DRUG NAME: Mitotane

SYNONYM(S)[1]**:** o,p'-DDD

COMMON TRADE NAME(S): LYSODREN®

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Mitotane is described as an adrenal cytotoxic agent, although its exact mechanism of action is unknown. Mitotane directly suppresses the adrenal cortex, both with and without cellular destruction. Production of corticosteroids is inhibited and peripheral steroid metabolism is modified, leading to increased excretion of 17-hydroxycorticosteroids and 17-ketosteroids.[1-3] Mitotane is structurally related to the insecticide chlorophenothane (DDT).[2] Mitotane is an immunosuppressive agent.[1]

PHARMACOKINETICS:

Oral Absorption	35-40%[1,2,4]	
Distribution	distribution between plasma and tissues complete within 12 hours[2,4]; 20-30% stored in tissues, primarily in fat[1,4]; detected in most tissues	
	cross blood brain barrier? [2]	no; small amounts of metabolite detected in CSF
	volume of distribution	no information found
	plasma protein binding	no information found
Metabolism	converted partly to water-soluble metabolites o,p'-DDE and o,p'-DDA by liver[2,3,5]	
	active metabolite(s)	activity not characterized[1]
	inactive metabolite(s)	activity not characterized[1]
Excretion	blood levels persist several weeks or months due to slow release from tissues[1,2]; biliary excretion significant for metabolites	
	urine[1]	10-19% as water-soluble metabolites
	feces[1-3,6]	40-60% unchanged in stool, less if administered in milk or oil emulsion; 1-17% in bile, as metabolites; no unchanged drug in bile.
	terminal half life[2,7]	18-159 days
	clearance	no information found

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Adrenocortical carcinoma

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***Adrenal insufficiency*** develops in most patients.[1,2] Adrenal steroid replacement should begin at the start of treatment, as opposed to waiting for insufficiency to develop.[7,8] Steroid replacement should be continued for at

least two months after treatment is discontinued, and in some cases, if adrenal insufficiency persists, steroid replacement may be permanently required.[2,3,8,9] Higher than usual replacement doses may be necessary as mitotane affects the extra-adrenal metabolism of steroids.[2,3,10] Temporary withdrawal of mitotane is recommended following infection, shock, or severe trauma, accompanied by appropriate administration of exogenous glucocorticoids and mineralocorticoids.[1,7,11] It is advised that patients carry a wallet card, or wear a medical alert bracelet/tag, in case of emergency. Caregivers and emergency contacts should be made aware of mitotane use.[8]

- ***Liver disease*** may impair metabolism, causing accumulation of drug,[1] although routine dosage reduction is not considered necessary.[2]
- All possible tumour tissue from ***large metastatic masses*** should be surgically removed prior to treatment to minimize tumour infarction and hemorrhage, due to a rapid cytotoxic effect of therapy.[1,7]
- ***Brain damage and impairment of function*** has been associated with long-term continuous administration of high doses. Behavioural and neurological assessments are recommended at regular intervals for treatment exceeding two years.[1]

Carcinogenicity: no information found

Mutagenicity: no information found

Fertility: no information found

Pregnancy: FDA Pregnancy Category C.[7] There are no controlled studies in women or animals. Mitotane should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding is not recommended due to the potential secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[8,12]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	facial or periorbital swelling[2]
auditory/hearing	decreased hearing[2] (≤1%)
blood/bone marrow/ febrile neutropenia	leukopenia[2,13] (≤13%)
	thrombocytopenia[2] (≤1%)
cardiovascular (general)	flushing
	hypertension (≤1%)[7]
	orthostatic hypotension (≤1%)[7]
constitutional symptoms	***asthenia/fatigue***[2] (51%, severe 2%)[13]
	hyperpyrexia (≤1%)[7]
dermatology/skin	***maculopapular rash*** (12-15%)[2,4,7]; transient, not dose related[2,4]; see paragraph following **Side Effects** table
	urticaria[2]
endocrine	***adrenal insufficiency***[1,2] (≥10%); see statement in **Caution** section
	gynecomastia[2,14] (9%)[13]
	impotence[14]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
gastrointestinal	*emetogenic potential: low-moderate*[15]
	anorexia (24-57%)[4,7,13]; see paragraph following **Side Effects** table
	diarrhea (13-31%)[4,7,13]; see paragraph following **Side Effects** table
	nausea (39-55%)[4,7,13]; diminishes with continued use[8]; see paragraph following **Side Effects** table
	vomiting (37-55%)[4,7,13]; diminishes with continued use[8]; see paragraph following **Side Effects** table
metabolic/laboratory	albuminuria (≤1%)[7]
	alkaline phosphatase elevation[2,16] (up to 100%)
	AST/ALT elevation[2,13,16] (49%)[13]
	bilirubin elevation[2] (≤1%)
	estrogens, increase in urinary excretion[2]
	gamma-glutamyltransferase elevation[13,16] (85-100%, severe 15%)
	hypercholesterolemia, LDL and HDL[2,14,16] (1-10%); triglyceride levels not significantly affected[16]
	hyperprolactinemia, slight[16]
	hypouricemia[2] (1-10%); within 1 day, maximal in 5-10 days
	protein bound iodine reduction[7]
	serum cortisol reduction[16]
	serum lipoprotein elevation[2]
	serum thyroxin reduction; TSH and radioactive iodine uptake normal[14,16]
	testosterone (free), reduced in males[16]
musculoskeletal	muscle tremor (3%)[4,7]
	weakness (12%)[4,7]
neurology	ataxia[13] (15%, severe 9%); see paragraph following **Side Effects** table
	confusion (3-23%, severe 4%)[1,4,13]; see paragraph following **Side Effects** table
	CNS depression (25-32%)[1,4,7]; see paragraph following **Side Effects** table
	dizziness/vertigo (15-28%, severe 9%)[1,4,13]; see paragraph following **Side Effects** table
	headache (5%)[1,4]; see paragraph following **Side Effects** table
	lethargy/somnolence (25%)[7]; initially severe[2]; see paragraph following **Side Effects** table
ocular/visual	blurred vision (≤2%)[7,13]
	diplopia (≤1%)[7]
	lens opacity (≤1%)[7]
	optic neuritis[2] (≤1%)
	toxic retinopathy, with papilledema and retinal hemorrhage[2] (≤1%)[7]
pain	generalized aches

