PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrLYSODREN®

Mitotane tablets
Tablets, 500 mg, oral administration

Antineoplastic Agent

HRA Pharma Rare Diseases
200 Avenue de Paris
Châtillon, France 92320

Date of Initial Authorization:
December 31, 1979

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LYSODREN® (mitotane tablets) is indicated for:

- The treatment of inoperable adrenocortical carcinoma of both functional and non-functional type.

1.1 Pediatrics (<18 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of LYSODREN in patients <18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use. Neuropsychological impairment has been reported in children and adolescents receiving LYSODREN therapy (see 7 WARNINGS AND PRECAUTIONS, Neurologic section).

1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

- LYSODREN is contraindicated in patients with known hypersensitivity to mitotane or any excipients. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Lactation (see 7 WARNINGS AND PRECAUTIONS)
- Concomitant use with spironolactone (see 9 DRUG INTERACTIONS)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Severe neurologic toxicity can occur with mitotane plasma levels above 20 mg/L, therefore this threshold should not be exceeded. Mitotane plasma concentrations should be measured at frequent intervals (see 7 WARNINGS AND PRECAUTIONS, Neurologic section).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

Before Initiating Treatment: All possible tumour tissue should be surgically removed from large metastatic masses before LYSODREN administration is instituted (see 7 WARNINGS AND PRECAUTIONS).

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. No information on the use of mitotane in patients with hepatic impairment was provided to Health Canada. The use of mitotane in patients with severe hepatic

impairment is not recommended. If a decision is made to use mitotane in patients with mild or moderate hepatic impairment, liver function and mitotane plasma levels should be regularly monitored in these patients.

Renal Impairment: There are insufficient data to support the use of mitotane in patients with renal impairment. Biliary excretion is the major elimination pathway of mitotane, however renal elimination also plays an important role. Therefore, the use of mitotane in patients with severe renal impairment is not recommended. If a decision is made to use mitotane in patients with mild or moderate renal impairment, mitotane plasma levels should be regularly monitored in these patients.

4.2 Recommended Dose and Dosage Adjustment

Treatment in adults should be started with 2 - 3 g mitotane per day and increased progressively (e.g., at two week-intervals) until mitotane plasma levels reach the therapeutic window 14 – 20 mg/L.

If it is urgent to control Cushing's symptoms in highly symptomatic patients, higher starting doses between 4 - 6 g per day could be necessary and daily dose increased more rapidly (e.g., every week). A starting dose higher than 6 g/day is generally not recommended.

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.

Health Canada has not authorized and indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics).

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.

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 after each dose adjustment and at

frequent intervals (e.g., every two weeks), until the target concentration range is reached, usually within 3 to 5 months. Monitoring should be more frequent (e.g., every week) when a high starting dose has been used. It should be taken into account that dose adjustments do not produce immediate changes in plasma levels of mitotane. In addition, because of tissue accumulation, 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 (14 - 20 mg/L). 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.

4.4 Administration

The total daily dose may be divided in two or three doses according to patient's convenience. Tablets should be taken with a glass of water during meals containing fat-rich food.

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.

4.5 Missed dose

In case of missed dose, the next dose should be taken as scheduled. A double dose should not be taken.

5 OVERDOSAGE

LYSODREN overdose may lead to severe central nervous system impairment (i.e., dizziness, cognitive disorder, speech disorder, disturbance in attention, memory impairment, balance disorder), especially if mitotane plasma levels are above 20 mg/L (see 7 WARNINGS AND PRECAUTIONS). No proven antidotes have been established for LYSODREN overdose. Temporary interruption of LYSODREN should be considered. The patient should be followed closely, taking into account that the central nervous system impairment may or may not be reversible after discontinuation of LYSODREN. Given the long half-life (see 10.3 Pharmacokinetics) 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 renal or hepatic impairment, obese patients, or patients with a recent weight loss) (see 7 WARNINGS AND PRECAUTIONS).

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 500 mg	Colloidal silicon dioxide, corn starch, microcrystalline cellulose, polyethylene glycol

Description

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.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

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.

Shock, Severe Trauma and infection

LYSODREN should be temporarily discontinued immediately following shock, severe trauma or infection, 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. Because of an increased risk of acute adrenocortical insufficiency, patients should be instructed to contact their physician immediately if injury, infection, or any other concomitant illness occurs.

