Date of Approval: December 18, 2025

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-614

LAVERDIA®

(verdinexor tablets)

Coated tablet

Dogs

LAVERDIA® is indicated for the treatment of lymphoma in dogs.

Sponsored by:

Anivive Lifesciences, Inc.

Executive Summary

LAVERDIA® (verdinexor tablets) is approved for the treatment of lymphoma in dogs. The Food and Drug Administration (FDA) conditionally approved the drug in January 2021 for the same use. At that time, the sponsor demonstrated that LAVERDIA® was safe and had a reasonable expectation of effectiveness for treating lymphoma in dogs. The sponsor has now demonstrated that the drug meets the standard of substantial evidence of effectiveness for full approval. The labeled dosage regimen for LAVERDIA® is a starting dose of 1.25 mg/kg administered orally twice a week with at least 72 hours between doses, and if tolerated after two weeks, an increase to 1.5 mg/kg twice per week with at least 72 hours between doses. The dose must be administered with food or immediately after a meal.

Verdinexor is a selective inhibitor of nuclear export that blocks chromosome region maintenance 1. By inhibiting the export of tumor suppressor proteins and growth regulatory proteins out of a cell's nucleus, verdinexor allows these proteins to continue carrying out their normal functions of controlling cell growth and proliferation. The drug is selectively cytotoxic for cells with genomic damage (i.e., for tumor cells).

Safety and Effectiveness

The sponsor conducted a field effectiveness study comparing LAVERDIA® to control in client-owned dogs. The study included dogs with B-cell or T-cell lymphoma that were naïve or relapsed from prior treatment. Enrolled dogs represented a range of weights and ages (all were at least one year of age). The staging of lymphoma was similar in both groups. The LAVERDIA® group included 106 dogs, and the control group included 28 dogs. The time to progression (TTP) was the primary effectiveness endpoint, defined as the time from study start to progressive disease (PD) for target and non-target lesions. The TTP of dogs treated with LAVERDIA® was statistically significantly longer (p-value = 0.011) than that of dogs in the control group. TTP 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).

The most common adverse events seen in dogs in both the LAVERDIA® and control groups were anorexia, vomiting, lethargy, weight loss, and diarrhea, although these adverse events occurred more often in dogs treated with LAVERDIA®. Concomitant medications were used primarily for gastrointestinal adverse events or sedation for diagnostics.

The sponsor conducted a laboratory safety study in 32 young, healthy, intact female and male Beagles. LAVERDIA® was given orally at up to 1.17X (1.75 mg/kg) the maximum intended dose 3 times weekly for 13 weeks. The drug is labeled for an initial dose of 1.25 mg/kg administered twice weekly with at least 72 hours between doses. Adverse reactions included vomiting, abnormal feces, inappetence, thin body condition, decreased body weight, excessive shedding, sparse hair, loss of skin elasticity, lacrimation, slight depression, and slight decrease of forelimb strength. Clinical pathology findings included decreases in lymphocytes, eosinophils, monocytes, and chloride; and increases in fibrinogen, albumin, and blood urea nitrogen. Anatomic pathology findings included decreased weight of the testes, thymus, and thyroid/parathyroid gland with histologic lesions in the testes, epididymides, and thymus.

LAVERDIA® is an anti-neoplastic drug treating a terminal disease; adverse reactions are expected based on how the drug works and the safety profile is acceptable.
The bioavailability of verdinexor in fed dogs is three- to five-fold greater than in fasted dogs. Because the drug can cause inappetence and nausea, dogs may have poor food intake, leading to lower drug bioavailability. Dogs in both the field effectiveness and laboratory safety studies were fed before dosing, and the dosing instructions on the drug's labeling states to feed immediately before giving LAVERDIA®.

User Safety
LAVERDIA® is an anti-neoplastic drug with potential safety concerns for people who handle, administer, or are exposed to the drug. The plasma half-life of verdinexor in dogs is approximately 4 to 6 hours, and within 60 hours, the drug typically undergoes 10 half-lives of elimination and less than 0.09% of the initial dose is present. Therefore, the potential risk to people from coming into contact with the bodily fluids of a treated dog (such as feces, urine, vomit, and saliva) is minimal beyond 3 days (72 hours) after dosing. The package insert includes detailed user safety information and special instructions for handling and administering the drug. LAVERDIA® also comes with a Client Information Sheet for prescribing veterinarians to give to their clients. This sheet is written specifically for dog owners and explains how to safely handle LAVERDIA®, how to safely clean up after a treated dog, and other important safety information.

LAVERDIA® may cause birth defects and can affect female fertility based on animal studies. Pregnant women, women who may become pregnant, and nursing women should not handle or administer the drug or touch the feces, urine, vomit, or saliva of treated dogs. Children also should not touch LAVERDIA® or the feces, urine, vomit, or saliva of treated dogs.

Conclusions
Based on the data submitted by the sponsor for the approval of LAVERDIA®, FDA determined that the drug is safe and effective when used according to the label.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-614

B. Sponsor

Anivive Lifesciences, Inc.
3777 Worsham Ave.
Long Beach, CA 90808

Drug Labeler Code: 086121

C. Proprietary Name

LAVERDIA®

D. Drug Product Established Name

verdinexor tablets

E. Pharmacological Category

Antineoplastic

F. Dosage Form

Coated tablet

G. Amount of Active Ingredient

Four tablet sizes containing 2.5 mg, 10 mg, 22.5 mg, or 50 mg of verdinexor per tablet.

H. How Supplied

Each presentation 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.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

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.

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

LAVERDIA® is indicated for the treatment of lymphoma in dogs.

II. EFFECTIVENESS

The effectiveness of LAVERDIA® was demonstrated in one adequate and well-controlled clinical field study. The study enrolled 160 dogs of any breed, or any sex diagnosed with naïve or relapsed lymphoma of either B-cell or T-cell immunophenotypes. The effectiveness analysis of 134 dogs (106 dogs in the LAVERDIA® group and 28 dogs in the control group) demonstrated a statistically significant longer (p-value = 0.011) time to progression of disease for dogs in the LAVERDIA® group than that of dogs in the control group (37 days versus 23 days).

