Date of Approval: January 15, 2021

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-539

ThyroKare™

levothyroxine sodium tablets

Dogs

For replacement therapy for diminished thyroid function in dogs.

Sponsored by:

Neogen Corp.

Executive Summary

ThyroKare™ (levothyroxine sodium tablets) is approved for replacement therapy for diminished thyroid function in dogs. Synthetic levothyroxine sodium is identical to endogenous thyroxine hormone.

Proprietary Name	Established Name	Application Type and Number	Sponsor
ThyroKare™	Levothyroxine sodium tablets	New Animal Drug Application (NADA) 141-539	Neogen Corp.

Safety and Effectiveness
The sponsor conducted a field effectiveness and safety study in client-owned dogs that were diagnosed with hypothyroidism but had never been treated with levothyroxine sodium. The study included dogs of varying breeds and weights of both genders (the majority were neutered or spayed). The average age of the enrolled dogs was 8.5 years. There was no concurrent control group in the study. Owners administered ThyroKare™ orally to their dog every 12 hours. The drug was given consistently either with or without food to minimize day-to-day variations in serum total thyroxine (tT4) concentrations.

On Day 84, 87 of 107 dogs (81.3%) evaluated for effectiveness were a treatment success. Dogs continued receiving daily treatment with ThyroKare™ through Day 168. The drug remained effective at Day 168, with 87 of 107 dogs (81.3%) evaluated for effectiveness considered a treatment success (the 87 treatment successes on Day 168 were not necessarily the same 87 treatment successes on Day 84). The clinical signs of hypothyroidism also improved during the study. The most common adverse reactions were polydipsia, polyuria, tachypnea, lethargy, anorexia, vomiting, and muscle tremors or shaking.

A range of sources was evaluated to support the safety of ThyroKare™ in dogs. The sources included: (1) a comprehensive review of publicly-available literature on the use of levothyroxine in dogs, (2) pharmacovigilance data for ThyroKare™ that were voluntarily reported to the sponsor, and (3) reports to an animal poison control center of accidental overdoses of natural or synthetic thyroid hormone products in dogs.

The published literature included prospective field studies, experimental studies, pharmacokinetic studies, retrospective studies on therapeutic use and acute overdoses of levothyroxine sodium, and case reports in dogs. Dogs of both genders (intact and neutered) of varying ages, breeds, body weights, and health status were represented in the studies. Reported oral exposure to levothyroxine sodium was well tolerated in the dogs included in these studies, even at doses multiple times higher than the initial recommended ThyroKare™ daily dose. Adverse reactions included increased activity, hyperthermia, polydipsia, polyuria, anorexia or polyphagia, diarrhea, tachycardia, and tachypnea. More severe adverse reactions were reported in dogs in the experimental studies that evaluated parenteral exposures to levothyroxine greater than 2.5X to 25X the initial oral ThyroKare™ daily dose. These adverse reactions included cardiovascular and dynamic conduction changes, polycythemia, fine muscle tremors, and death. Multiple publications reported

weight loss, tachycardia, and hyperthermia in dogs exposed to chronic oral and parenteral overdoses of thyroxine.

The pharmacovigilance data supported the safety of the clinical use of ThyroKare™ in dogs. Based on the pharmacovigilance data and reports to the animal poison control center, dogs that developed thyrotoxicosis from either acute or chronic oral exposure to levothyroxine sodium had a good to excellent prognosis for recovery.

ThyroKare™ can be used safely in dogs with appropriate monitoring of tT4 concentrations. Additionally, appropriately adjusting the dose of ThyroKare™ can reduce the risk of dogs developing adverse reactions related to iatrogenic hyperthyroidism or experiencing an exacerbation of an underlying condition.

Conclusions
Based on the data submitted by the sponsor for the approval of ThyroKare™, 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 141-539

B. Sponsor

Neogen Corp.
944 Nandino Blvd.
Lexington, KY 40511

Drug Labeler Code: 059051

C. Proprietary Name

ThyroKare™

D. Drug Product Established Name

Levothyroxine sodium tablets

E. Pharmacological Category

Hormone

F. Dosage Form

Tablet

G. Amount of Active Ingredient

0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, or 1.0 mg of levothyroxine sodium per tablet.

