PRODUCT MONOGRAPH

Pr LYSODREN®

(mitotane)

Tablets, 500 mg

Antineoplastic Agent

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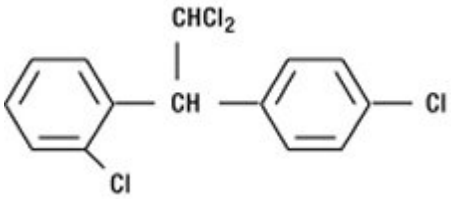
THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

DESCRIPTION

LYSODREN (mitotane) 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.

LYSODREN is tasteless and has a slight pleasant aromatic odor.

ACTION

LYSODREN (mitotane) 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 and also directly suppresses 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-β-hydroxy cortisol.

INDICATIONS

LYSODREN is indicated only in the treatment of inoperable adrenal cortical carcinoma of both functional and non-functional type.

CONTRAINDICATIONS

LYSODREN is contraindicated in patients with known hypersensitivity to mitotane or any excipients.

WARNINGS

LYSODREN should be administered under the supervision of a qualified physician experienced in the uses of cancer chemotherapeutic agents.

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

Hepatic Impairment: 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.

Before Initiating Treatment*:* All possible tumour tissue 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 tumour due to a rapid, positive effect of the drug.

Monitoring of plasma levels*:* Mitotane plasma levels should be monitored in order to adjust the mitotane dose, particularly if high starting doses are considered necessary. Dose adjustments may be necessary to achieve the desired plasma levels in the therapeutic window (between 14 and 20 mg/L), and avoid specific adverse reactions which ensures optimal efficacy of LYSODREN with acceptable safety. Severe neurologic toxicity has been reported with mitotane levels above 20 mg/L and therefore, this threshold should not be exceeded. Mitotane plasma concentrations should be measured at frequent intervals (e.g., after each dose adjustment) until the target concentration range is reached, usually within 3 to 5 months. Because of tissue accumulation (see Mitotane Tissue Accumulation below), mitotane plasma levels should be monitored regularly (e.g. monthly) once the maintenance dose has been reached.

If toxicity occurs at mitotane plasma levels above 20 mg/L, treatment should be withheld and restarted when plasma levels are within the therapeutic range. If unacceptable toxicity occurs and mitotane plasma levels are within the therapeutic window, the dose should be reduced until a maximum tolerated dose is reached. Dose adjustments do not produce immediate changes in plasma levels of mitotane. Due to the prolonged half-life, significant serum concentrations may persist; thus, regular monitoring (e.g. every two months) of mitotane plasma levels is necessary after interruption of treatment.

Central Nervous System Disorder*:* Administration of LYSODREN may lead to brain damage and

impairment of function, which may or may not be reversible after discontinuation of LYSODREN. Behavioural and neurological assessments should be made at regular intervals, especially when mitotane plasma levels exceed 20 mg/L.

Ovarian Macrocysts in Premenopausal Women: Ovarian macrocysts have been observed with higher incidence in this population. Isolated cases of complicated cysts have been reported (adnexal torsion and haemorrhagic cyst rupture). Improvement after mitotane discontinuation has been observed. Women should be urged to seek medical advice if they experience gynecological symptoms such as bleeding and/or pelvic pain (see ADVERSE EFFECTS). Periodic ovarian ultrasound monitoring is recommended in premenopausal women treated with LYSODREN.

Risk of Adrenal Insufficiency*:* LYSODREN modifies the metabolism of exogenous steroids resulting in a substantial percentage of patients treated with LYSODREN showing signs of adrenal insufficiency. In these patients, steroid replacement therapy should be considered. Since LYSODREN increases hormone binding proteins, free cortisol and corticotropin (ACTH) levels should be monitored to determine the optimal dose of steroid replacement as a somewhat higher dose than normal replacement therapy may be required (see PRECAUTIONS).