A. Dosage Characterization

The dose of LAVERDIA® (verdinexor tablets) administered orally, twice weekly at 1.25 mg/kg with at least 72 hours between doses followed by a dose increase to 1.5 mg/kg after 2 weeks, was based on 3 pilot studies. During development, verdinexor was also referred to as KPT-335.

1. Study Title: Spontaneous Tumors in Dogs. (Study No. KS-50)

   A single site, pilot clinical study using verdinexor (non-final formulation) was conducted to assess safety, dosing schedule, and indications of antitumor activity in dogs with various cancer types. Dogs with lymphoma (n = 6) or metastatic osteosarcoma (n = 1) were treated twice weekly with verdinexor at 1 to 3 mg/kg

(average dose 1.5 mg/kg twice per week). Two dogs with lymphoma experienced partial response (PR) to therapy, and another two dogs with lymphoma experienced stable disease (SD). Adverse events associated with verdinexor included mild anorexia and diarrhea at doses of 1.75 mg/kg and below, and severe anorexia and liver value elevations at doses of 2 to 3 mg/kg and higher.

2. Study Title: Preclinical Evaluation of the Novel, Orally Bioavailable Selective Inhibitor of Nuclear Export (SINE) KPT-335 in Spontaneous Canine Cancer: A Phase I Study. (Study No. KARYO-1)

   A three-center, open label, dose escalating clinical study in 17 dogs with lymphoma or measurable solid tumors was conducted to assess safety and pharmacokinetics of verdinexor (non-final formulation). The majority of dogs enrolled in the dose escalation portion of the study had lymphoma (14 dogs), and most (12 dogs) had also received prior therapy including surgery, chemotherapy, and/or prednisone. Verdinexor treatment consisted of twice or three-times weekly dosing; dogs received between 1 and 2 mg/kg at each dosing. Dose reductions in incremental levels of 0.25 mg/kg were made for dogs that experienced adverse reactions.

   Clinical toxicities included anorexia, weight loss, vomiting, diarrhea, and lethargy. The maximum tolerated dose was established as 1.75 mg/kg administered twice per week (with at least 72 hours between doses). Dose limiting toxicities above 1.75 mg/kg administered twice per week were anorexia, weight loss, and elevated liver enzymes.

   Prednisone was administered to 10 dogs during the course of verdinexor treatment. In eight cases, the dogs entered the study on prednisone and continued to receive prednisone. In 2 cases, the dogs were started on prednisone after the first 28 days of verdinexor treatment to address inappetence issues associated with administration of verdinexor.

   The median TTP for all dogs was 35 days (range: 14 to 246 days). Two dogs had a PR for 71 and 246 days, and 8 dogs had SD for a median of 58.5 days (range 28 to 84 days). Of the 3 dogs that received verdinexor at a starting dose of 1.25 mg/kg twice weekly, 1 dog had a PR and 2 dogs had SD, and all 3 dogs remained on the study for at least 10 weeks.

   A dose expansion cohort of 6 dogs with lymphoma received verdinexor at a dose of 1.5 mg/kg on a 3 times weekly regimen (Monday/Wednesday/Friday). Prednisone was administered to all six dogs during the course of verdinexor treatment. In four cases, the dogs entered the study on prednisone. In 2 cases, the dogs were started on prednisone after the first 28 days of verdinexor treatment to address inappetence issues associated with administration of verdinexor. Two dogs had a PR for 35 and 354 days, and 2 dogs experienced SD for longer than 28 days (75 and 91 days). The other 2 dogs had progressive disease at day 13.

   The most common adverse reactions included anorexia, weight loss, vomiting, and diarrhea. Additional adverse reactions included elevated liver enzymes.

3. Study Title: An Exploratory Study of the Oral Selective Inhibitor of Nuclear Export (SINE) KPT-335 in Dogs with Lymphoma. (Study No. KARYO-2)

   The study was an open-label, multi-center, single arm, exploratory clinical field study. Fifty-eight dogs with treatment naïve lymphoma (35 dogs) or first relapse lymphoma (23 dogs) were enrolled. Dogs received verdinexor (not commercial formulation) at either (1) 1.5 mg/kg 3 times weekly, (2) 1.25 mg/kg 3 times weekly, or (3) 1.25 mg/kg 2 times weekly then increased to 1.5 mg/kg 2 times weekly if well-tolerated. Dose modifications in 0.25 mg/kg increments, reductions in dosing frequency, and drug interruptions due to drug intolerance were utilized.

   All dogs experienced at least one adverse reaction. Twenty-one dogs (36%) experienced a Veterinary Co-operative Oncology Group (VCOG) Grade 3 (severe), 4 (life-threatening), or 5 (death) adverse reaction.[1] The most common adverse reactions included anorexia, vomiting, diarrhea, weight loss, lethargy, cough/dyspnea, fever, edema/swelling, polyuria, polydipsia, hematuria, proteinuria, low urine specific gravity, urinary tract infection, elevated liver enzymes, elevated blood urea nitrogen, thrombocytopenia, lymphopenia, neutrophilia, leukopenia, and anemia.

   For all dogs enrolled, the median TTP was 29 days (range: 7 to 244 days). A subset (17 dogs) of the overall enrolled population had a TTP of at least 56 days.

Conclusion: These 3 studies supported an initial dose of 1.25 mg/kg administered orally twice per week with at least 72 hours between doses. If tolerated after 2 weeks, the dose is increased to 1.5 mg/kg twice per week with at least 72 hours between doses.

B. Substantial Evidence

1. Clinical Field Study

Title: A Multi-Center Pivotal Field Study to Confirm the Effectiveness and Safety of Verdinexor for the Treatment of Lymphoma in Dogs. (Study No. ANIV-126b-401)

Study Dates: February 2022 to July 2025

Study Locations:

Akron, OH
Athens, GA
Dallas, TX
Denver, CO
Franklin, IN
Highland Heights, OH
North Grafton, MA
Pittsburgh, PA
Quakertown, PA
Salt Lake City, UT

Study Design: This was a multi-center, prospective, randomized, masked, controlled field study.