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 highly recommended when treating overweight patients and patients with recent weight loss (e.g., every two weeks) (see 5 OVERDOSAGE).

Carcinogenesis and Mutagenesis

The carcinogenic and mutagenic potentials of mitotane are unknown.

Cardiovascular

LYSODREN should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities. For patients with risk factors for QT-interval prolongation, regular ECG monitoring is recommended.

Driving and Operating Machinery

Since LYSODREN may cause dizziness and sedation, patients should not drive or operate machinery, or other hazardous pursuits requiring mental and physical alertness, until these effects have passed (see 8 ADVERSE REACTIONS).

Endocrine and Metabolism

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

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. Glucocorticoid insufficiency is more frequent, but mineralocorticoid insufficiency may also be associated and the steroid substitution may need to be adapted accordingly.

Mitotane has a long half life (see 10.3 Pharmacokinetics) and is an inducer of hepatic Cytochrome P-450 enzymes. 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 (see 9.4 Drug-Drug Interactions).

Hypogonadism: Hypogonadism in males (with symptoms such as gynaecomastia, libido decreased, erectile dysfunction, fertility disorders) has been described in patients treated with LYSODREN.

Patients with severe Cushing's syndrome: Severe Cushing's syndrome is known to increase the risk of opportunistic infections, such as Pneumocystis jirovecii pneumonia, due to immunosuppression and anti-inflammatory effect of hypercortisolism. Generally, infection must be anticipated in such patients and careful management is warranted. Initiation of an appropriate prophylactic treatment may be considered.

Hematologic

All blood cells can be affected with mitotane treatment. Leucopenia (including neutropenia), anemia and thrombocytopenia have been reported frequently during mitotane treatment (see 8 ADVERSE

REACTIONS). Red blood cell, white blood cell and platelet counts should be monitored during mitotane treatment.

Hepatic/Biliary/Pancreatic

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.

Hepatotoxicity has been observed in patients treated with mitotane. Cases of liver damage (hepatocellular, cholestatic and mixed) and autoimmune hepatitis were observed. Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin and alkaline phosphatase [ALP] levels) should be periodically monitored, especially during the first months of treatment or when it is necessary to increase the dose. If AST and/or ALT are increased >5 ULN, or ALP or bilirubin > 2 ULN, there is risk of liver injury/failure. In this case, LYSODREN treatment should be interrupted and should be restarted at a lower dose. Treatment can be resumed at physician's discretion depending on the severity of the event as well as the patient's clinical condition.

Monitoring and Laboratory Tests

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.

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, mitotane plasma levels should be monitored regularly (e.g. monthly) once the maintenance dose has been reached.

Patients on coumarin type anticoagulants should be closely monitored for a change in anticoagulation dosage requirements when administering LYSODREN.

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be periodically monitored, especially during the first months of treatment or when it is necessary to increase the dose (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Red blood cell, white blood cell and platelet counts should be monitored during mitotane treatment (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

Regardless of LYSODREN dosage, triglycerides should be monitored regularly especially in patients with or at risk of dyslipidemia (such as metabolic syndrome, alcohol abuse, high fat diet). Triglyceride-lowering therapy and discontinuation of LYSODREN may be considered in case of severe hypertriglyceridemia as it is a potential cause of acute pancreatitis.

Substances metabolised through cytochrome P450 and particularly cytochrome 3A4: Mitotane is a hepatic enzyme inducer and it should be used with caution in case of concomitant use of medicinal products influenced by hepatic metabolism.

Neurologic

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.

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 8 ADVERSE REACTIONS).

Peri-Operative Considerations

Prolonged bleeding time has been reported in patients treated with LYSODREN, which should be taken into account when surgery is considered. In some patients, bleeding time may be normal but with pathologic adenosine diphosphate (ADP)-induced platelet aggregation. Routine *in vitro* bleeding time is not suitable to detect this platelet defect and to assess bleeding risk. ADP-induced platelet aggregometry testing prior to surgery is recommended to determine mitotane-induced bleeding risk.

Psychiatric

Caution is advised when prescribing LYSODREN to patients with a history of depression or those at risk of developing depression.

Renal

LYSODREN should be administered with care to patients with renal impairment, since the metabolism of LYSODREN may be interfered with and the drug may accumulate.

