LAVERDIA®
(verdinexor tablets)

2.5 mg · 10 mg · 22.5 mg · 50 mg

Coated Tablets

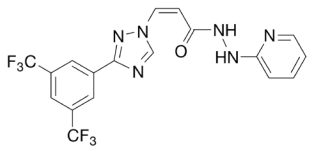
Antineoplastic

For oral use in dogs only

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: LAVERDIA (verdinexor tablets) is a selective inhibitor of nuclear export (SINE) that blocks chromosome region maintenance 1 (CRM1).

LAVERDIA has the following structural formula:



Chemical Formula: $C_{18}H_{12}F_6N_6O$
Molecular Weight: 442.33

INDICATION:

LAVERDIA is indicated for the treatment of lymphoma in dogs.

DOSAGE AND ADMINISTRATION:
Always provide the Client Information Sheet to the dog owner with each prescription.

Dosing Instructions:

1. **Feed the dog immediately before giving LAVERDIA.**
2. Wear protective disposable chemotherapy resistant gloves when handling LAVERDIA (see **USER SAFETY WARNINGS**).
3. Use an appropriate combination of tablets to administer the dose:

a) Administer LAVERDIA at an **initial** dose of 1.25 mg/kg administered orally twice per week (e.g., Monday and Thursday or Tuesday and Friday) with at least 72 hours between doses.
b) If tolerated after 2 weeks, **increase** the dose of LAVERDIA to 1.5 mg/kg twice per week with at least 72 hours between doses.
c) Dose reductions of 0.25 mg/kg to a minimum dose of 1 mg/kg twice per week with at least 72 hours between doses or dose interruptions may be considered if the dog has adverse reactions (see **ANIMAL SAFETY WARNINGS**, **PRECAUTIONS**, and **ADVERSE REACTIONS**).

4. Do not split or crush tablets.

CONTRAINDICATIONS:
Do not use in dogs that are pregnant, lactating or intended for breeding. LAVERDIA is a possible teratogen and can affect female and male fertility. Laboratory studies in the rat have shown reduced fertility, embryotoxicity, teratogenicity and maternal toxicity. Administration of LAVERDIA caused degeneration/atrophy and vacuolation in the seminiferous tubules and oligospermia in the epididymides in male dogs in the margin of safety study (see **TARGET ANIMAL SAFETY**).

WARNINGS:
USER SAFETY WARNINGS:
NOT FOR USE IN HUMANS. KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. CHILDREN SHOULD NOT COME INTO CONTACT WITH LAVERDIA. Children should not come in contact with the feces, urine, vomit, or saliva of treated dogs.

Pregnant women, women who may become pregnant, and nursing women should not handle or administer LAVERDIA or come in contact with the feces, urine, vomit, or saliva from LAVERDIA-treated dogs. Based on animal studies, LAVERDIA can cause birth defects and affect female fertility.

LAVERDIA can affect male fertility based on animal studies and studies in humans.

Wear protective disposable chemotherapy resistant gloves when handling LAVERDIA to avoid exposure to drug.

Wear protective disposable chemotherapy resistant gloves to prevent direct contact with moistened, broken, or crushed LAVERDIA tablets.

Wear protective disposable chemotherapy resistant gloves to prevent contact with feces, urine, vomit, and saliva during treatment and for **3 days** after the dog has received the last treatment. Place all waste material in a plastic bag and seal before general disposal. Wash hands immediately and thoroughly with soap and water if contact with the feces, urine, vomit, or saliva from LAVERDIA-treated dogs occurs.

Any items that come in contact with feces, urine, vomit, or saliva should not be washed with other laundry during treatment and for **3 days** after the last treatment with LAVERDIA.

Wear protective disposable chemotherapy resistant gloves when handling the dog's toys, food bowl, and water bowl. Wash food and water bowls separately from other items during treatment and for **3 days** after the dog has received the last treatment.

