREN is found in most tissues of the body; however, fat tissues are the primary site of storage. LYSODREN is converted to a water-soluble metabolite.

No unchanged LYSODREN has been found in urine or bile.

INDICATIONS AND USAGE

LYSODREN is indicated in the treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types.

CONTRAINDICATIONS

LYSODREN (mitotane tablets, USP) should not be given to individuals who have demonstrated a previous hypersensitivity to it.

WARNINGS

LYSODREN should be temporarily discontinued immediately following shock or severe trauma, since adrenal suppression is its prime action. Exogenous steroids should be administered in such circumstances, since the depressed adrenal may not immediately start to secrete steroids.

LYSODREN should be administered with care to patients with liver disease other than metastatic lesions from the adrenal cortex, since the metabolism of LYSODREN may be interfered with and the drug may accumulate.

All possible tumor tissues should be surgically removed from large metastatic masses before LYSODREN administration is instituted. This is necessary to minimize the possibility of infarction and hemorrhage in the tumor due to a rapid cytotoxic effect of the drug.

Long-term continuous administration of high doses of LYSODREN may lead to brain damage and impairment of function. Behavioral and neurological assessments should be made at regular intervals when continuous LYSODREN treatment exceeds 2 years.

A substantial percentage of the patients treated show signs of adrenal insufficiency. It therefore appears necessary to watch for and institute steroid replacement in those patients. However, some investigators have recommended that steroid replacement therapy be administered concomitantly with LYSODREN. It has been shown that the metabolism of exogenous steroids is modified and consequently somewhat higher doses than normal replacement therapy may be required.

PRECAUTIONS

General

Adrenal insufficiency may develop in patients treated with LYSODREN, and adrenal steroid replacement should be considered for these patients.

Since sedation, lethargy, vertigo, and other CNS side effects can occur, ambulatory patients should be cautioned about driving, operating machinery, and other hazardous pursuits requiring mental and physical alertness.

Drug Interactions

LYSODREN has been reported to accelerate the metabolism of warfarin by the mechanism of hepatic microsomal enzyme induction, leading to an increase in dosage requirements for warfarin. Therefore, physicians should closely monitor patients for a change in anticoagulant dosage requirements when administering LYSODREN to patients on coumarin-type anticoagulants. In addition, LYSODREN should be given with caution to patients receiving other drugs susceptible to the influence of hepatic enzyme induction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic and mutagenic potentials of LYSODREN (mitotane tablets, USP) are unknown. However, the mechanism of action of this compound suggests that it probably has less carcinogenic potential than other cytotoxic chemotherapeutic drugs.

Pregnancy

Pregnancy "Category C". Animal reproduction studies have not been conducted with LYSODREN. It is also not known whether LYSODREN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LYSODREN should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from mitotane, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of LYSODREN did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

A very high percentage of patients treated with LYSODREN have shown at least one type of side effect. The main types of adverse reactions consist of the following:

1. Gastrointestinal disturbances, which consist of anorexia, nausea or vomiting, and in some cases diarrhea, occur in about 80% of the patients.
2. Central nervous system side effects occur in 40% of the patients. These consist primarily of depression as manifested by lethargy and somnolence (25%), and dizziness or vertigo (15%).
3. Skin toxicity has been observed in about 15% of the cases. These skin changes consist primarily of transient skin rashes which do not seem to be dose related. In some instances, this side effect subsided while the patients were maintained on the drug without a change of dose. Infrequently occurring side effects involve the eye (visual blurring, diplopia, lens opacity, toxic retinopathy); the genitourinary system (hematuria, hemorrhagic cystitis, and albuminuria); cardiovascular system (hypertension, orthostatic hypotension, and flushing); and some miscellaneous effects including generalized aching, hyperpyrexia, and lowered protein bound iodine (PBI).

OVERDOSAGE

No proven antidotes have been established for LYSODREN overdose.

DOSAGE AND ADMINISTRATION

The recommended treatment schedule is to start the patient at 2 to 6 g of LYSODREN per day in divided doses, either three or four times a day. Doses are usually increased incrementally to 9 to 10 g per day. If severe side effects appear, the dose should be reduced until the maximum tolerated dose is achieved. If the patient can tolerate higher doses and improved clinical response appears possible, the dose should be increased until adverse reactions interfere. Experience has shown that the maximum tolerated dose (MTD) will vary from 2 to 16 g per day, but has usually been 9 to 10 g per day. The highest doses used in the studies to date were 18 to 19 g per day.