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	myalgia (≤1%)[7]
pulmonary	shortness of breath[2]
	wheezing[2]
renal/genitourinary	hematuria (≤1%)[7]
	hemorrhagic cystitis (≤1%)[7]

Adapted from standard reference[1] unless specified otherwise.

Gastrointestinal side effects, consisting of anorexia, nausea, vomiting, and sometimes diarrhea, occur in about 80% of patients,[1,4,14] and are more frequently observed in the first 3-6 months.[16] Symptoms tend to recur with any dose increases.[16] Severe toxicity may require a temporary (4-5 days) cessation of treatment, and it is recommended to restart with two thirds of the previous daily dose if vomiting is caused by the mitotane and/or fatty vehicle.[12] Gastrointestinal symptoms may also be the result of inadequate corticoid replacement, leading to an Addisonian crisis (especially during stressful periods).[12]

Central nervous system side effects are reported in 40-50%[1,4,14] of patients, consisting primarily of CNS depression, manifested by lethargy and somnolence in 25-32%,[1,7] and dizziness or vertigo in 15-28% of patients.[1,13] Confusion, fatigue, headache, irritability, mental depression, tremors, or weakness may also occur. Ataxia, encephalopathy, hallucinations, memory impairment, myelopathy, neuropathy, psychosis, and speech impairment are more rare.[2] CNS side effects are more commonly reported in patients with diminished performance status at treatment initiation.[8] Symptoms worsen with increased serum levels.[14] Prolonged administration of high doses has been linked to brain damage and functional impairment.[1,2] Ambulatory patients should be cautioned about driving and other activities which require mental and physical alertness.[1]

Dermatologic toxicity, usually manifesting as a maculopapular rash, is reported in 15% of patients. Skin changes are not dose related and usually subside with ongoing treatment.[1,4,7] Urticaria, erythema multiforme, hyperpigmentation, chloasma, perinasal scaling, facial or periorbital swellling and alopecia are also rarely reported.[2,10]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
adrenal steroid tests[2,17]	reduced urinary excretion of 17-hydroxy corticosteroids and aldosterone; cortisol secretion rate, serum cortisol, and serum aldosterone levels possibly unchanged	increased extra-adrenal metabolism of cortisol	monitor peak diurnal plasma cortisol, urinary free cortisol excretion, and serum aldosterone as well as urinary 17-hydroxy corticosteroids if testing is necessary
spironolactone[7,18]	decreased effect of mitotane	adrenolytic effects blocked by spironolactone; higher diuretic doses appear to present higher risk	monitor for increased mitotane toxicity if spironolactone dose is decreased or if stopped; avoid concurrent therapy if possible

AGENT	EFFECT	MECHANISM	MANAGEMENT
thyroid function tests[2,14,16]	decreased serum protein-bound iodine and total serum thyroxine; TSH and free thyroxine concentrations unchanged	increased thyroxine-binding globulin; competitive binding to thyroxine-binding globulin	use alternate diagnostic test: resin triiodothyronine uptake tests unaffected
warfarin[18]	decreased hypoprothrombinemic effect of warfarin	unknown; possibly hepatic microsomal enzyme induction	monitor prothrombin times and adjust warfarin as necessary

Hepatic microsomal hydroxylases may be induced by mitotane, and the metabolism of other drugs may be affected. In the absence of specific information regarding isoenzymes involved, caution is suggested with concurrent therapies susceptible to the influence of enzyme induction.[1,3,9,10,17,18]