If LAVERDIA is accidentally ingested, or if there is significant contact with feces, urine, vomit, or saliva of dogs during treatment or within **3 days** after the last treatment without proper precautions, seek medical advice immediately.
It is important to show the treating physician a copy of the package insert, label, or client information sheet.

Special instructions for handling and administering the product

- It is recommended that LAVERDIA be administered under the supervision of, or in consultation with, a veterinarian experienced in the use of cancer therapeutic agents.
- Use standard measures for the safe handling of all chemotherapeutic drugs. Refer to Occupational Safety and Health Administration (OSHA) for appropriate guidelines, recommendations, and regulations for handling antineoplastic agents.
- Do not eat, drink or smoke while handling the product.
- Do not store near food, in or near a food preparation area, or with medications intended for use in humans.

Skin contact

- In case of contact with skin, wash the affected area immediately and thoroughly with soap and water.

Accidental eye exposure

- Rinse eyes with large amounts of tap water (use eyewash station if present) for 10 minutes while holding back the eyelid.
- Remove contact lenses.
- Seek medical advice immediately and show the package insert or label to the physician.

Accidental oral exposure or ingestion

- Seek medical advice immediately and show the package insert or label to the physician.

ANIMAL SAFETY WARNINGS:

LAVERDIA can cause severe anorexia. Dogs should be carefully monitored for inappetence, vomiting, diarrhea, dehydration and weight loss, and supportive care should be provided as clinically indicated (see **ADVERSE REACTIONS**).
In the studies used to support approval, appetite stimulants, anti-nausea medication, and corticosteroids (prednisone) were found to reduce the incidence of anorexia and gastrointestinal adverse reactions associated with LAVERDIA.

Keep LAVERDIA in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

PRECAUTIONS:
Safe use of LAVERDIA has not been evaluated in dogs with concurrent serious infections; in dogs with concurrent renal, cardiovascular, or hepatic disease; in dogs with concurrent diabetes mellitus; in dogs with clinically relevant hypercalcemia; or in dogs with concurrent malignancy.

LAVERDIA can cause hematologic and serum chemistry abnormalities. Dogs should be frequently monitored for evidence of hematologic and serum chemistry abnormalities when initiating and maintaining treatment with LAVERDIA (see **ADVERSE REACTIONS** and **TARGET ANIMAL SAFETY**).

The safety and effectiveness of LAVERDIA has not been evaluated in conjunction with other chemotherapeutic agents or other treatment modalities for lymphoma.

The effect of concomitant medications on the metabolism of LAVERDIA has not been evaluated.

The safe use of LAVERDIA has not been evaluated in dogs younger than 7 months of age.

The primary metabolism of LAVERDIA *in vitro* and *in vivo* is thought to be inactivation by glutathione (GSH) conjugation. Therefore, administration of LAVERDIA with drugs which undergo substantial GSH conjugation (e.g., acetaminophen) should be minimized.

ADVERSE REACTIONS:

A randomized, masked, controlled, multicenter clinical field study evaluated the effectiveness and safety of LAVERDIA for the treatment of lymphoma. One hundred and twenty-seven dogs received at least one dose of LAVERDIA. Thirty-three dogs received control tablets.

The Veterinary Cooperative Oncology Group - common terminology criteria for adverse events (VCOG-CTCAE) definitions[1] were used to grade the adverse reactions observed: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death or euthanasia). Most adverse reactions during the study were Grade 1 or 2. The adverse reactions observed in the study and number of dogs experiencing each adverse reaction are summarized in Table 1 below.