H. How Supplied

ThyroKare™ (levothyroxine sodium tablets), USP is available as colored tablets in nine strengths: 0.1 mg-yellow; 0.2 mg-pink; 0.3 mg-green; 0.4 mg-light pink; 0.5 mg-white; 0.6 mg-dark blue-violet; 0.7 mg-pinkish orange; 0.8 mg-light blue; and 1.0 mg-tan, in bottles of 180 and 1,000 tablet counts.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The initial dose is 0.1 mg/10 lb (0.01 mg/lb, 0.022 mg/kg) body weight twice daily. To minimize day-to-day variations in serum total thyroxine (tT4) concentrations, owners should consistently administer ThyroKare™ either with or without food. To maintain serum levothyroxine sodium concentrations over time, therapeutic monitoring should be conducted every 4 weeks until an adequate maintenance dose is established and then as needed for continued maintenance.

When switching from another levothyroxine sodium formulation to ThyroKare™, monitor serum tT4 concentrations and clinical response due to potential differences in recommended starting doses and potential differences in bioavailability.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

For replacement therapy for diminished thyroid function in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

1. Pharmacokinetics

   Levothyroxine sodium tablets contain synthetic levothyroxine sodium identical to the endogenous thyroxine hormone. Pharmacokinetic studies of orally administered levothyroxine sodium in the dog have reported substantial differences in intra- and inter-dog variability in the absorption, metabolism, and half-life upon administration of levothyroxine sodium.[1] Levothyroxine sodium is mainly eliminated in feces. Compared to the fasted state, food reduced the bioavailability of levothyroxine sodium in an oral solution by approximately 55%.[2]

   When ThyroKare™ was administered as a single oral dose of 0.1 mg/10 lb body weight (0.01 mg/lb, 0.022 mg/kg) to 7 thyroidectomized, fasted Beagles, the absolute bioavailability of levothyroxine sodium was low (19%). After 7 days of twice daily dosing of 0.1 mg/10 lb (0.01 mg/lb, 0.022 mg/kg), the mean (± standard deviation) concentration at steady state (Css) and minimum concentration at steady state (Cmin) were 3.0 (± 1.0) µg/dL and 2.2 µg/dL, respectively. The peak serum total thyroxine (tT4) concentrations were reached within 1.3 to 4 hours. The mean (± standard deviation) terminal phase half-life was 9.6 (± 3.4) hours.

2. Dose Selection

   The initial oral, levothyroxine sodium dose of 0.1 mg/10 lb (0.01 mg/lb, 0.022 mg/kg), administered twice daily, was selected based on data reported in unpublished and peer reviewed journal articles and information in a veterinary drug compendium.[2-5]

References:

1. I. C. van Dijl, G. Le Traon, B. D. A. M. van de Meulengraaf, S. Burgaud, L. J. I. Horspool and H. S. Kooistra, "Pharmacokinetics of total thyroxine after repeated oral administration of levothyroxine solution and its clinical efficacy in hypothyroid dogs," *J Vet Intern Med*, vol. 28, no. 4, pp. 1229-1234, 2014. Nachreiner, unpublished data.
2. G. Le Traon, S. Burgaud and L. J. I. Horspool, "Pharmacokinetics of total thyroxine in dogs after administration of an oral solution of levothyroxine sodium," *J Vet Pharmacol Therap*, vol. 31, pp. 95-101, 2008.
3. R. Nachreiner and M. Rick. Comparative Pharmacokinetics of Three Commercially Available Oral Veterinary Levothyroxine Products, Diagnostic Center for Population and Animal Health, College of Veterinary Medicine, Michigan State University; Lansing, Michigan. Unpublished data, 2005.
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5. R. Nachreiner, K. Refsal, W. Ravis, J. Hauptman, E. J. Rosser, and W. M. Pedersoli. Pharmacokinetics of L-thyroxine after its oral administration in dogs. *Am J Vet Res*, vol. 54, no. 12, pp. 2091-2098, 1993.

B. Substantial Evidence

1. Field Effectiveness and Safety Study

Title: Clinical Study: An Effectiveness Study Protocol for the Use of Oral Levothyroxine Sodium in Dogs. (Study No. 153-130-HPO)

Study Dates: September 2016 to January 2019

Study Locations: The study enrolled cases at 22 sites in the United States.