Objective: To evaluate the field effectiveness and safety of LAVERDIA® for the treatment of lymphoma in dogs, compared to control group.

Study Animals: The study enrolled 160 dogs with lymphoma and at least one measurable peripheral lymph node. Sixty percent of dogs were naïve to treatment and 40% of dogs had relapsed following prior chemotherapy. The population included dogs with B-cell (80.6% of dogs) or T-cell lymphoma (18.3%). The dogs were 3 to 14 years old, weighing 9.3 to 72.7 kg, and the most common breeds were mixed breed, Labrador Retriever, and German Shepherd. There were 73 males and 54 females in the LAVERDIA® group. There were 14 males and 19 females in the control group. The distribution of staging was similar between groups with most enrolled dogs being Stage III (generalized lymphadenopathy) or IV (hepatosplenomegaly). All 160 dogs were evaluable for safety (127 in the LAVERDIA® group and 33 in the control group) and 134 dogs were evaluable for effectiveness (106 in the LAVERDIA® group and 28 in the control group).

Experimental Design:

Table II.1. Control and Treatment Groups

Treatment Group	Number of Dogs in Group	Dose
LAVERDIA®	127	Appropriate combination of tablets for initial dose of 1.25 mg/kg twice per week followed by increase to 1.5 mg/kg if tolerated after 2 weeks. Dose reductions were allowed.
Control*	33	Appropriate combination of tablets equivalent to initial dose of 1.25 mg/kg twice per week followed by increase to 1.5 mg/kg if tolerated after 2 weeks. Dose reductions were allowed.

*Tablets were identical to LAVERDIA® but only contained excipients without verdinexor.

Randomization and Masking: Dogs were randomly allocated to LAVERDIA® or control group in a 4:1 ratio in blocks of 5 stratified by site by the Electronic Data Capture system. All study personnel conducting observations, collecting data, and administering treatment were masked to treatment group. Owners were also masked to their dog's treatment assignment. The study was conducted in accordance with Good Clinical Practice.

Inclusion Criteria:

- Dog was ≥ 1 year.
- Dog weighed ≥ 9 kg.
- Dog had naïve or first relapse lymphoma:
  - Naïve: dog who had not received any treatment for lymphoma.
  - First relapse: dog had failed a single round of any chemotherapy completed at least 14 days prior to study entry and had recovered from any acute toxicity from prior chemotherapy or was on prednisone and has exhibited progressive disease.
- Evidence of disease (progression) at the time of screening was based on direct measurement of at least one peripheral lymph node ≥ 20 mm longest diameter (LD).
- Dog had histological or cytological diagnosis of B-cell or T-cell lymphoma (confirmed, or confirmation was pending, by flow cytometry or Polymerase Chain Reaction (PCR) Antigen Receptor Rearrangements (PARR), prior to or during screening procedures. Lymphoma was Stage II, III, or IV:
  - Stage II: Regional lymphadenopathy (restricted to one side of diaphragm),
  - Stage III: Generalized lymphadenopathy (enlargement of lymph nodes),
  - Stage IV: Hepatosplenomegaly (provided there is also lymphadenopathy such that the Investigator / Examining Veterinarian could assess disease status through a physical exam).
- A modified Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 1 [0 = normal activity, 1 = restricted activity, decreased from pre-disease status].
- Dog had a life expectancy of at least 28 days.
- If on non-steroidal anti-inflammatory drugs (NSAIDs) treatment, the dog was on stable NSAID dose for more than 2 weeks prior to enrollment.

Exclusion Criteria:

- Dog had Stage I lymphoma.
- Dog had clinical evidence of Stage V lymphoma involving, but not limited to, the CNS, gastrointestinal tract, or pulmonary system.
- Dog had a lymphocyte count greater than 15,000 per µL.
- Dog had received prior radiation specifically for the treatment of lymphoma.
- Dog had a clinically relevant abnormal laboratory result that in the opinion of the Investigator / Examining Veterinarian may have interfered with the outcome of the study.
- Dog had a serious, concurrent medical condition (e.g., renal, cardiovascular, hepatic, endocrine, concurrent malignancy) that may have precluded a successful lymphoma treatment outcome.
- Dog had significant bulky disease such that clinical deterioration was likely to occur even in the setting of stable disease.
- Dog was participating in another study or received investigational therapy.
- Dog was receiving complementary or alternative medicines that the Investigator/Examining Veterinarian believed could interfere with the primary endpoint of the study.
- Dog was lactating, pregnant or intended for breeding.

- Dog was owned by study site employees.

Drug Administration: Dogs were fed immediately before administration of dose. If a dog vomited within 15 minutes of dosing and tablets were visible, the dog was administered the dose again with new tablets. Body weight at each scheduled exam was utilized to determine the dose. Dogs weighing less than 9.7 kg did not incur dose increases because they could not be accurately dosed.

Prohibited therapies included radiation, cytotoxic or homeopathic therapies, and NSAIDs unless the dog had been stable on their NSAID dose for at least 2 weeks prior to study start. Use of appetite stimulants followed by prednisone at 0.5 to1 mg/kg per day was allowed if necessary for appetite stimulation.