Table 1. Adverse Reactions Reported During the Field Study

Adverse reaction	LAVERDIA (n=127)	%	Control (n=33)	%
Anorexia*	94	74.0%	17	51.5%
Emesis	78	61.4%	12	36.4%
Lethargy	78	61.4%	18	54.5%
Weight loss	66	52.0%	4	12.1%
Diarrhea	54	42.5%	11	33.3%
Polyuria/pollakiuria	19	15.0%	3	9.1%
Polydipsia	17	13.4%	3	9.1%
Hyperthermia	15	11.8%	4	12.1%
Muscle tremor	14	11.0%	0	0%
Muscle weakness	12	9.4%	3	9.1%
Conjunctivitis or eye redness	11	8.7%	1	3%
Ocular discharge	9	7.1%	0	0%
Ataxia	8	6.3%	0	0%
Inappropriate urination	8	6.3%	0	0%
Convulsion	5	3.9%	1	3%
Impaired vision/ abnormal vision	3	2.3%	0	0%
Laboratory abnormality	**LAVERDIA (n=127)**	**%**	**Control (n=33)**	**%**
Elevated serum alkaline phosphatase (ALP)	29	22.8%	2	6.1%
Elevated alanine transaminase (ALT)	28	22.0%	3	9.1%
Thrombocytopenia	23	18.1%	5	15.2%
Anemia	14	11.0%	3	9.1%
Increased blood urea nitrogen (BUN) or creatinine	14	11.0%	3	9.1%
Elevated total bilirubin	14	11.0%	1	3.0%
Elevated aspartate aminotransferase (AST)	13	10.2%	3	9.1%
Increased band neutrophilia	13	10.2%	3	9.1%
Hypercalcemia	8	6.3%	1	3%
Proteinuria	7	5.5%	0	0%
Urinary tract infection	5	3.9%	0	0%
Neutropenia	5	3.9%	1	3%
Lymphopenia	3	2.4%	0	0%

* Of the dogs who had anorexia, 53/94 (56%) in the LAVERDIA group and 5/17 (29%) in the control group received a concomitant medication added to improve appetite.

During the study, additional reported adverse reactions for hematologic and serum chemistry abnormalities included neutrophilia, leukocytosis, leukopenia, hypokalemia, hypochloremia.

Serious Adverse Reactions:

Serious adverse events (SAEs) were reported in 22% (28 of 127) dogs in the LAVERDIA group and 15.2% (5 of the 33) dogs in the control group. Twenty-two dogs in the LAVERDIA group and 4 dogs in the control group were euthanized or died. SAEs reported in other dogs in the LAVERDIA group included thrombocytopenia (one dog), pleural effusion (two dogs), elevated total bilirubin (one dog), neutropenia (one dog), and ventricular arrythmias/swollen face/collapse (one dog). In the control group, one dog had necrosis of the skin on tail secondary to self-trauma.

Conditional Approval Experience:

LAVERDIA was conditionally approved and marketed from 2021-2025 under the proprietary name LAVERDIA-CA1. The following adverse events were voluntarily reported for LAVERDIA-CA1 during the conditional approval: anemia, polyuria/pollakiuria, leukocytosis, neutrophilia, muscle weakness, and lymphopenia.

Dechra

CONTACT INFORMATION:

To report suspected adverse events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS) contact Dechra Veterinary Products at 1-866-933-2472.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or at www.fda.gov/reportanimalae

INFORMATION FOR DOG OWNERS:

Always provide the Client Information Sheet with each prescription and review it with the dog owner or person responsible for care of the dog. Advise dog owners about possible adverse reactions, when to contact a veterinarian, how to handle and administer the product, and how to clean up any feces, urine, vomit, or saliva from dogs treated with LAVERDIA. The Client Information Sheet also contains warnings for humans and what to do in case of accidental human exposure to LAVERDIA.

CLINICAL PHARMACOLOGY:

Mechanism of action:

Verdinexor is a reversible, selective inhibitor of nuclear export (SINE) that specifically blocks chromosome region maintenance 1 (CRM1), also known as exportin 1 (XPO1). Verdinexor inhibits the export of tumor suppressor proteins (TSP) and growth regulatory proteins (GRP) from the nucleus where they carry out their normal functions; it is selectively cytotoxic for cells with genomic damage (i.e. for tumor cells).