Fort Collins, CO
Ocala, FL
Carmel, IN
Franklin, IN
Zachary, LA
Catonsville, MD
Battle Creek, MI (2)
Springfield, MO
Hickory, NC
Reidsville, NC
Canandaigua, NY
Liverpool, NY
Fairfax, OH
Worthington, OH
Harrisburg, PA
Quakertown, PA
Wayne, PA
Farragut, TN
Dallas, TX
Seguin, TX
New Braunfels, TX

Study Design:

Objective: The objective of this prospective field study was to demonstrate the safety and effectiveness of ThyroKare™ as replacement therapy for diminished thyroid function in client-owned dogs.

Study Animals: Hypothyroid client-owned dogs, naïve to levothyroxine sodium treatment, were enrolled in the study. Diagnosis of hypothyroidism

was based on clinical signs and laboratory thyroid function tests. To be enrolled into the study each dog was required to meet the following criteria:

i. Thyroid function tests:

- Serum total thyroxine (tT4) < 1.0 µg/dL; AND
- Free thyroxine (fT4) < 0.7 ng/dL

ii. Exhibit at least two of the following clinical signs associated with hypothyroidism:

- Consistent lethargy: score of 1-2 on a scale of 1 (notable lack of activity) to 4 (significant activity level)
- Body Condition Score: score of ≥ 6 out of 9 on the Purina® Body Condition System[1]
- Bradycardia: resting heart rate < 70 bpm
- Consistent cold intolerance: score of 1-2 on a scale of 0 (no heat seeking or cold intolerance) to 2 (frequent heat seeking or consistent cold intolerance)
- Dermatologic condition: one or more of the following:
    - Bilateral alopecia on dorsum or multiple high-friction areas (i.e., dock of tail, behind ears, elbows, shoulders)
    - Multi-focal to diffuse seborrhea
    - Multi-focal to diffuse hyperpigmentation
    - Myxedema, particularly head and face
    - Multifocal hyperkeratosis
    - Multifocal to diffuse scaling and excoriation
    - Multifocal to diffuse pyoderma

Dogs were excluded from the study upon not meeting the inclusion criteria or if they had participated in previous research anticipated to confound the objectives of the study; previously received levothyroxine sodium for the treatment of hypothyroidism; were under current therapy with any medication that could not be withdrawn from use (sulfonamide antibiotics, tricyclic antidepressants, furosemide, amiodarone, phenobarbital, propranolol, glucocorticoids, and/or non-steroidal anti-inflammatory drugs); had a history of, or currently suffering from, an illness that could interfere with successful treatment for hypothyroidism (e.g., renal failure, worsening liver failure, chronic/persistent diarrhea, pancreatitis, or uncontrolled endocrinopathy conditions such as hyperadrenocorticism); were a pregnant or lactating female dog; had a history of coprophagia of their own feces; or were fed a "raw diet".

A total of 120 dogs were enrolled in the study. Of the dogs enrolled, there were 59 males (53 neutered) and 61 females (59 spayed). The average age was 8.5 years (range 2.8 to 16.0 years) and the average body weight was 61.2 pounds (range 4.9 to 181.1 pounds).

Experimental Design: No concurrent control group was included in this study. The study evaluated the initial oral, levothyroxine sodium dose of 0.1 mg/10 lb body weight (0.01 mg/lb, 0.022 mg/kg), given approximately every 12 hours. Study personnel conducting statistical analyses of the data or determining ThyroKare™ success were masked to treatment results until appropriate. The study was conducted in accordance with Good Clinical Practice (GCP).

Drug Administration: Dose administration of the initial dose of ThyroKare™ was based on a dog's body weight during the Day -7 screening physical examination and calculated at 0.1 mg/10 lb (0.01 mg/lb, 0.022 mg/kg). Owners administered ThyroKare™ orally, twice daily, in a consistent manner with or without food. ThyroKare™ was administered for the duration of the study (168 ± 5 days). Dose adjustments of ½– to 2- times the current dose were permissible following evaluations by the investigators which included physical examinations, observed clinical signs, and serum tT4 concentration values. The twice daily frequency of administration could not be changed.

Measurements and Observations: Six planned study visits with the investigators were scheduled during the study: Day -7 (screening), Day 0 (enrollment, drug initiation), Day 28 ± 5, Day 56 ± 5, Day 84 ± 5, and Day 168 ± 5. Assessments of clinical signs occurred at each visit (except Day 0) and laboratory blood tests (tT4, hematology, and blood chemistry profile) were collected 4 to 6 hours post-tablet administration at each post enrollment visit. Owners completed daily dosing diaries, including comments on any abnormalities observed in their dog, during the study period.