Measurements and Observations:

- Physical examinations on Days -7/-1, 0, 7, 14, 28, 42, and 56.
- Lymphoma diagnosis and phenotype on Day -7/-1.
- Complete Blood Count and serum chemistry on Days -7/-1, 7, 14, 28, and 56. Urinalysis on Days -7/-1, 28, and 56.
- Thoracic radiographs and abdominal ultrasound on Days -7/-1, 28, and 56.
- Peripheral lymph node (minimum of 1 and maximum of 5) were defined as the target lesions and were measured on Days -7/-1, 0, 7, 14, 28, 42, and 56. Lymph nodes were measured by two independent, masked evaluators who each measured the longest diameter (LD) of each target lymph node in millimeters (mm), using calibrated calipers. The LD of at least one of the target lesions had to be greater than 20 mm. The sum LD of the target lesion was calculated separately for each evaluator and the mean of the two sum LDs was used for tumor response.
- Treatment response assessment by the Investigator/Examining Veterinarian on Days 7, 14, 28, 42, and 56.
- Assessment of Health-Related Quality of Life (HRQoL) by the owner on Days -7/-1, 0, 7, 14, 28, 42, and 56.
- Adverse events were recorded by the Investigator/Examining Veterinarian on Days 0, 7, 14, 28, 42, and 56.
- Dosing and observations were recorded by Owners throughout the study.

Response to treatment was based on a modified VCOG response criteria for peripheral lymphoma in dogs (v1.0)[1]. This definition of progressive disease allowed for managing dogs that demonstrate clinical benefit despite their lymph nodes showing an initial response followed by enlargement to a size greater than nadir but still 50% below that of baseline (Day 0 measurements).

<u>Definition of response for target lesions:</u>

- Complete response (CR) was defined as disappearance of all evidence of disease. All lymph nodes were non-pathologic in size in the judgement of the evaluator(s).

- Partial response (PR) was defined as at least a 30% decrease in the mean sum of the longest diameter (LD) of target lesions taking as reference the baseline sum longest dimensions.

- Progressive disease (PD) was defined in the absence of prior objective response to therapy, at least a 20% increase in the mean sum LD, taking as reference the mean sum LD at baseline (Day 0 measurements). In the setting of objective response to therapy (CR or PR), at least a 50% increase in the mean sum LD taking as reference the smallest mean sum LD and/or a decline in clinical status definitively associated with disease progression when compared to the smallest mean sum LD.

    - Clinical status was assessed by both the established modified ECOG (Eastern Cooperative Oncology Group)[2] performance status and through constitutional clinical signs defined by the Veterinary Cooperative Oncology Group – Common Terminology Criteria for Adverse Events (VCOG-CTCAE) v2 (2021)[3].

      Decline in clinical status due to disease progression was defined as:
      - Dogs exhibiting a performance status of ≥ 2 or Grade ≥ 2 constitutional signs for 7 days or longer.
      - Dogs experiencing performance status of ≥ 3 or Grade ≥ 3 constitutional signs for any length of time.

- Stable disease (SD) was defined as neither sufficient decrease in lymph node measurement to qualify as PR nor sufficient increase to qualify for PD, always using as reference the baseline Mean Sum LD (Day 0 measurements).

<u>Definition of response for non-target lesions:</u>

- Complete response (CR) was defined as all pathologic lymph nodes must be considered to have returned to normal size in the judgment of the evaluator(s), and no new lesions should be observed. Spleen and liver were considered within normal limits.

- Progressive disease (PD) was defined as
    - Unequivocal PD of existing non-target lesions.
    - Any new non-target lesion that is a peripheral lymph node, confirmed as lymphoma, > 15 mm in its LD.
    - Any new non-target lesion, confirmed as lymphoma, or an unequivocal change reflective of lymphoma progression compared to baseline.
    - An increase in circulating lymphoblasts to greater than 30,000 per µL, and new paraneoplastic disorder such as marked hypercalcemia.

Safety was monitored through physical examinations, collection of adverse events using Veterinary Cooperative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE v1.1.; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = death)[3], and clinical pathology (complete blood count, blood chemistry, and urinalysis).

Statistical Methods: The primary effectiveness endpoint was time to progression (TTP). Progression was defined as the time from Day 0 to progressive disease (PD) for target and non-target lesions. Dogs that did not progress were censored at the last follow-up. The median and confidence interval of TTP for each treatment group were estimated using the LIFETEST procedure in SAS®.

The effect of treatment on TTP was tested using a statistical model that included a fixed effect of treatment, a covariate of prednisone for appetite stimulation, and two random effects of site and site-by-treatment interaction. The NLMIXED procedure in SAS® was used for this analysis. Initial values of the parameters for the fixed effects were obtained from a fixed-effect-only model, and initial values of the variances for the random effects were set at the default value of 1.0. The individual dog was the experimental unit for statistical analysis. Effectiveness was assessed using a two-sided test at a significance level of 0.05.

The secondary variable, treatment response of stable disease, was summarized using frequency and percent by treatment group and study day.

Results: Time to progression or last follow-up was calculated for the 134 evaluable cases. The estimated median TTP 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). There was a statistically significant effect of treatment group (p-value = 0.011) for TTP of dogs treated with LAVERDIA® compared to control group.

The majority of dogs tolerated dosing according to the labeled dosage and administration. The primary reason that dogs did not complete the study was due to progressive disease, adverse events, and/or death. Dogs were allowed to stay in the study and continue on LAVERDIA® if the dog was clinically stable even if they had progressed according to the definition of response for lesions. Thirty-one dogs (29.2%) in the LAVERDIA® group completed the 56-day study while 2 dogs (7.1%) in the control group completed the study.

Concomitant medications: Concomitant medications were used primarily for gastrointestinal adverse events or sedation for diagnostics. The most commonly used concomitant medications included maropitant, prednisone, capromorelin, butorphanol, metronidazole, ondansetron, gabapentin, dexmedetomidine, trazadone, atipamezole, isotonic solutions, amoxicillin and clavulanic acid, heartworm preventatives, and flea and tick medications. Thirteen dogs in the LAVERDIA® group and zero dogs in the control group started prednisone during the study due to hyporexia.

The secondary variable response by frequency and percent for each study day is presented in Table II.2 below. There were 106 dogs in the LAVERDIA® group and 28 in the control group, but some dogs progressed prior to Day 7. The “n” in each group in Table II.2 represents dogs who had not met disease progression criteria (for target or non-target lesions) and had not been removed from the study for other reasons (such as an adverse event or death) prior to the study day. If a dog had progressive disease in both the target lesion and the non-target lesion, then the dog is presented in each progressive disease row in the table on that study day. Because dogs are not presented in the table after they progressed, 10 dogs in the

LAVERDIA® group and 1 control dog who remained on study because they were clinically stable are not included in the "n" at Day 56.