Reproductive Health: Female and Male Potential

Non-malignant ovarian macrocysts, often bilateral and multiple, have been observed with higher incidence in this population. The ovarian macrocysts may be symptomatic (e.g., pelvic pain or discomfort, vaginal bleeding or menstrual disorders) or asymptomatic. 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 8 ADVERSE REACTIONS). Periodic ovarian ultrasound monitoring is recommended in premenopausal women treated with LYSODREN.

Women of childbearing potential must use effective contraception during treatment and after discontinuation of treatment as long as mitotane plasma levels are detectable, which may require several months.

Mitotane has been shown to increase plasma levels of hormone binding proteins (e.g. sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin [CBG]). LYSODREN-induced increases in hormone-binding proteins may result in gynecomastia.

- **Fertility**
  No data are available.

- **Function**
  No data are available.

- **Teratogenic Risk**
  No data are available.

7.1 Special Populations

7.1.1 Pregnant Women

Data, based on a limited number of exposed pregnancies, indicate abnormalities on the foetal adrenals after exposure to mitotane. Mitotane has been detected in umbilical cord blood. Pregnant women should be advised of a potential risk to the foetus.

Animal reproduction studies have not been conducted with mitotane. Animal studies with similar substances have shown reproductive toxicity.

LYSODREN is not recommended during pregnancy and in women of childbearing potential not using contraception.

Women of childbearing potential:
Women of childbearing potential must use an effective contraception during treatment and after discontinuation of treatment as long as mitotane plasma levels are detectable. The prolonged elimination of mitotane from the body after discontinuation of Lysodren should be considered.

7.1.2 Breast-feeding

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 10.3 Pharmacokinetics).

7.1.3 Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of LYSODREN in patients <18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use. Neuropsychological impairment has been reported in children and adolescents receiving LYSODREN therapy (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

7.1.4 Geriatrics

No data are available.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

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

Neurologic

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

Skin

Skin toxicity was observed in about 15% of the cases. These skin changes consisted primarily of transient skin rashes which do not seem to be dose related. In some instances, however, this side effect subsided while the patients were maintained on drug.

Ovarian macrocysts

Non-malignant ovarian macrocysts (pelvic pain, bleeding or asymptomatic) have been observed in pre-menopausal women (see 7 WARNINGS AND PRECAUTIONS).

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, hypogonadism in males.

Very rare reactions

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

8.5 Post-Market Adverse Reactions

The following additional adverse reactions have been identified during post approval 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: anemia, leukopenia, thrombocytopenia

Endocrine Disorders: adrenal insufficiency, growth retardation, hypothyroidism, thyroid disorder, sex hormone disturbances, hypogonadism (in males)

Eye Disorders: maculopathy

Gastrointestinal disorders: mucosal inflammation, epigastric discomfort, dysgeusia, dyspepsia

General Disorders and Administration Site Conditions: asthenia

Immune system disorders: hypersensitivity reactions

Infections and infestations: Opportunistic infection

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), blood free testosterone decreased (in males), sex hormone binding globulin increased, corticosteroid binding globulin increased, thyroxin binding globulin increased

Hepatobiliary Disorders: hepatitis, hepatic enzymes increased, liver injury (hepatocellular / cholestatic / mixed)

Metabolism and nutrition disorders: hypercholesterolemia, hypertriglyceridaemia, hypouricaemia

Muscoloskeletal and connective tissue disorders: muscular weakness

Nervous System Disorders: dysarthria, headache, ataxia, mental impairment, paresthesia / polyneuropathy, movement disorder, balance disorder

Psychiatric Disorders: neuropsychological disturbance, confusion

Renal and urinary disorders: haemorrhagic cystitis, haematuria, proteinuria

Reproductive System and Breast Disorders: gynecomastia, ovarian macrocysts

Respiratory, thoracic and mediastinal disorders: dyspnea

Skin and subcutaneous tissue disorders: pruritus

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Mitotane has a long half life (see 10.3 Pharmacokinetics) and is an inducer of hepatic Cytochrome P-450 enzymes. 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.