Statistical Methods: The primary effectiveness endpoint was the treatment success or failure for each dog at the Day 84 ± 5 pivotal timepoint. Treatment success was defined as normalization of each dog's serum tT4 concentration within the therapeutic reference range (1.0 – 5.4 µg/dL). The therapeutic reference range was created by combining the reference laboratory's normal tT4 concentration range (1.0 – 4.0 µg/dL) and therapeutic monitoring tT4 range (2.1 – 5.4 µg/dL). A one-sided 95% confidence interval of the percent treatment success rate for all dogs was calculated by t-type confidence limit. A conclusion of effectiveness was made if the lower bound of the 95% confidence interval for overall treatment success at Day 84 was greater than or equal to 70%.

The secondary effectiveness endpoint was the resolution of clinical signs associated with hypothyroidism by Day 84, where resolution was defined as the absence of a clinical sign present at baseline. A secondary analysis of the primary effectiveness endpoint was also performed on the results at Day 168 ± 5 at the end of the study period. A one-sided 95% confidence interval of the percent success rate was calculated. No statistical hypothesis testing was performed on the safety endpoints (e.g., adverse events, physical examinations and laboratory test results).

Results: All dogs that completed the study through the Day 84 pivotal time point without major protocol deviations were included in the effectiveness population (N = 107). Of the 13 dogs excluded from the evaluable population

at Day 84, 10 did not have the Day 84 assessment performed and 3 were enrolled at sites that failed to enroll the required minimum of two cases.

Overall, 84 of 120 (70%) dogs required at least one dose adjustment during the study. Sixty-one (61, 50.8%) dogs required dose adjustment between Day 0 and Day 28, 36 (30.0%) dogs had dose adjustment between Day 28 and Day 56, 24 (20.0%) dogs had dose adjustment between Day 56 and Day 84, and 2 dogs had dose adjustment after Day 84.

The average initial dose was 0.11 mg/10 lb twice daily (0.011 mg/lb, 0.024 mg/kg), ranging from 0.10 to 0.20 mg/10 lb (0.01 to 0.02 mg/lb, 0.022 mg/kg to 0.044 mg/kg) twice daily. The highest initial doses were administered to dogs weighing less than 10 lb in body weight. Final administered doses calculated for Day 168 ranged from 0.04 to 0.18 mg/10 lb (average 0.09 mg/10 lb) or 0.009 to 0.040 mg/kg (average 0.020 mg/kg) twice daily.

1) Primary Effectiveness Endpoint:

   i. Treatment Success at Day 84

      The primary effectiveness variable was normalization of each dog's serum tT4 at Day 84. Success was defined as the normalization of each dog's serum tT4 within a therapeutic reference range of 1.0 – 5.4 µg/dL. Of the 107 dogs in the effectiveness population, 87 dogs (81.3%) were considered a treatment success. The lower bound of the one-sided 95% confidence interval (CI) was estimated as 74.3%.

      Twenty (18.7%) of the 107 dogs in the effectiveness population were considered a treatment failure. Of the 20 treatment failures, 18 dogs had tT4 concentrations outside the therapeutic range and two were included as treatment failures due to withdrawal from the study at the request of the owner or investigator due to an adverse event suspected to be related to ThyroKare™.

2) Secondary Effectiveness Endpoints:

   i. Treatment Success at Day 168

      A secondary analysis of the primary effectiveness endpoint was performed on the results at Day 168.

      ThyroKare™ remained effective at Day 168 with 81.3% (87/107) of evaluable cases considered a treatment success, and the lower bound percentage success rate estimated as 73.6%. Of the 20 dogs (18.7%) that were considered treatment failures, 15 had tT4 concentrations outside the therapeutic range and five were included as treatment failures due to withdrawal at the request of the owner or investigator due to an adverse event suspected to be related to the ThyroKare™ (the 2 dogs excluded for the Day 84 evaluation) or missing serum tT4 data (3 dogs).

ii. Resolution of Clinical Signs of Hypothyroidism

Clinical signs of hypothyroidism (lethargy, weight gain, bradycardia, cold intolerance, and dermatologic conditions such as alopecia, seborrhea, hyperpigmentation, myxedema, hyperkeratosis, scaling, and pyoderma) and hypercholesterolemia improved during the study.