Table II.2. Disease Progression by Study Day

Study Day	Response	LAVERDIA®	Control
Day 7		**n=102**	**n=27**
	Complete Response- target lesion	1 (1.0%)	0
	Partial Response- target lesion	3 (2.9%)	0
	Stable Disease- target lesion	94 (92.2%)	26 (96.3%)
	Progressive Disease- target lesion	4 (3.9%)	1 (3.7%)
	Progressive Disease- non-target lesion	8 (7.8%)	4 (14.8%)
Day 14		**n=86**	**n=19**
	Complete Response- target lesion	2 (2.3%)	0
	Partial Response- target lesion	8 (9.3%)	1 (5.3%)
	Stable Disease- target lesion	71 (82.6%)	15 (78.9%)
	Progressive Disease- target lesion	5 (5.8%)	3 (15.8%)
	Progressive Disease- non-target lesion	8 (9.3%)	2 (10.5%)
Day 28		**n=57**	**n=10**
	Complete Response- target lesion	0	0
	Partial Response- target lesion	12 (21.1%)	0
	Stable Disease- target lesion	41 (71.9%)	7 (70.0%)
	Progressive Disease- target lesion	4 (7.0%)	3 (30.0%)
	Progressive Disease- non-target lesion	12 (21.1%)	3 (30.0%)
Day 42		**n=31**	**n=5**
	Complete Response- target lesion	1 (3.2%)	0
	Partial Response- target lesion	9 (29.0%)	0
	Stable Disease- target lesion	20 (64.5%)	1 (20.0%)
	Progressive Disease- target lesion	1 (3.2%)	4 (80.0%)
	Progressive Disease- non-target lesion	2 (6.5%)	1 (20.0%)
Day 56		**n=21**	**n=1**
	Complete Response- target lesion	1 (4.8%)	0
	Partial Response- target lesion	7 (33.3%)	0
	Stable Disease- target lesion	12 (57.1%)	1 (100%)
	Progressive Disease- target lesion	1 (4.8%)	0
	Progressive Disease- non-target lesion	3 (14.3%)	0

Adverse Reactions: Field safety was evaluated in 127 dogs administered LAVERDIA® and 33 dogs administered control. Most adverse reactions were Grade 1 or 2[3]. The adverse reactions observed in the study and number of dogs experiencing each adverse reaction are summarized in Table II.3 below.

Table II.3. 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	0.0%
Muscle weakness	12	9.4%	3	9.1%
Conjunctivitis or eye redness	11	8.7%	1	3.0%
Ocular discharge	9	7.1%	0	0.0%
Ataxia	8	6.3%	0	0.0%
Inappropriate urination	8	6.3%	0	0.0%
Convulsion	5	3.9%	1	3.0%
Impaired vision/abnormal vision	3	2.3%	0	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%
Neutrophilia	15	11.8%	4	12.1%
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%
Leukocytosis	8	6.3%	3	9.0%
Hypercalcemia	8	6.3%	1	3.0%
Proteinuria	7	5.5%	0	0.0%
Urinary tract infection	5	3.9%	0	0.0%
Neutropenia	5	3.9%	1	3.0%
Leukopenia	3	2.4%	1	3.0%
Lymphopenia	3	2.4%	0	0.0%
Hypokalemia	2	1.6%	0	0.0%
Hypochloremia	1	0.8%	0	0.0%

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

Serious adverse events (SAEs) were reported in 22% (28 of 127) of the dogs in the LAVERDIA® group and 15.2% (5 of the 33) of the dogs in the control group. Twenty-two dogs in the LAVERDIA® group and four 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 arrhythmias/swollen face/collapse (one dog). In the control group, one dog had necrosis of the skin on tail secondary to self-trauma.

Conclusion: LAVERDIA® at an initial dose of 1.25 mg/kg twice a week and if tolerated after 2 weeks, increased to 1.5 mg/kg twice a week is effective and has an adequate safety profile for the treatment of lymphoma in dogs.

III. TARGET ANIMAL SAFETY

The safety of LAVERDIA® (verdinexor tablets) for the treatment of lymphoma in dogs was demonstrated in the laboratory study (ANIV-126b-901) described below. The study demonstrated that LAVERDIA® has an adequate margin of safety for the treatment of lymphoma when administered at an initial dose of 1.25 mg/kg administered orally twice per week with at least 72 hours between doses, with an increase to 1.5 mg/kg after 2 weeks. Clinical observation/examination findings related to administration of LAVERDIA® included vomiting, abnormal feces, inappetence, thin body condition, decreased body weight, excessive shedding, sparse hair, loss of skin elasticity, lacrimation, slight depression, and slight decrease of forelimb strength. Clinical pathology findings related to administration of LAVERDIA® included decreases in lymphocytes, eosinophils, monocytes, and chloride; and increases in fibrinogen, albumin, and blood urea nitrogen. Anatomic pathology findings included lower testes, thymus, and thyroid/parathyroid gland weights with histologic lesions in the testes, epididymides, and thymus.

A. Target Animal Safety Study

Title: A 13-Week (13-cycle) Oral Tablet Target Animal Safety Study of Verdinexor in Dogs. (Study No. ANIV-126b-901)

Study Dates: February 26, 2018 to May 30, 2019

Study Location: Mattawan, MI

Study Design:

Objective: This study was conducted to evaluate the safety of LAVERDIA® (verdinexor tablets), when administered orally at up to 1.17X (1.75 mg/kg) the maximum intended clinical dose 3 times weekly for 13 weeks to healthy Beagle dogs.