9.3 Drug-Behavioural Interactions

No data available.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Drug	Source of Evidence	Effect	Clinical comment
Drugs metabolized by CYP3A4, such as etoposide, midazolam and sunitinib	C	↓ conc.	LYSODREN has been shown to have an inductive effect on cytochrome P450 enzymes, including CYP3A4. LYSODREN should be given with caution to patients receiving drugs metabolized by this route. Medications metabolized by Cytochrome P-450 enzymes should be used with caution and dose adjusted as appropriate when coadministered with mitotane. Enzyme induction is likely to persist after discontinuation of mitotane treatment. A pharmacokinetic interaction between mitotane and etoposide has been reported resulting in accelerated clearance of etoposide (2-fold higher) and might contribute to a reduced efficacy in ACC patients treated concomitantly with mitotane and etoposide.
Coumarin-type anticoagulants, such as warfarin	C	↓ conc.	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.
Drugs with central nervous system action	T	↑ toxicity	Since central nervous system toxicity has been associated with LYSODREN, coadministration of medicinal products with central nervous system action may have an additive effect.
Spironolactone	T	↓ effect	LYSODREN must not be given in combination with spironolactone, since this substance may block the action of mitotane.
Hormone binding protein, such as sex hormone-binding globulin (SHBG) and corticosteroid-binding globulin (CBG)	C	↑ conc.	Mitotane has been shown to increase plasma levels of hormone binding proteins. This should be taken into account when interpreting the results of hormonal assays and may result in gynaecomastia.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of 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.

10.3 Pharmacokinetics

Absorption:
One study with adrenal carcinoma patients indicated that about 40% of oral LYSODREN was absorbed.

Distribution:
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.

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.

Metabolism:
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.

Elimination:
About 10% of oral LYSODREN was recovered in the urine as a water-soluble metabolite. A small amount of oral LYSODREN 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.

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.

Special Populations and Conditions

Hepatic Insufficiency: 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 (see 7 WARNINGS AND PRECAUTIONS).

Renal Insufficiency: There is no experience in the use of mitotane in patients with renal impairment, so data are insufficient to give a dose recommendation in this group. Biliary excretion is the major elimination pathway of mitotane, however renal elimination also plays an important role. Therefore, the use of mitotane in patients with severe renal impairment is not recommended and, in cases of mild to moderate renal impairment, caution should be exercised. Monitoring of mitotane plasma levels is specially recommended in these patients (see 7 WARNINGS AND PRECAUTIONS).

Obesity: LYSODREN can accumulate in fat tissue, which may result in prolongation of plasma half-life. Close monitoring of mitotane plasma levels is recommended when treating overweight patients and patients with recent weight loss (see 7 WARNINGS AND PRECAUTIONS).

11 STORAGE, STABILITY AND DISPOSAL

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

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

12 SPECIAL HANDLING INSTRUCTIONS

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.

PART II: SCIENTIFIC INFORMATION

13 PART II: SCIENTIFIC INFORMATION

Drug Substance

Proper name: mitotane

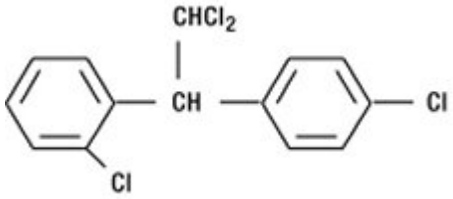
Chemical name: o,p'-DDD

1, 1 dichloro-2(o-chlorophenyl)-2-(p-chlorophenyl) ethane

Molecular formula and molecular mass:

$C_{14}H_{10}Cl_4$ - 320.04 g/mol

Structural formula:



Physicochemical properties:

Mitotane is a white granular solid composed of clear colorless crystals.

Mitotane is tasteless and has a slight pleasant aromatic odor.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Hutter and Kayhoe (1966)

This study 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.

14.2 Study Results

Hutter and Kayhoe (1966)

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.

Clinical effectiveness can be shown by reduction in tumor mass, reduction in pain, weakness or anorexia, and reduction of steroid symptoms.

16 NON-CLINICAL TOXICOLOGY

Dogs were used for much of the experimental work with LYSODREN. 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr LYSODREN®
Mitotane Tablets

Read this carefully before you start taking **LYSODREN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LYSODREN**.

Serious Warnings and Precautions
At high doses, LYSODREN can cause severe brain damage and problems with how the brain works. This is called neurologic toxicity. If you are taking high doses of LYSODREN, your healthcare professional will monitor your behaviour and how your brain is working.