Mitotane Tissue Accumulation*:* LYSODREN can accumulate in fat tissue, which may result in prolongation of plasma half-life. Consequently, despite LYSODREN dose remaining constant, mitotane plasma levels may increase. Therefore, regular monitoring of mitotane plasma levels is necessary once the maintenance dose is established (e.g., monthly). Monitoring should continue after interruption of treatment (e.g., every two months), as prolonged release of mitotane can occur. Close monitoring of mitotane plasma levels is recommended when treating overweight patients and patients with recent weight loss (e.g., every two weeks) (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Bleeding Time*:* Prolonged bleeding time has been reported in patients treated with LYSODREN, which should be taken into account when surgery is considered.

Substances Metabolized through Cytochrome P450*:* Mitotane has a long half life (see PHARMACOKINETIC STUDIES OF LYSODREN IN HUMAN) and is an inducer of hepatic Cytochrome P-450 enzymes (see PRECAUTIONS). Enzyme induction is likely to persist after discontinuation of mitotane treatment. Medications metabolized by Cytochrome P-450 enzymes should be used with caution and dose adjusted as appropriate when coadministered with mitotane and for a period of approximately 6 months after discontinuation of mitotane treatment.

Pregnant Women: Animal reproduction studies have not been conducted with LYSODREN. Data from mitotane exposure in humans are limited. Abnormal pregnancy outcomes have been reported in patients exposed to mitotane during pregnancy. Treatment of women who are, or who may become pregnant, should be undertaken only after consideration of the benefits versus the possibility of harm to mother and child.

Women of childbearing potential must use effective contraception during treatment and after

discontinuation of treatment as long as mitotane plasma levels are detectable.

Nursing Women*:* Mitotane has been detected in breast milk. Because of the potential for serious adverse reactions in nursing infants from mitotane, mothers should be advised to discontinue nursing during LYSODREN therapy and after treatment discontinuation as long as mitotane plasma levels are detectable (see PHARMACOKINETIC STUDIES OF LYSODREN IN HUMANS for plasma terminal half life of mitotane).

Pediatrics (<18 years of age): The safety and efficacy of LYSODREN in patients <18 years of age have not been established. Neuropsychological impairment has been reported in children and adolescents receiving LYSODREN therapy (see *Central Nervous System Disorders*).

PRECAUTIONS

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

Effects on Ability to Drive and to Use Machines*:* Since CNS side effects can occur, ambulatory patients should be cautioned about driving, operating machinery, and other hazardous pursuits requiring mental and physical alertness (see ADVERSE EFFECTS).

***Substances Metabolized through Cytochrome P450*:** LYSODREN has been shown to have an inductive effect on cytochrome P450 enzymes, including CYP3A4 (see WARNING). LYSODREN should be given with caution to patients receiving drugs metabolized by this route.

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.

High-fat Meal*:* Pharmacokinetic data using various LYSODREN formulations suggest that administration with high-fat meal enhances absorption of mitotane.

Hormone-Binding Protein*:* Mitotane has been shown to increase plasma levels of hormone-binding proteins (e.g. sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin [CBG]), which should be taken into account when interpreting the results of hormonal assays. LYSODREN-induced increases in hormone-binding proteins may result in gynecomastia.

Medicinal Products Active on Central Nervous System*:* Since central nervous system toxicity has been associated with LYSODREN, coadministration of medicinal products with central nervous system action may have an additive effect (see WARNINGS and ADVERSE EFFECTS).

Carcinogenesis and Mutagenesis: The carcinogenic and mutagenic potentials of mitotane are unknown.

ADVERSE EFFECTS

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:

Gastrointestinal disturbances, which consisted of anorexia, nausea or vomiting, and in some cases diarrhea, occurred in about 80% of the patients.

Central nervous system side effects occurred in 40% of the patients. These consisted primarily of depression as manifested by lethargy and somnolence (25%), and dizziness or vertigo (15%).

Skin toxicity was observed in about 15% of the cases. These skin changes consisted primarily of transient skin rashes. In some instances, however, this side effect subsided while the patients were maintained on drug.

Infrequently occurring side effects involve the eye (visual blurring, diplopia, lens opacity, toxic retinopathy); the genito-urinary system (hematuria, hemorrhagic cystitis, and albuminuria); cardiovascular system (hypertension, orthostatic hypotension, and flushing); and some miscellaneous complaints including generalized aching, hyperpyrexia, and lowered protein bound iodine (PBI).