SUPPLY AND STORAGE:

Oral: Bristol-Myers Squibb Canada supplies mitotane as a 500 mg tablet. Store at room temperature.[1]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

Additional information: Absorption may be increased and fecal excretion may be decreased by administration with fat-rich foods and beverages.[6,19] To minimize variations, tablets should be taken at the same times each day. Tablets may be taken with meals or on an empty stomach as long as timing in relation to meals is consistent.[8,12,20]

BCCA usual dose noted in ***bold, italics***

Oral[1,8,11]: Starting dose of ***2***-6 ***g/day***, in divided doses 3-4 times per day; ***titrate by 1 g/day once every 1-2 weeks to maximum tolerated dose*** (range 2-16 g/day). Usual dose is 8-10 g PO daily, in divided doses, but maximum tolerated dose is highly variable. Maximum dose = 19 g/day.

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure[19]*:* no information found; caution in mild to moderate impairment, not recommended in severe impairment

Dosage in hepatic failure[2,19]*:* plasma levels may increase; accumulation possible; routine dose adjustment not considered necessary; not recommended in severe impairment

Dosage in dialysis: no information found

Children:

Oral[2,12,21]:

Starting dose of 0.5-1 g/day, in divided doses 3-4 times per day; titrate to individual response and tolerance. Doses of 1-10 g/day have been used.

1-2 g/m²/day, divided 4 times per day; increase weekly by 1-2 g/m² to a maximum dose of 4 g/m²/day at 4 weeks.

REFERENCES:

1. Bristol-Myers Squibb Canada. LYSODREN® product monograph. St. Laurent, Quebec; 26 October 2004.
2. McEvoy GK, editor. AHFS 2008 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1166-1168.
3. Hogan TF, Citrin DL, Johnson BM, et al. o,p'-DDD (mitotane) therapy of adrenal cortical carcinoma: observations on drug dosage, toxicity, and steroid replacement. Cancer 1978;42(5):2177-2181.
4. Gutierrez ML, Crooke ST. Mitotane (o, p′-DDD). Cancer Treat Rev 1980;7(1):49-55.
5. Amgen Canada. VECTIBIX® product monograph. Mississauga, Ontario; 5 March 2009.
6. Moolenaar AJ, van Slooten H, van Seters AP, et al. Blood levels of o,p'-DDD following administration in various vehicles after a single dose and during long-term treatment. Cancer Chemother Pharmacol 1981;7:51-54.
7. Rose BD editor. Mitotane. UpToDate 17.1 ed. Waltham, Massachusetts: UpToDate®; 2009.
8. Joseph Connors MD. Personal communication. BC Cancer Agency Endocrine Tumour Group; 9 July 2009.
9. Robinson BG, Hales IB, Henniker AJ, et al. The effect of o,p'-DDD on adrenal steroid replacement therapy requirements. Clin Endocrin 1987;27:437-444.
10. Hague RV, May W, Cullen DR. Hepatic microsomal enzyme induction and adrenal crisis due to o,p'DDD therapy for metastatic adrenocortical carcinoma. Clin Endocrin 1989;31:51-57.
11. BC Cancer Agency Endocrine Tumour Group. (ENMITO) BCCA Protocol Summary for Treatment of Adrenal Cortical Cancer with Mitotane. Vancouver, British Columbia: BC Cancer Agency; 1 February 2008.
12. Jeff Davis MD. Personal communication. BC Cancer Agency Cancer Drug Manual Editorial Review Board; 6 July 2009.
13. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant Mitotane Treatment for Adrenocortical Carcinoma. NEJM 2007;356(23):2372-2380.
14. van Slooten H, Moolenaar AJ, van Seter AP, et al. The treatment of adrenocortical carcinoma with o,p′-DDD: Prognostic simplications of serum level monitoring. European Journal of Cancer and Clinical Oncology 1984;20(1):47-53.
15. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 March 2008.
16. Daffara F, De Francia S, Reimondo G, et al. Prospective evaluation of mitotane toxicity in adrenocortical cancer patients treated adjuvantly. Endocr Relat Cancer 2008;15(4):1043-1053.
17. Elias AN, Gwinup G. Effects of some clinically encountered drugs on steroid synthesis and degradation. Metabolism 1980;29(6):582-595.
18. Drug Interaction Facts (database on the Internet). Mitotane. Facts and Comparisons 4.0, 2009. Available at: http://online.factsandcomparisons.com. Accessed 26 May 2009.
19. Laboratoire HRA Pharma and Bristol-Myers Squibb. Mitotane summary of product characteristics. Paris, France; 2009.
20. Roberta Esau. Personal communication. BC Cancer Agency Cancer Drug Manual Editorial Review Board; 11 June 2009.
21. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2006. p. 1156.