Treatment should be instituted in the hospital until a stable dosage regimen is achieved.

Treatment should be continued as long as clinical benefits are observed. Maintenance of clinical status or slowing of growth of metastatic lesions can be considered clinical benefits if they can clearly be shown to have occurred.

If no clinical benefits are observed after 3 months at the maximum tolerated dose, the case would generally be considered a clinical failure. However, 10% of the patients who showed a measurable response required more than 3 months at the MTD. Early diagnosis and prompt institution of treatment improve the probability of a positive clinical response. Clinical effectiveness can be shown by reduction in tumor mass; reduction in pain, weakness or anorexia; and reduction of symptoms and signs due to excessive steroid production.

A number of patients have been treated intermittently with treatment being restarted when severe symptoms have reappeared. Patients often do not respond after the third or fourth such course. Experience accumulated to date suggests that continuous treatment with the maximum possible dosage of LYSODREN is the best approach.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁷ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

LYSODREN[®] (mitotane tablets, USP)

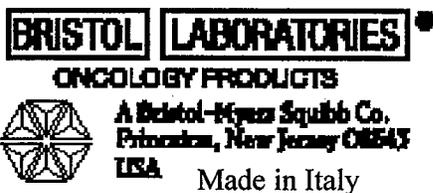
NDC 0015-3080-60—500 mg Tablets, bottle of 100

STORAGE

Tablets may be stored at room temperature.

References:

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.
2. 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.
3. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA*. 1985;253:1590-1591.
4. 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.
5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia*. 1983;1:426-428.
6. 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.
7. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990;47:1033-1049.
8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines.). *Am J Health-SystPharm*. 1996;53-1669-1685



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Revised April 1999

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Revised

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

NDA 16-885/S022

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**DIVISION OF ONCOLOGY DRUG PRODUCTS
LABELING REVIEW**

NDA: 16-885/SLR-022

SPONSOR: Bristol-Myers Squibb Company

DRUG: LYSODREN® (mitotane tablets, USP)

DATE OF SUBMISSION: January 9, 2003

BACKGROUND:

SLR-022 was submitted to comply with the Federal Register Notice of August 27, 1997, entitled "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling." Below is a comparison between the proposed labeling submitted with SLR-022 and that of the most recently approved labeling, SLR-020. Any differences between these two labels have been noted below.

I. Review

In S-022, the following paragraph has been added between the **Pediatric Use** and **ADVERSE REACTIONS** sections.

Geriatric Use

Clinical studies of LYSODREN did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Comment: This change should be reviewed by a medical officer.

II. Changes to be made to SLR-022

The references section should read as follows:

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.
2. 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.
3. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA*. 1985;253:1590-1591.
 4. 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.
 5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia*. 1983;1:426-428.
 6. 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.
 7. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990;47:1033-1049.
 8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines.). *Am J Health-SystPharm*. 1996;53-1669-1685

III. Recommendation

A Medical Officer should review all revisions and suggested changes to S-022. If all changes are found acceptable, an approval letter should be sent to the sponsor.

Amy Baird
Consumer Safety Officer

Cottrell for Pease 7-1-03
Concur:
Dotti Pease
Chief, Project Management Staff

Talarico 7-7-03
Lilia Talarico, M.D.
Associate Director

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/s/

Amy Baird
7/9/03 05:37:13 PM
CSO

Christy Cottrell
7/10/03 11:05:50 AM
CSO
Signing for Dotti Pease



NDA 16-885/S-022

Bristol-Myers Squibb
Attention: Steven J. Knapp
Executive Director, Life Cycle Management
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Mr. Knapp:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: LYSODREN[®] Tablets (mitotane tablets, USP)

NDA Number: 16-885

Supplement number: 022

Date of supplement: January 9, 2003

Date of receipt: January 10, 2003

This supplemental application proposes the following change: the addition of a "Geriatric Use" subsection to the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 11, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 10, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Document Room HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

NDA 16-885/S-022

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Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and research
Division of Oncology Drug Products, HFD-150
Attention: Document Room 150
1451 Rockville Pike
Rockville, Maryland 20854

If you have any question, call Amy Baird, Regulatory Project Manager, at (301) 594-5779.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Amy Baird
1/24/03 02:53:19 PM
for Dotti Pease