Adverse Reactions: The 120 dogs enrolled in the study that were administered a minimum of one dose of ThyroKare™ were evaluated for safety.

The percentage of dogs experiencing adverse reactions are included in Table II.1.

Table II.1. Percentage of dogs experiencing adverse reactions

Adverse Reaction	Percent
Polydipsia	30.8
Polyuria	20.0
Tachypnea	16.7
Lethargy	11.7
Anorexia	10.0
Emesis	10.0
Muscle tremor/shaking	10.0
Hyperactivity	8.3
Anxiety	5.8
Desquamation/scaling/seborrhea	5.8
Diarrhea	5.0
Polyphagia/increased appetite	5.0
Alopecia and increased shedding	4.2
Otitis externa and otorrhea	4.2
Increased serum alanine aminotransferase (ALT)	4.2
Increased serum alkaline phosphatase (ALP)	3.3
Pruritus, including pinnal	3.3
Tachycardia	3.3
Aggression	1.7
Dermatitis and eczema	1.7
Lymphopenia	1.7
Temporal muscle atrophy	1.7
Weight loss	1.7
Adipsia	0.8
Hypersalivation	0.8
Hypersensitivity reaction	0.8

Clinical pathology findings were consistent with stimulation of hematopoiesis as a result of replacement therapy with ThyroKare™. Hematocrit and red blood cell counts exceeded the upper limit of the reference range in 6 dogs at the end of the study; 3 of these dogs also had elevated reticulocyte counts. Nine (9) dogs had transient elevations in neutrophil counts exceeding the

reference range at Day 28 that resolved by Day 56. Liver enzyme elevations associated with ThyroKare™ returned to the reference range by the end of the study in 2 of 4 dogs with increased ALP, and 4 of 5 dogs with increased ALT.

One dog was withdrawn from the study at the owner's request because of an elevated tT4 concentration and abnormal behavior. A second dog was removed from the study by request of the investigator due to anemia.

A dog with preexisting hypoalbuminemia exhibited declining serum albumin concentrations after experiencing prolonged elevated serum tT4 concentrations. Although reducing the ThyroKare™ dose resulted in serum tT4 levels in the therapeutic range, the dog experienced a serious adverse event that included marked weight loss, lethargy, tachypnea, tachycardia, hyperthermia, anorexia, diarrhea, leukocytosis, neutrophilia, monocytosis, elevated ALP, hypoproteinemia, hypocalcemia, and hypoglycemia. The dog received supportive veterinary care and completed the study while remaining on the same ThyroKare™ dose. Serum albumin returned to near baseline and total protein normalized by the end of the study.

Concurrent Medications: ThyroKare™ was administered concurrently with other drug products. These drug products included antimicrobials, vaccinations, heartworm preventatives, non-steroidal anti-inflammatory drugs, ectoparasite control products, antihistamines, corticosteroids, topical ear cleansers/ointments, ophthalmic and otic medications, and varied nutritional supplements.

Conclusions: ThyroKare™ was effective and was determined to have an adequate safety profile for replacement therapy for diminished thyroid function in dogs at a starting dose of 0.1 mg/10 lb (0.01 mg/lb, 0.022 mg/kg) twice daily. Synthetic levothyroxine sodium is identical to endogenous thyroxine hormone which may have effects on metabolism and multiple physiologic functions and organ systems. The most common adverse reactions associated with ThyroKare™ administration were polydipsia, polyuria, tachypnea, lethargy, anorexia, emesis, muscle tremor, hyperactivity, anxiety, desquamation and seborrhea, diarrhea, increased appetite, alopecia and increased shedding, otitis externa and otorrhea, increased serum alanine aminotransferase, increased serum alkaline phosphatase, pruritus (including pinnal), tachycardia, aggression, dermatitis and eczema, lymphopenia, temporal muscle atrophy, and weight loss.

Reference:

1. D. Laflamme. Development and Validation of a Body Score System for Dogs. *Canine Practice*, vol. 22, no. 4, pp. 10-15, 1997.