The following additional adverse reactions have been identified during postapproval use of LYSODREN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: leukopenia

Endocrine Disorders: growth retardation, hypothyroidism, thyroid disorder, sex hormone disturbances

Psychiatric Disorders: neuropsychological disturbance, confusional state

Nervous System Disorders: dysarthria, headache, ataxia, mental impairment

Eye Disorders: maculopathy

Hepatobiliary Disorders: hepatitis, hepatic enzymes increased

Reproductive System and Breast Disorders: gynecomastia, ovarian macrocyst

General Disorders and Administration Site Conditions: asthenia

Investigations: bleeding time prolonged, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, blood uric acid decreased, blood cholesterol increased, blood triglycerides increased. blood androstenedione decreased (in females), blood testosterone decreased (in females), sex hormone binding globulin increased, blood free testosterone decreased (in males)

Ovarian macrocysts

Non-malignant ovarian macrocysts (pelvic pain, bleeding) have been observed in pre-menopausal women (see WARNINGS).

Sex hormone disturbances

The following sex hormone disturbances have occurred in patients treated with mitotane: decreased blood androstenedione and decreased blood testosterone in females, increased sex hormone binding globulin in females and males, decreased blood free testosterone in males.

ANIMAL STUDIES

Dogs were used for much of the experimental work with LYSODREN (1). Doses as low as 4 mg/kg/day may produce some effects upon the canine adrenals. However, most of the data suggest that toxicity occurs between 80-200 mg/kg/day, primarily as a result of LYSODREN'S effect upon the adrenals. At doses of 100 mg/kg and higher of LYSODREN, deaths occurred in some of the dogs after two to four weeks of administration.

The primary action of LYSODREN is upon the adrenal cortex. The toxicity observed in animals appears to result from suppression of the activity of the adrenal cortex. The production of adrenal steroids has been shown to be reduced in most of the studies.

A toxicity study was conducted in rats at doses as high as 300 mg/kg/day for 28 days. There were no deaths nor was there any evidence of organ changes in these animals. In this study even the adrenal cortex showed no evidence of change, indicating that the rodent appears to be highly resistant to LYSODREN.

In both dogs and rats, there was a dose-related rise in alkaline phosphatase. In dogs, there were signs of histological changes in the liver at the high doses (50-100 mg/kg/day).

A dose of 300 mg/kg/day administered to guinea pigs resulted in deaths in one of three animals and a reduction in cortisol levels. Death was probably due to adrenal insufficiency (2).

PHARMACOKINETIC STUDIES OF LYSODREN IN HUMANS

One study (3) with adrenal carcinoma patients indicated that about 40% of oral LYSODREN was absorbed, and approximately 10% was recovered in the urine as a water-soluble metabolite. A small amount was excreted in the bile and the balance was apparently stored in the tissues. When administered parenterally, approximately 25% of the dose was found in the urine as a water-soluble metabolite.

Plasma concentrations of mitotane were determined during and following administration of LYSODREN. Both unchanged drug and a metabolite were measured. The levels in patients

receiving doses from 5-15 grams per day varied from 7-90 micrograms/ml of unchanged LYSODREN and 29-54 micrograms/ml of the metabolite.

Following discontinuation of the drug, blood levels fell, but persisted for several weeks due to the long terminal elimination half-life of mitotane (median 53 days; range 18-159 days). In most patients blood levels became undetectable after six to nine weeks. In one patient who had received a total of 1900 grams of LYSODREN, high blood levels were found ten weeks after stopping the drug. Autopsy data have provided evidence that LYSODREN is found in most tissues of the body. Fat tissues were the primary site of storage. In one patient a very large number of tissues were examined and the drug was found in essentially every tissue.

LYSODREN appears to be converted, in part, to a water-soluble metabolite. This material has not been characterized, but is only found in the urine and blood of patients receiving LYSODREN. Examination of bile was made and found to contain no unchanged LYSODREN. There was metabolite in the bile, and this would indicate that biliary excretion is a significant route of removal of this metabolite from the body.