Study Animals: Sixteen male and 16 female Beagle dogs were selected. The dogs were approximately 7 months old at the initiation of dose administration. Body weights ranged from 7.1 kg to 10.8 kg for the males and 4.9 kg to 7.2 kg for the females at the initiation of dosing.

Experimental Design: This was a masked, randomized, sham (untreated) controlled laboratory study. The thirty-two dogs were randomly assigned to four treatment groups of eight dogs each (four males and four females). Masking was maintained by separation of function. Persons performing masked observations or duties did not perform unmasked duties (dose administration). Masked observations and procedures included body weight and food consumption measurements, clinical observations, clinical pathological analyses, ophthalmological examinations, physical examinations including neurological assessment, necropsies, and gross pathology evaluation. This laboratory study was conducted in accordance with Good Laboratory Practice (GLP) regulations.

Drug Administration: Dogs in the LAVERDIA® treatment groups were administered a combination of 2.5 and/or 10 mg LAVERDIA® tablets 3 times weekly (every Monday, Wednesday, and Friday) for 13 weeks. The control group was sham dosed by simulating the dosing procedure in the same manner as the LAVERDIA® treatment groups. Dogs were fed prior to dosing.

Table III.1. Treatment Groups for Target Animal Safety Study

Treatment Group	Treatment	Dosage Level (mg/kg)	Number and Sex of Animals
1	Sham	0	4M, 4F
2	LAVERDIA®	1.0	4M, 4F
3	LAVERDIA®	1.5	4M, 4F
4	LAVERDIA®	1.75	4M, 4F

Measurements and Observations: Clinical observations were performed once daily pre-study and twice daily throughout the study period, and at 2 to 3 hours following dose administration. In addition, all dogs were observed 15 and 60 minutes following dose administration. A veterinarian conducted physical examinations pre-study, and on study Days 1 (pre-dose), 15, 29, 43, 57, 71, 85, and 92. Individual body weights were recorded pre-study and weekly throughout the study. Individual food weights were recorded once daily pre-study and through the end of the study. Heart rates were recorded on study Days 1 (pre-dose) and 84. Respiratory rates were recorded pre-study, and on study Days 1 (pre-dose), 15, 29, 43, 57, 71, 85, and 92. Indirect blood pressures were recorded on study Days 1 (pre-dose), 29, 57, and 84. Neurobehavioral assessments to examine motor, sensory, and autonomic pathways were conducted once pre-study and on study Day 89. Blood and urine samples for clinical pathology evaluations (hematology, coagulation, serum chemistry, and urinalysis) were collected twice pre-study, and on study Days 4, 32, 60, and 91. Ophthalmoscopic examinations were conducted pre-study and on study Day 89. A

complete set of tissues were collected for gross pathology and histopathology evaluations on study Day 92. Selected organs were weighed.

Statistical Methods: The experimental unit used for this study was the individual animal. The analysis of variance (ANOVA) model included treatment, sex, and treatment by sex as fixed effects. The analysis of covariance (ANCOVA) included treatment, sex, and treatment by sex as fixed effects and the pretreatment measurement as a covariate. The repeated analysis of covariance (RMANCOVA) model included treatment, sex, time, treatment by sex, sex by time, treatment by time, and treatment by sex by time terms as fixed effects, and animal identified as the subject in the repeated statement of the GLIMMIX procedure in SAS. Pretreatment values (prior to the first dose) was used as a covariate. The three-way interaction (treatment by sex by time) was performed at the 0.05 level of significance. All statistical comparisons of main effects (treatment, time, sex), and two-way interactions (treatment by time, treatment by sex, time by sex) were performed at the 0.10 level of significance.

Results:

Mortality

All animals survived to the scheduled necropsy.

Clinical Observations and Physical Examinations

There were five instances of vomiting post-dosing in a total of four dogs administered LAVERDIA®. Two dogs at 1 mg/kg and 1 dog at 1.5 mg/kg vomited 15 minutes post-dosing. Tablets or partial tablets were present in the vomit; therefore, these dogs were re-dosed. One dog at 1.75 mg/kg vomited 15 minutes post-dosing and 1 hour post-dosing on different days. No tablets were seen in the vomit; therefore, the dog was not re-dosed.

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

There were no LAVERDIA®-related effects on heart rate, respiration, or body temperature.

Neurobehavioral Assessment

On study Day 89, slight depression was observed in 2 dogs administered 1.75 mg/kg LAVERDIA® and slight decrease of forelimb strength was observed in 2 dogs, 1 dog administered 1.5 mg/kg and 1 dog administered 1.75 mg/kg LAVERDIA®.

Body Weights

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

Individually, 1 dog in the sham control, 7 dogs in the 1.0 mg/kg group, 8 dogs in the 1.5 mg/kg group, and 4 dogs in the 1.75 mg/kg group lost weight during the study (i.e., weighed less on study Day 91 compared to study Day -1).

Food Consumption

There were no statistically significant effects on the mean dry food consumption. However, in general, there was a decrease in dry food consumption values in dogs administered LAVERDIA® that lost body weight.

Four dogs in the sham control, 5 dogs in the 1.0 mg/kg group, 4 dogs in the 1.5 mg/kg group, and 7 dogs in the 1.75 mg/kg group received supplemental food at the direction of the attending veterinarian due to test article-related effects of body weight loss, thin body condition, and abnormal feces.

Indirect Blood Pressures

There were no LAVERDIA®-related effects on blood pressure.

Ophthalmoscopic Examination

There were no LAVERDIA®-related findings on ophthalmoscopic examination.

Clinical Pathology

Hematology: Mean lymphocyte counts were lower in dogs in the 1.5 mg/kg group on study Day 60 and in a non-dose-dependent manner in all LAVERDIA® groups on study Day 91.

Individually, there were 16 dogs with lymphocyte counts < 1.95 k/µL (reference range low 1.95 k/µL for males; 1.88 k/µL for female) at various timepoints throughout the study. Decreased lymphocyte counts were observed in 1 dog in the sham control, 4 dogs in the 1.0 mg/kg group, 8 dogs in the 1.5 mg/kg group, and 3 dogs in the 1.75 mg/kg group. The greatest incidence of low lymphocyte counts occurred on Day 91. The lowest lymphocyte count was in a dog in the 1.5 mg/kg group on study Day 91 with a lymphocyte count of 1.22 k/µL.