Pharmacokinetics:

Following oral administration of a non-final formulation of verdinexor three times per week for 13 weeks to fed healthy young adult Beagle dogs, overall mean exposure in terms of area under the plasma concentration time curve from time zero to the last quantifiable plasma concentration (AUC_{last}) and maximum plasma concentration (C_{max}) showed an increase from 1.25 mg/kg to 1.5 mg/kg; however, exposure at 1.75 mg/kg was either similar or lower than exposure for the 1.5 mg/kg dose group on both evaluation days. The increase in exposure as assessed by dose normalized AUC_{last} and dose normalized C_{max} was approximately dose proportional from 1.25 mg/kg to 1.5 mg/kg and less than dose proportional from 1.5 mg/kg to 1.75 mg/kg in males on both evaluation days. In females, the increase in AUC_{last} and C_{max} was greater than dose proportional from 1.25 mg/kg to 1.5 mg/kg and there was minimal increase in exposure from 1.5 mg/kg to 1.75 mg/kg on both evaluation days.

Inter-animal variability was relatively high across all dose groups (%CV ranging from 16% to 81% for AUC_{last}); therefore, pharmacokinetic differences or trends should be interpreted cautiously.

Following oral administration of a non-final formulation of verdinexor to fed and fasted dogs, there was a significant food effect on the pharmacokinetics of verdinexor with a 3-fold and 5-fold increase in AUC and C_{max}, respectively, when verdinexor was administered orally in the presence of food. Time to reach C_{max} (T_{max}) was markedly more variable (1-18 hour) when dogs were dosed under fasted conditions as compared to when verdinexor was administered under fed conditions (1.1-2.5 hour).

Table 2. Arithmetic mean (± standard deviation) of verdinexor pharmacokinetic parameters following the first administration of a non-final formulation of verdinexor (maximum proposed label dose 1.5 mg/kg body weight) in fed male and female healthy young adult Beagle Dogs

Parameter	Estimate
AUC_{last} (h*ng/mL)	1478 ± 456
C_{max} (ng/mL)	349 ± 103
$T_{1/2}$ (h)	2.95 ± 1.04
T_{max} (h)#	1.00 (1.00-2.00)

AUC_{last} = area under the curve from the time of dosing to the last quantifiable plasma concentration

C_{max} = maximum plasma concentration

$T_{1/2}$ = half-life

T_{max} = time to maximum plasma concentration

#Median (range)

EFFECTIVENESS:

The effectiveness and safety of LAVERDIA for the treatment of lymphoma was evaluated in a randomized, controlled, masked, multicenter clinical field study. LAVERDIA was compared to control (identical tablets without verdinexor) using time to progression (TTP) as the primary endpoint. Progression was monitored at Days 7, 14, 28, 42, and 56. Progression was defined as the time from Day 0 to progressive disease (PD) for target and non-target lesions using assessment by a modified response evaluation criteria for peripheral nodal lymphoma in dogs[2]. The modification accommodated dogs that had an initial response to treatment and demonstrated clinical benefit despite lymph node (the target lesion) enlargement.

One hundred and sixty (160) dogs were enrolled and randomly assigned to treatment with either LAVERDIA (n=127) or control (n=33). LAVERDIA was administered as described in the **DOSAGE AND ADMINISTRATION** section with food or immediately after a meal. The population included dogs with B-cell (80.6% of dogs) or T-cell lymphoma (18.3%) that were naïve to chemotherapy (60% of dogs) or relapsed after chemotherapy (40%), aged 3 to 14 years old, weighing between 9.3 and 72.7 kg, with the most common breeds being mixed breeds, Labrador retriever, and German Shepherd. Use of concomitant appetite stimulants was allowed. If no response to appetite stimulants occurred, prednisone administered at 0.5-1 mg/kg per day was allowed.