CLINICAL STUDIES

Hutter and Kayhoe (4) reported on the clinical features and the results of LYSODREN treatment of 138 patients with adrenal cortical carcinoma, and compared their findings with 48 treated patients previously reported in the literature. Subsequent to their report, 115 patients given drug were studied.

There is no evidence of a cure as a consequence of the administration of LYSODREN. A number of patients have been treated intermittently, treatment being restarted when severe symptoms reappear. 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 would be the best approach.

A substantial percentage of the patients treated showed signs of adrenal insufficiency. It therefore appears necessary to watch for and institute steroid replacement in those patients. It has been shown that metabolism of exogenous steroids is modified and consequently somewhat higher doses than just replacement therapy may be required.

There was significant reduction in tumour mass following LYSODREN administration in about 50%, and a significant reduction in elevated steroid excretion in about 80% of the evaluable patients studied to date (4). Clinical effectiveness can be shown by reduction in tumor mass, reduction in pain, weakness or anorexia, and reduction of steroid symptoms.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control

Centre.

LYSODREN overdose may lead to severe central nervous system impairment, especially if mitotane plasma levels are above 20 mg/L (see WARNINGS). No proven antidotes have been established for LYSODREN overdose. The patient should be followed closely. Given the long half-life (see PHARMACOKINETIC STUDIES OF LYSODREN IN HUMAN) and the lipophilic nature of mitotane, it may take weeks to return to normal. Other effects should be treated symptomatically. Because of its lipophilic nature, mitotane is not likely to be dialysable.

It is recommended that the frequency of mitotane plasma level monitoring be increased (e.g. every two weeks) in patients at risk of overdose (e.g. patients with hepatic impairment, obese patients, or patients with a recent weight loss) (see WARNINGS).

DOSAGE AND ADMINISTRATION

Two dosage regimens may be used. The patient may be started on 2-6 g a day, in divided doses q.i.d. or t.i.d. and the dosage increased incrementally to as much drug as can be tolerated, preferably arriving at 8-10 g or more (see WARNINGS for plasma monitoring).

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 within the therapeutic range until adverse reactions interfere.

Experience has shown that the maximum tolerated dose (MTD) will vary from 2-16 g per day, but has usually been 8-10 g per day. The highest doses used in the studies to date were 18-19 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 three months at the maximum tolerated dose, the case may be considered a clinical failure. However, 10% of the patients who showed a measurable response required more than three months at the MTD.

Early diagnosis and prompt institution of treatment improve the probability of a positive clinical response.

Care must be taken whenever handling cytostatic products. Always take steps to prevent exposure.

To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing LYSODREN tablets. This includes all handling activities in clinical settings, pharmacies, storerooms and home healthcare settings, including during unpacking and inspection,

transport within a facility and dose preparation and administration.

LYSODREN tablets should not be crushed. Personnel should avoid exposure to crushed and/or broken tablets. If contact with broken tablets occurs, wash immediately and thoroughly.

Procedures for proper handling and disposal of anti-cancer drugs should be considered.

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STORAGE

LYSODREN tablets may be stored at room temperature (15 - 30°C).

HOW SUPPLIED

LYSODREN is available as a 500 mg one-half inch, biconvex, round compressed white tablet in bottles of 100. They are bisected on one side and impressed with “BL” over “L1" on the other side.

This document plus the full product monograph, prepared for health professionals can be found at: http://www.hra-pharma.com.

BIBLIOGRAPHY

1. a) Nelson, A.A., and G. Woodward: Archives of Pathology 48: 387, 1949.

   b) Nichols, J: "Studies on an Adrenal Cortical Inhibitor", Pg. 83, The Adrenal Cortex, Harper and Row, Scranton, Pa. 1961.

2. Kupfer, D., et al.: Life Sciences 3: 959, 1964.
3. Moy, R.H.: J. Lab. Clin. Med. 58: 296, 1961.
4. Hutter, A.M. and D.E. Kahoe: Amer. J. Med. 41: 572, 581, 1966.
5. Moolenaar AJ et al. Blood levels of o,p'-DDD following administration in various vehicles after a single dose and during long-term treatment. *Cancer Chemotherapy and Pharmacology* 1981;7:51-54