Beginning on study Day 32 throughout the dosing period, there were non-dose-dependent decreases in mean eosinophil counts compared to sham controls in all LAVERDIA® groups.

Individually, there were 15 dogs with eosinophil counts < 0.08 k/µL (reference range low 0.08 k/µL for male; 0.06 k/µL for female) at various timepoints throughout the study. Decreased eosinophil counts were observed in 3 dogs in the sham control, 5 dogs in the 1.0 mg/kg group, 4 dogs in the 1.5 mg/kg group, and 3 dogs in the 1.75 mg/kg group. The incidence of low eosinophils was similar at Days 32, 60, and 91

(with fewer incidences on Day 4). The lowest eosinophil count was in a dog in the 1.0 mg/kg group on study Day 60 with an eosinophil count of 0.02 k/µL.

Mean monocyte counts were lower in a non-dose-dependent manner in all LAVERDIA® groups compared to controls overall (i.e., pooled timepoints).

Individually, there were 17 dogs with monocyte counts < 0.27 k/µL (reference range low 0.27 k/µL for male; 0.26 k/µL for female) at various timepoints throughout the study. Decreased monocyte counts were observed in 2 dogs in the sham control, 5 dogs in the 1.0 mg/kg group, 6 dogs in the 1.5 mg/kg group, and 4 dogs in the 1.75 mg/kg group. The incidence of low monocytes was similar at all time points. The lowest monocyte count was in a dog in the 1.75 mg/kg group on study Day 60 with a monocyte count of 0.12 k/µL.

Coagulation: Mean fibrinogen concentrations were higher in dogs in the 1.75 mg/kg group compared to sham controls overall (i.e., pooled timepoints).

Individually, there were 14 dogs with fibrinogen > 288 mg/dL (reference range high 343 mg/dL for male; 288 mg/dL for female) at various timepoints throughout the study. Elevated fibrinogen levels were observed in 1 dog in the sham control, 4 dogs in the 1.0 mg/kg group, 5 dogs in the 1.5 mg/kg group, and 4 dogs in the 1.75 mg/kg group. The highest fibrinogen level was observed in a dog in the 1.75 mg/kg group on study Day 91 with a fibrinogen level of 428 mg/dL.

Clinical Chemistry: Beginning on study Day 4 and persisting throughout the dosing period, non-dose-dependent mean serum albumin levels were higher than sham controls in all LAVERDIA® treatment groups.

Individually, there were 15 dogs with albumin > 3.3 g/dL (reference range high 3.3 g/dL for male; 3.4 g/dL for female) at various timepoints throughout the study. Elevated albumin levels were observed in 0 dogs in the sham control, 5 dogs in the 1.0 mg/kg group, 4 dogs in the 1.5 mg/kg group, and 6 dogs in the 1.75 mg/kg group. The majority of elevated albumin levels were observed on study Days 32 and 60. The highest albumin level was observed in a dog in the 1.0 mg/kg group on study Day 32 with an albumin level of 3.7 g/dL.

Beginning on study Day 32 and generally persisting throughout the dosing period, non-dose-dependent mean serum blood urea nitrogen levels were higher than sham controls in all LAVERDIA® treatment groups.

Individually, there were 11 dogs with blood urea nitrogen > 21 mg/dL (reference range high 21 mg/dL for male; 22 mg/dL for female) at various timepoints throughout the study. Elevated blood urea nitrogen levels were observed in 0 dogs in the sham control, 2 dogs in the 1.0 mg/kg group, 4 dogs in the 1.5 mg/kg group, and 5 dogs in the 1.75 mg/kg group. The majority of elevated blood urea nitrogen levels were observed on study Days 32 and 60. The highest blood urea nitrogen level was observed in a dog in the 1.0 mg/kg group on study Day 60 with a blood urea nitrogen level of 31 mg/dL.

Mean serum chloride levels were lower than sham controls on study Days 4 and 32 in the 1.5 and 1.75 mg/kg groups, on study Day 60 in the 1.75 mg/kg group, and on study Day 91 in a non-dose-dependent manner in all LAVERDIA® treatment groups.

Individually, there were 7 dogs with chloride < 108 mEq/L (reference range low 108 mEq/L for male and female) at various timepoints throughout the study. Decreased chloride levels were observed in 0 dogs in the sham control and 1.0 mg/kg groups, 4 dogs in the 1.5 mg/kg group, and 3 dogs in the 1.75 mg/kg group. The majority of decreased chloride levels were observed on Days 4 and 32. The lowest chloride level was observed in a dog in the 1.75 mg/kg group on Day 91 with a chloride level of 105 mEq/L.

Urinalysis: There were no LAVERDIA® related findings on urinalysis.

Gross Pathology and Histopathological Findings

Macroscopically, body thinness was observed in 1 dog in the sham control group, 2 dogs in the 1.0 mg/kg group, 3 dogs in the 1.5 mg/kg group, and 6 dogs in the 1.75 mg/kg group. Sparse hair was observed in 1 dog in the 1.0 mg/kg group (cranial region), 1 dog in the 1.5 mg/kg group (cranial region), and 2 dogs in the 1.75 mg/kg group (right ear and nose/muzzle).

Compared to sham control dogs, there were lower mean testes weights (absolute and relative to body and brain weights) in males in all LAVERDIA® treatment groups, lower mean thymus weights (absolute and relative to body and brain weights) in the 1.5 mg/kg and 1.75 mg/kg groups, and lower thyroid/parathyroid gland weights (absolute and relative to body and brain weights) in all LAVERDIA® treatment groups.