III. TARGET ANIMAL SAFETY

The safety of ThyroKare™ in dogs was evaluated by critically reviewing publicly available literature regarding the use of levothyroxine in dogs and analyzing pharmacovigilance data for ThyroKare™ reported to Neogen Corp. Reports of natural

and synthetic thyroid hormone product exposures reported to an animal poison control center were also evaluated. Safety conclusions from a systematic review of information using data from other formulations were able to be extrapolated to the ThyroKare™ formulation because (1) the dose of levothyroxine sodium is adjusted and monitored individually for each dog to obtain serum total thyroxine measurements within a defined therapeutic range and desired clinical response and (2) the ThyroKare™ formulation does not contain any bioavailability enhancing factors. Reported findings were generally consistent with thyroxine's mechanism of action and impact on gene expression, protein synthesis, and enzymatic activity. These actions affect multiple physiologic functions and organ systems including growth, development, thermogenesis, cardiovascular activity, and metabolism.

A. Comprehensive Literature Review

A comprehensive literature review identified 34 publications that reported clinical signs and adverse reactions resulting from oral and parenteral levothyroxine exposure in dogs. Primary evidence was provided by 12 publications that reported exposure to oral levothyroxine sodium formulations and included individual dog data. Supportive evidence was provided by 22 publications that reported mean treatment group data, reported parenteral levothyroxine exposure, or described adverse events but did not include data. Events reported from dogs exposed to desiccated thyroid products were excluded. The publications included clinical therapeutic studies, experimental studies, pharmacokinetic studies, retrospective studies on therapeutic use and acute overdoses of levothyroxine sodium, and case reports. Dogs of varying ages, breeds, body weight, and health status of both genders (intact and neutered) were represented in the studies. Concurrent non-thyroidal diseases included diabetes mellitus, dilated cardiomyopathy, and von Willebrand disease. Daily oral levothyroxine sodium exposures ranged from 0.02 mg/kg/day to 10 mg/kg/day (equivalent to 0.5X to 250X the initial ThyroKare™ daily dose). The length of the dosing regimens ranged from a single oral dose to longer than one year. Other experimental studies evaluated parenteral exposures to levothyroxine of 0.1 mg/kg/day to 1 mg/kg/day (approximately 2.5X to 25X the initial ThyroKare™ daily dose) and ranged in duration from 7 days to 150 days of exposure.

Reported oral exposure to levothyroxine sodium, even at high-doses, was well tolerated in the dogs included in the studies. Adverse reactions reported in naturally hypothyroid and euthyroid dogs exposed to 0.5X to 2X the initial ThyroKare™ daily dose were restlessness, lethargy, hyperactivity, anorexia, polyphagia, polyuria, polydipsia, periodic lateral recumbency, tachypnea, syncope, tachycardia, hyperthermia, pruritus, alopecia, skin scaling, dermatitis, otitis externa, change in coat color, weight loss, vomiting, borborygmus, diarrhea, epistaxis, leukocytosis, and elevated serum tT4.[1-9] In one study of naturally hypothyroid dogs, the group median serum ALT and white blood cell count (WBC) were elevated relative to baseline and above the upper level of the reference range after 9 to 28 days (ALT) and 29 to 70 days (WBC) of levothyroxine sodium supplementation, without apparent clinical effect. By 77 to 112 days of supplementation, the median values were within the reference range.[3] In a 6-month study of naturally hypothyroid dogs administered levothyroxine sodium, seven dogs had hematocrit and red blood cell counts above the upper reference range at the end of the study.[9] In the same study,

three dogs had elevations in liver enzymes (ALT, ALP, or aspartate aminotransferase (AST)) after approximately 6 weeks of supplementation that resolved by approximately 10 and 18 weeks of the study for two of these dogs, respectively. In a study of euthyroid dogs, exposure to 0.5 mg/m^2 levothyroxine sodium (approximately equivalent to 1X the initial ThyroKare™ daily dose) for 8 weeks was associated with a decrease in pituitary thyrotrope volume density and morphologic changes consistent with thyroid gland inactivity. After cessation of treatment, the changes were reversible.[10]

Daily exposure of euthyroid dogs to levothyroxine sodium equivalent to 1X to 5X the initial ThyroKare™ daily dose during a 26-week study resulted in instances of excitation, tachycardia, tachypnea, vomiting, and diarrhea. Dogs in the treated groups exhibited mild decreases in serum albumin, globulin, and total protein, and increases in ALT, hemoglobin, hematocrit, and red blood cell counts compared to untreated euthyroid dogs.[11]