Effectiveness was evaluated in 134 dogs (106 dogs in the LAVERDIA group and 28 in control). Including the administration of prednisone as a covariate in the statistical model, the TTP of dogs treated with LAVERDIA was statistically significantly longer (p-value = 0.011) than that of dogs treated with control. Time to progression was 37 days in the LAVERDIA group (with a 95% confidence interval of 29 to 57 days) and 23 days in the control group (with a 95% confidence interval of 14 to 30 days).

Thirty-one (29.2%) dogs in the LAVERDIA group completed the 56-day study while 2 (7.1%) dogs in the control group completed the study. The primary reason that dogs did not complete the study was due to progressive disease, adverse events, and/or death.

Concomitant medications were used primarily for gastrointestinal adverse events or sedation for diagnostics during the study. The most commonly used concomitant medications included maropitant, prednisone, capromorelin, butorphanol, metronidazole, ondansetron, gabapentin, dexmedetomidine, trazadone, atipamezole, isotonic solutions, amoxicillin and clavulanic acid, and heartworm, flea, and tick preventives.

TARGET ANIMAL SAFETY:

In a 13-week margin of safety study, 32 healthy Beagle dogs (4/sex/group), approximately 7 months old at study initiation, were administered LAVERDIA at either 0, 1.0, 1.5, or 1.75 mg/kg of body weight 3 times a week (Monday, Wednesday, and Friday). Dogs in the control group were sham-dosed. Dogs were fed prior to dosing. All dogs survived to study termination.

Dose-dependent LAVERDIA-related clinical findings included vomiting, inappetence, decreased body condition, decreased body weight, loss of skin elasticity, lacrimation, slight depression, and slight decrease of forelimb strength. Non-dose-dependent LAVERDIA-related findings included abnormal feces (soft, watery, or mucoid feces), excessive shedding, and sparse hair.

Dogs in the 1.0 mg/kg group and dogs in the 1.5 and 1.75 mg/kg groups had lower body weight values, starting on study days 28 and 21 respectively, that continued to the end of the study compared to control dogs.

Dose-dependent LAVERDIA-related clinical pathology findings included decreases in chloride and increases in fibrinogen. Non-dose-dependent LAVERDIA-related clinical pathology findings included decreases in lymphocytes, eosinophils, and monocytes, and increases in albumin and blood urea nitrogen.

Dose-dependent organ weight findings in the dogs administered LAVERDIA included lower testes, thymus, and thyroid/parathyroid gland weights. Dose-dependent histopathological findings in the dogs administered LAVERDIA included lesions in the testes and epididymides (moderate to marked seminiferous tubules degeneration/atrophy, minimal to moderate vacuolation, and minimal Leydig cell hypertrophy in the testes; and severe oligospermia/germ cell debris in the epididymides) and in the thymus (minimal to mild cortical lymphoid depletion).

HOW SUPPLIED:

LAVERDIA (verdinexor tablets) is presented as immediate release coated tablets in four dosage strengths, 2.5 mg, 10 mg, 22.5 mg, and 50 mg. Each tablet strength is supplied in a 16-count and 50-count HDPE bottle with a heat sealed, child-resistant cap and a desiccant included in each bottle.

DISPOSAL:

Dispose of any unused product or waste materials in accordance with proper procedures for cytotoxic drugs.

STORAGE INFORMATION:

Store the bottles at controlled room temperature 20° to 25°C (68° – 77°F).

REFERENCES:

1. Veterinary Cooperative Oncology Group- Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2) following investigational therapy in dogs and cats. *Vet Compar Oncol*. 2021, Vol.19(2), p.311-352.
2. Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0) - a Veterinary Cooperative Oncology Group (VCOG) consensus document. Vail DM, Michels GM, Khanna C, Selting KA, London CA; Veterinary Cooperative Oncology Group. *Vet Compar Oncol*. 2010; 8(1), p. 28-37.

Manufactured for:

Dechra Veterinary Products, LLC
7015 College Boulevard, Suite 525, Overland Park, KS 66211

Product inquiries should be directed to Dechra Veterinary Products, (866) 933-2472.

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