What is LYSODREN used for?

LYSODREN is used to treat a type of cancer that affects the adrenal gland. This cancer is called adrenocortical carcinoma of functional or non-functional type. Patients who take LYSODREN have a cancer that cannot be removed by surgery.

How does LYSODREN work?

Mitotane is the active ingredient in LYSODREN. The way it works is not exactly known. However, it seems to affect how steroids are broken down. As well, it seems to stop the activity of the adrenal cortex. This is where the cancer is located.

What are the ingredients in LYSODREN?

Medicinal ingredients: mitotane

Non-medicinal ingredients: colloidal silicon dioxide, corn starch, microcrystalline cellulose, polyethylene glycol

LYSODREN comes in the following dosage forms:

Tablet: 500 mg

Do not use LYSODREN if:

- you are allergic to mitotane or to any other ingredients in this medicine
- you are breastfeeding
- you take a medication containing spironolactone

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LYSODREN. Talk about any health conditions or problems you may have, including if you:

- have recently experienced a shock, severe trauma or infection
- have a condition called Cushing's syndrome. You may be at a higher risk of experiencing infections.
- have or have had liver problems
- have or have had kidney problems
- have or are at risk of having heart problems
- have a history of depression or are at risk of developing depression
- take medication that acts on your central nervous system
- take medication that makes your blood thinner, such as warfarin
- are overweight or obese
- have recently lost weight
- have recently had or plan to have a surgery
- have metastases. This means that your cancer has spread outside of the adrenal gland.

Other warnings you should know about:

Adrenal insufficiency can happen with LYSODREN treatment. This is when the adrenal glands don't make enough of the hormone cortisol. If you experience adrenal insufficiency, you may need to take other medicines.

Cysts on the ovaries (called **ovarian macrocysts**) are possible in women treated with LYSODREN. If you are a woman and you have unusual vaginal bleeding or pain in the pelvis, contact your healthcare professional. Ovarian macrocysts may also produce no symptoms. If you are pre-menopausal, you may need ultrasound scans of your ovaries.

Female patients – Pregnancy and breastfeeding:

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- Avoid becoming pregnant while you are taking LYSODREN. It may harm your unborn baby.
- If you are able to get pregnant, you must use effective birth control during your treatment. You must also use this birth control after stopping LYSODREN. Your healthcare professional will do blood tests to determine when you can stop using this birth control. It will depend on the results of these tests.
- Do not breastfeed while you are taking LYSODREN. Mitotane may pass into your breastmilk. Your healthcare professional will tell you when you can start breastfeeding. It will depend on blood test results.

Driving and operating machines: LYSODREN can affect your brain and nervous system. This may affect your ability to drive and use machines. If you feel tired or dizzy, do not drive or use machines. Ask your healthcare professional for advice.

Blood tests:

- Taking LYSODREN can affect your blood cells

- Your healthcare professional will do blood tests during your treatment. These tests will be done regularly (e.g. monthly).
    - If you are overweight or have recently lost weight, suffer from metabolic syndrome, abuse alcohol or eat a high fat diet these tests may be done every 2 weeks.
    - If you are taking blood thinners like warfarin, you will have regular blood tests to see if there are changes in how clots form in your blood.
- Tell your healthcare professional that you are taking LYSODREN each time you have blood work. It can affect some blood tests.

Liver problems:

- Taking LYSODREN can cause liver damage or autoimmune hepatitis. Autoimmune hepatitis occurs when your body's immune system turns against the liver cells.
- Liver function tests will be completed periodically during your treatment. Especially during the first months of treatment or when your dose is increased.

Heart rhythm problems:

- Taking LYSODREN can cause heart rhythm problems called QT prolongation.
- You are at a higher risk if you have heart problems, have an electrolyte imbalance, are dehydrated or experience a lot of vomiting, diarrhea, or sweating, or if you take medication that can affect your heart rhythm or electrolyte balance.
- Your healthcare professional may monitor your heart rhythm with ECG tests periodically during your treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LYSODREN:

- steroid replacement therapy (such as cortisol, hydrocortisone, prednisolone or dexamethasone)
- medicine containing spironolactone
- medicines used as blood thinners like warfarin
- the anti-cancer drugs etoposide and sunitinib
- medicines that act on the central nervous system
- midazolam, used before surgery to make you drowsy and reduce anxiety

How to take LYSODREN:

- This medicine should not be handled by persons other than the patient and his/her caregivers, and especially not by pregnant women. Always wear gloves when handling the LYSODREN bottle and tablets. If you touch broken tablets, wash thoroughly with soap and water right away.
- Do not crush, break, split or cut the tablets.
- Swallow the tablets whole with a glass of water.
- Take your LYSODREN with a meal that contains foods high in fat like milk, chocolate or oil.