Dose-dependent microscopic findings were present in the testes and epididymides (moderate to marked degeneration/atrophy in the seminiferous tubules; minimal to moderate vacuolation, and minimal Leydig cell hypertrophy in the testes; and severe oligospermia/germ cell debris in the epididymides) in males in all LAVERDIA® treatment groups, and in the thymus (minimal to mild cortical lymphoid depletion) in all LAVERDIA® treatment groups.

Conclusions: The study demonstrated that LAVERDIA® has an adequate margin of safety for the treatment of lymphoma when administered at an initial dose of 1.25 mg/kg administered orally twice per week with at least 72 hours between doses, with an increase to 1.5 mg/kg after two weeks. Clinical observation/examination findings related to the administration of LAVERDIA® included vomiting, abnormal feces, inappetence, thin body condition, decreased body weight, excessive shedding, sparse hair, loss of skin elasticity, lacrimation, slight depression, and slight decrease of forelimb strength. Clinical pathology findings related to the administration of LAVERDIA® included decreases in lymphocytes, eosinophils, monocytes, and chloride; and increases in fibrinogen, albumin, and blood urea nitrogen. Anatomic pathology findings related to the administration of LAVERDIA® included lower testes, thymus, and thyroid/parathyroid gland weights with histologic lesions in the testes, epididymides, and thymus.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

User safety data, including published literature (Sadowksi, et al., 2018)[4], indicate that the plasma half-life of verdinexor in dogs is approximately 4 to 6 hours. Within 60 hours, verdinexor is expected to undergo at least 10 half-lives of drug elimination and less than 0.09% of the initial drug dose is present. Therefore, the potential risk of drug exposure to humans from coming into contact with bodily fluids of a treated dog (such as feces, urine, vomit, and saliva) is minimal beyond 3 days (72 hours) following treatment and a 3-day precautionary period following treatment with LAVERDIA® is recommended to ensure user safety.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to LAVERDIA®:

On the package insert:

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.

<u>On the Client Information Sheet:</u>

HANDLING INSTRUCTIONS:

What do I need to know to handle LAVERDIA® (verdinexor tablets) safely?
ALWAYS WEAR GLOVES when handling LAVERDIA® and its packaging. Because LAVERDIA® is an anti-cancer drug, extra care must be taken when handling the tablets, giving the drug to your dog, and cleaning up after your dog.

- LAVERDIA® is not for use in humans.
- Do not eat, drink or smoke while handling the product.
- Keep LAVERDIA® in a secure storage area:
  - Out of the reach of children. Children should not come in contact with LAVERDIA®.
  - Out of reach of dogs, cats, and other animals to prevent accidental ingestion or

overdose.
- Do not store near food or near a food preparation area, or with medications intended for use in humans.
- 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.
- LAVERDIA® may harm an unborn baby. For pregnant and nursing women, accidental ingestion of LAVERDIA® may have adverse effects on pregnancy or the nursing baby.
- LAVERDIA® may affect female and male fertility.

How to minimize exposure to the active ingredient when handling LAVERDIA®?
ALWAYS WEAR GLOVES when handling LAVERDIA® and its packaging. The following handling procedures will help to minimize exposure to the active ingredient in LAVERDIA® for you and other members of your household:
- Anyone who administers LAVERDIA® to your dog should wear protective chemotherapy resistant gloves when handling LAVERDIA®. Check with your veterinarian to ensure you have the appropriate gloves.
- Minimize the number of people handling LAVERDIA®.
- When you or others are handling LAVERDIA® tablets:
  - Do not split or crush the tablets because this will disrupt the protective film coating.
  - LAVERDIA® tablets should be administered to your dog immediately after they are removed from the bottle.
  - Protective disposable chemotherapy resistant gloves should be worn if handling broken or moistened tablets. If your dog spits out the LAVERDIA® tablet, the tablet will be moistened and should be handled with protective disposable chemotherapy resistant gloves.
  - If the LAVERDIA® tablet is “hidden” in a treat, make sure that your dog has eaten the entire dose. This will minimize the potential for exposure to children or other household members to LAVERDIA®.
- Return any unused LAVERDIA® tablets to your veterinarian.

What should I do in case of accidental contact when handling LAVERDIA®?
- In case of contact with skin, wash the affected area immediately and thoroughly with soap and water.
- In the case of accidental eye exposure:
  - Rinse the 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, label, or client information sheet to the physician.
- **If LAVERDIA® is accidentally ingested, seek medical advice immediately. If there is significant contact with feces, urine, vomit, or saliva from your dog 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.**

How do I safely clean up after my dog during treatment with LAVERDIA®?

Because LAVERDIA® is a cancer treatment drug, extra care must be taken when cleaning up after your dog during treatment and for **3 days** after the last treatment with LAVERDIA®.

- Avoid direct contact with feces, urine, vomit, or saliva during treatment and for **3 days** after the dog has completed treatment with LAVERDIA®.
- Any skin that comes in contact with feces, urine, vomit, or saliva should be washed immediately with soap and water.
- When cleaning up feces, urine, vomit, or saliva you should wear protective disposable chemotherapy resistant gloves and collect the contaminated material with disposable absorptive material (such as paper towels) and place them into a plastic bag. Carefully remove the gloves and place them in the bag and tie or fasten it securely. Wash your hands thoroughly afterwards.
- You should not wash any items soiled with feces, urine, vomit, or saliva from your dog with other laundry during treatment and for **3 days** after the dog has completed treatment.
- Do not let your dog urinate or defecate in areas where people may come in direct contact with the urine or feces.
- Children should not come in contact with the feces, urine, vomit, or saliva of treated dogs.
- I**f there is significant contact with feces, urine, vomit, or saliva from your dog 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.**

Because LAVERDIA® may be present in your dog's saliva during treatment and for **3 days** after the last treatment, 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.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that LAVERDIA®, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose lymphoma, and to monitor safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

LAVERDIA®, as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time

we are approving this active moiety in a new animal drug application submitted under section 512(b)(1) of the FD&C Act. Any applicable exclusive marketing rights and exclusivity for this drug run concurrently.

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.

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