**Drug Monograph**



## A - Drug Name

# mitotane

**COMMON TRADE NAME(S):** Lysodren®

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## B - Mechanism of Action and Pharmacokinetics

Mitotane is a derivative of the insecticide DDT and causes direct necrosis and atrophy of the adrenal cortex; it also modifies the peripheral metabolism of steroids.

| | | |
|---|---|---|
| Absorption | Oral absorption: 35-40%<br><br>Fat-rich foods increase absorption of mitotane. Peak plasma concentrations occur 3-5 hours after a single oral dose of mitotane. Target plasma concentrations (14-20 mg/L) usually reached within 3 to 5 months. | |
| Distribution | Found in all body tissues, but primarily in fat. Slow release from fat and other tissues. | |
| | Cross blood brain barrier? | Mitotane: no<br>Metabolite: trace |
| | Cross blood brain barrier? | No information found |
| Metabolism | Metabolized in the liver or other tissues. o,p'-DDA (major), o,p'-DDE (minor) and hydroxylated o,p'-DDA metabolites have been identified. | |
| | Active metabolites | acyl chloride intermediate, o,p'-DDA, o,p'-DDE |

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| Elimination | Bile appears to be a significant route of excretion of metabolites. Mitotane levels persist for several weeks after drug discontinuation, due to slow release from fat or other tissues. | |
| | Urine | 10% as metabolites in 24 hours |
| | Bile | 15% as metabolites in 24 hours |
| | Half-life | 18 - 159 days |

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## C - Indications and Status

**Health Canada Approvals:**

- Inoperable adrenocortical carcinoma (ACC); functional and non-functional

**Other Uses:**

- Adjuvant treatment of adrenocortical carcinoma

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## D - Adverse Effects

**Emetogenic Potential:** Moderate – Consider prophylaxis daily

**Extravasation Potential:** Not applicable

| ORGAN SITE | SIDE EFFECT* (%) | ONSET** |
|---|---|---|
| Cardiovascular | Flushing (infrequent) | E |
| | Hypertension (infrequent) | E |
| | Hypotension (orthostatic; infrequent) | E |
| Dermatological | Rash (15%) | E |
| Gastrointestinal | Anorexia (80%) | E |
| | Diarrhea (80%) | E |
| | Nausea, vomiting (80%) | E |

| | | |
|---|---|---|
| General | Fatigue (25%) | E D |
| Hematological | Myelosuppression (12%) | E |
| | Other Prolonged bleeding time (rare) | E |
| Hepatobiliary | Hepatitis (autoimmune; 7%) | E D |
| | ↑ LFTs (>10%, rarely severe) | E |
| Metabolic / Endocrine | Adrenal insufficiency (75-100%) | E |
| | Hyperlipidemia (>10%) | E |
| | Hypothyroidism (rare) | E |
| | Other Hypouricemia, growth retardation (infrequent) Gynecomastia (> 10%) | E D |
| Nervous System | Cognitive disturbance (>10%; may be severe) | E |
| | Dizziness (15%) (including vertigo) | E D |
| | Dysarthria (rare) | E |
| | Headache (also ataxia, confusion; rare) | E |
| | Paresthesia (>10%) | E |
| | Somnolence (25%) | E |
| Ophthalmic | Blurred vision (or double vision - infrequent) | E |
| | Retinopathy (also maculopathy, infrequent) | E |
| Renal | Proteinuria (infrequent) | D |
| Urinary | Hematuria (infrequent) | D |
| | Hemorrhagic Cystitis (infrequent) | D |

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Mitotane's main action is **adrenocortical suppression**. As such, glucocorticoid replacement, and sometimes mineralocorticoid replacement therapy is required. Free cortisol and corticotropin levels should be monitored to determine the optimal dose of steroid replacement therapy; higher than usual replacement doses may be required.

If **shock, severe trauma or infection** occurs, mitotane should be temporarily discontinued and steroids immediately given. When mitotane is discontinued, the steroid should be tapered slowly, but may need to be continued indefinitely. Patients should use a medical alert tag or bracelet warning of adrenal suppression.