Usual dose:

Your healthcare professional will tell you how much and how often to take LYSODREN. Do not take more than you are told.

Overdose:

Too much LYSODREN can cause severe brain damage that can cause dizziness or problems with memory, speech, attention or balance.

If you think you, or a person you are caring for, have taken too much LYSODREN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, skip it. Take your next dose as per your usual schedule. Do not take two doses at once to make for the missed dose.

What are possible side effects from using LYSODREN?

These are not all the possible side effects you may have when taking LYSODREN. If you experience any side effects not listed here, tell your healthcare professional.

- Skin rashes, itching
- Blood in urine
- Blurred or double vision
- Body aches
- Delayed growth
- Depression
- Diarrhea
- Dizziness, vertigo, confusional state
- Fever
- Flushing
- Growth of breast in men
- High blood pressure
- Infections
- Inflammation (swelling, heat, pain) of mucosa, upper abdominal pain, indigestion, taste disorder
- Lethargy (lack of energy), fatigue, weakness, drowsiness
- Loss of appetite
- Mental impairment (such as memory loss, concentration difficulty)
- Nausea, vomiting
- Quick drop of blood pressure when you stand up, that can cause dizziness, lightheadedness or fainting
- Sex hormones disturbances in males and females
- Shortness of breath

- Tingling or numbness in arms, hands, legs or feet

LYSODREN can cause abnormal blood test results. Your healthcare professional will conduct blood tests during your treatment and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE/UNKNOWN			
Adrenal insufficiency (adrenal glands don't make enough cortisol): fatigue, muscle weakness, loss of appetite, weight loss, abdominal pain, nausea, vomiting			x
Albuminuria (proteins in urine): swelling of the ankles, hands, abdomen or the face		x	
Allergic reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			x
Hemorrhagic cystitis (bladder inflammation): pain, discomfort, or burning when urinating, blood in urine		x	
Hepatitis (inflammation of the liver), **liver damage:** fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, light-colored stools, joint pain, jaundice		x	
Hypogonadism in males (the body doesn't make enough testosterone)**:** enlarged breast, libido decreased, erectile dysfunction, fertility disorders		x	
Hypothyroidism (underactive thyroid gland): fatigue, sensitivity to cold, constipation, dry skin, weight gain, swelling of the face, voice changed, muscle weakness		x	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Lens opacity (clouding of the lens of the eye): loss of vision, blurry or double vision, halos around light, trouble with bright lights, faded colors		x	
Leukopenia (low white blood cells): mouth or skin sores, sore throat, cough, trouble breathing, feeling light-headed, fever, chills, sweating, body aches		x	
Anemia (a decrease of red blood cells): skin pallor and fatigue		x	
Thrombocytopenia (a decrease in blood platelets): bruising and bleeding		x	
Maculopathy (a disease of the centre part of the retina called the macula): loss of vision, image distortion, central spot in vision		x	
Neurologic toxicity and brain damage: severe headache, difficulty speaking or slurred speech, loss of muscle coordination, loss of balance, movement and coordination disorders, mental impairment, confusion			x
Ovarian macrocysts (fluid-filled sacs on the ovaries): menstrual irregularity, bloating, lower abdominal / pelvic pain, lower back pain, vaginal bleeding		x	
Toxic retinopathy: loss of vision, diminished color vision, trouble reading		x	
Bleeding time prolonged in case of injury or surgery		x	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store in the original packaging at room temperature (15-30°C).

Keep out of sight and reach of children.

Do not use after the expiry date which is stated on the carton and the bottle after EXP.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

If you want more information about LYSODREN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html or the manufacturer's website (www.hra-pharma-rare-diseases.com).

This leaflet was prepared by HRA Pharma Rare Diseases.

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