**Gastrointestinal toxicity** occurs in 80% of patients and is reversible when the dose is reduced.

Skin **rashes** are usually transient and not dose-related.

**Adverse CNS effects** occur in 40% of patients, especially when levels are > 20 mg/L, and are manifested as lethargy, somnolence, dizziness, depression, irritability, confusion and tremors. More rare CNS side effects, consisting of speech difficulty, memory loss, ataxia and hallucinations, have been reported. Long-term use may cause brain damage or functional impairment.

Behavioral and neurological assessments should be performed periodically when continuous mitotane exceeds 2 years, especially when plasma levels are greater than 20 mg/L.

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## E - Dosing

Refer to protocol by which patient is being treated. Ideally, treatment should be started while the patient is hospitalized, and after debulking surgery has been performed (if applicable). Steroid replacement therapy may be required (e.g. glucocorticoid - cortisone acetate 25 mg qam and 12.5 mg qpm ±fludrocortisone (Florinef®) 0.1 mg daily for mineralocorticoid deficiency causing orthostatic hypotension).

If shock, severe trauma or infection occurs, mitotane should be temporarily discontinued and steroids immediately given. When mitotane is discontinued, the steroid should be tapered slowly, but may need to be continued indefinitely. Patients should use medical alert tag or bracelet warning of adrenal suppression.

### ***Adults:***

Oral: start at 2-6 g/day, in 3 or 4 divided doses, and then titrate (at 2 week intervals) up to 8-10 g /day. Maximum tolerated dose may vary from 2-16 g/day. Dose may be increased based on clinical response and patient tolerance.

Highest doses used in studies were 18-19 g/day. If available, mitotane levels should be monitored regularly to keep levels between 14-20 mg/L. Severe neurotoxicity may occur with levels > 20mg/L.

### ***Dosage with Toxicity:***

Mitotane has a long half life an accumulates in fat. Dose adjustments may not result in immediate improvement in drug related effects.

| Toxicity / Event | Dose |
|---|---|
| Severe trauma, stress or infection | Interrupt; start steroids |
| Myelosuppression | No dose adjustment required |
| Adrenal insufficiency | Use corticosteroid supplementation |
| Mild to moderate GI, skin or CNS toxicity | Decrease dose* or hold, depending on severity |
| Mitotane levels > 20 mg/L | Hold and monitor levels; restart when levels within therapeutic range |
| Grade 3 related non-hematologic toxicity | Hold, consider dose reduction* |
| Grade 4 related non-hematologic toxicity | Discontinue |

* reduce to maximum dose tolerated by patient

***Dosage with Hepatic Impairment:***

No specific dose adjustments found. Exercise caution in mild to moderate hepatic impairment (unless due to metastatic disease), as mitotane is mainly metabolized by the liver. Not recommended for use in patients with severe hepatic impairment.

***Dosage with Renal Impairment:***

No specific dose adjustments found. Exercise caution in mild to moderate renal impairment. Not recommended for use in patients with severe renal impairment. Mitotane is unlikely to be dialyzable in the case of an overdose.

***Dosage in the elderly:***

No specific dose adjustment found. Titrate dosage and monitor patient carefully; consider starting at the low end of the dosage range.

***Children:***

Safety and efficacy have not been formally established. Neuropsychological impairment and hypothyroidism have been reported.

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## F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- Swallow tablets whole; do not crush or chew.
- May be taken with or without food with a glass of water. Timing of the dose relative to meals must be consistent. Administration with a high fat meal enhances absorption.
- Consider steroid replacement.
- Patients should use medical alert tag or bracelet warning of adrenal suppression.

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## G - Special Precautions

**Contraindications:**

- Patients who have a hypersensitivity to this drug or any of its components
- Mitotane should be discontinued after severe shock, trauma or infection, and exogenous steroids administered

**Other Warnings/Precautions:**

- Large metastatic ACC tumours should be removed before starting mitotane, to minimize tumour infarction and hemorrhage due to the rapid action of the drug.
- Use with caution in patients with liver disease other than metastatic ACC.
- Prolonged bleeding time has been reported - Caution in patients undergoing invasive procedures
- Caution is required when driving or operating machinery. Avoid concurrent administration of other CNS depressants.
- Caution in obese patients and patients with rapid weight loss

**Pregnancy and Lactation:**

- Teratogenicity: Unknown
  Mitotane is not recommended for use in pregnancy; adverse pregnancy outcomes have been observed after drug exposure. Adequate contraception should be used by both sexes during

treatment, and for as long as mitotane levels are detectable, or for at least 6 months after the last dose (the long half-life of mitotane must be considered).

- Excretion into breast milk: Probable
  Breastfeeding is not recommended until mitotane levels are not detectable (or at least 6 months after last dose).
- Fertility effects: Unknown
  Effects on fertility have not be established; however, related compounds such as DDT are known to adversely affect fertility, pregnancy and development.

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## H - Interactions

Mitotane has a long half life and drug interactions are therefore possible for many weeks after the last dose.

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| Measurement of urinary adrenal steroids | false negative for cortisol secretion rate | Mitotane increases extra-adrenal metabolism of cortisol so less is excreted in urine | Obtain both urine and plasma levels of cortisol |
| Drug metabolized by CYP3A4 (barbituates, phenytoin, corticosteroids) | ↑ metabolism of these drugs | Mitotane induces hepatic microsomal enzyme oxidation system | Monitor pharmacological effects up to 6 months after last mitotane dose; adjust dose of glucocorticoid replacement, barbiturate or phenytoin as needed |
| CNS depressants | Enhanced CNS depression | Additive | Caution |
| Spironolactone | Blocks effects of mitotane | Uncertain | Avoid |
| Thyroid function test | ↓ in serum protein-bound iodine | Mitotane binds thyroxine-binding globulin | Resin triiodothyronine uptake tests are not affected. Free thyroxine concentrations apparently remain in the normal range |
| Warfarin | ↓ pharmacological response to warfarin | Enhanced metabolism of warfarin by hepatic microsomal enzyme | Monitor prothrombin times and adjust warfarin dose prn |

| | | | |
|---|---|---|---|
| | | oxidation system | whenever mitotane dose is started, changed or stopped |
| ↑ Hormone binding proteins (HBPs) | may effect interpretation of hormone assays | ↑ HBPs | Caution |
| Testosterone replacement | ↓ effectiveness | ↓ conversion to 5-alpha dihydrotestosterone via mitotane inhibition of 5-alpha reductase | Consider the use of 5-alpha reduced androgens for mitotane-induced male hyogonadism |

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## I - Recommended Clinical Monitoring

### Recommended Clinical Monitoring

| Monitor Type | Monitor Frequency |
|---|---|
| Observe for adrenal insufficiency | |
| Clinical CNS evaluation especially with long-term usage | |
| Regular clinical assessment of GI and skin toxicity, adrenal insufficiency, opthalmic and CNS effects | |

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

### Suggested Clinical Monitoring

| Monitor Type | Monitor Frequency |
|---|---|
| Urine test | periodic |
| Neurological assessments | Baseline and regular |
| Serum cortisol levels | Baseline and periodic |
| CBC | Baseline and regular |
| Liver function tests | Baseline and as clinically indicated |
| If mitotane plasma level testing is available and | |

| | |
|---|---|
| clinically necessary, consider levels q2 weeks after starting treatment, after each dose adjustment, in hepatic/renal impairment, obese patients or patients with recent weight loss; every 1 week monitoring if a high starting dose has been used. Monitor levels regularly (e.g. monthly) after reaching maintenance dose especially with toxicity and in obese patients. If treatment is interrupted, monitor levels q2 months. | |

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## K - References

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**June 2019** Updated emetic risk category.

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## L - Disclaimer

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