Chronic exposures to levothyroxine sodium at 25X the initial ThyroKare™ daily dose were found to cause transient increases in bone metabolism, but bone turnover returned to near normal levels after two months of continuous exposure. Dogs in these studies also exhibited transient increases in serum phosphorus and calcium, hyperthermia, tachycardia, and tachypnea.[12,13]

Polyphagia, fine muscle tremors, and hyperexcitability were reported in one study of 5 dogs exposed to levothyroxine sodium at 22.5X to 40X the initial ThyroKare™ daily dose.[14] Polydipsia was reported in one dog and tachycardia, tremor, and excitability were reported in 6 dogs exposed to 37.5X the initial ThyroKare™ daily dose.[15] Mean increases in serum AST and ALT were reported in dogs exposed from 4X to 90X the initial ThyroKare™ daily dose. The transaminases returned to baseline within two (AST) to four weeks (ALT) of the last dose administration.[16] In a case report of a single exposure, one dog exposed to levothyroxine sodium at approximately 250X the initial ThyroKare™ daily dose exhibited bilateral pupillary hippus and an elevated serum ALT.[17]

Adverse reactions reported in experimental studies that evaluated parenteral exposures to levothyroxine of 0.1 mg/kg/day to 1 mg/kg/day (approximately 2.5X to 25X the initial ThyroKare™ oral daily dose) were more severe. In one study, four experimentally induced hypothyroid dogs injected daily with 0.1 mg/kg levothyroxine intramuscularly (IM) for 6 weeks demonstrated increases in metabolic rate (2-3 fold increase) and progressive anorexia. Two of the four dogs died. A second group of experimentally induced hypothyroid dogs administered 0.06 mg/kg/day levothyroxine IM for 7 weeks also exhibited weight loss despite an increase in daily dietary ration intake of 5 to 10 times initial intake level.[18] In studies of euthyroid dogs exposed to 0.1 mg/kg to 1 mg/kg levothyroxine subcutaneously (SQ) daily for 7 to 150 days, the following observations were reported: tachycardia, hyperthermia, polycythemia, hyperexcitability, polyuria, diarrhea, fine muscle tremors, weight loss, decreased atrial–bundle of His (A-H) time interval, increased ventricular weight/body weight ratio, increased mean arterial pressure, increased left ventricular diastolic and systolic pressure, increased left ventricular velocity of shortening, increased left ventricular end-diastolic diameter, increased cardiac output, and increased small intestine contraction frequency and number of intestinal giant migrating contractions.[19-25]

Multiple publications provided additional supportive evidence for weight loss, tachycardia, and hyperthermia when exposed to chronic oral and parenteral overdoses of levothyroxine.[12-15,22,23,26-34]

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B. Pharmacovigilance Experience

As of 2020, 22 individual case reports describing 42 adverse reactions related to the clinical use of ThyroKare™ tablets in dogs were reported voluntarily to Neogen Corp. The following adverse events were reported: panting, anxiety, elevated or low serum tT4 concentrations, vomiting, diarrhea, lethargy, unspecified skin issues, folliculitis, hyperpigmentation, hair loss, hiding, polyuria, polydipsia, tachycardia, masseter and temporal muscle atrophy, reduced appetite, polyphagia, and seizure.

C. Animal Poison Control Center

Analysis of an electronic computer database of accidental oral exposures and overdoses of natural and synthetic thyroid hormone products in dogs reported to an animal poison control center was conducted. A total of 2,099 cases received between 2005 and 2014 were identified. Exposure to only products containing levothyroxine sodium occurred in 815 dogs; 642 dogs had multiple drug exposures. Of the 815 cases exposed to only levothyroxine sodium, 98 dogs were reported as symptomatic. None of the cases involved exposure to ThyroKare™.

Ninety-one of the symptomatic dogs had complete information on which to calculate the levothyroxine sodium exposure. The levothyroxine sodium dose ingested by the symptomatic dogs ranged between 0.003-8.6 mg/kg/day (0.07X to 200X the initial ThyroKare™ daily dose).

The following events related to exposure to levothyroxine sodium in the 98 symptomatic dogs were reported to the poison control center: agitation, lethargy, vomiting, diarrhea, tachycardia, tremors, hyperthermia, salivation, polydipsia, tachypnea/panting, gagging, vocalization, ataxia, increased serum tT4, erythema, hives, inappropriate elimination (urination), polyuria, mydriasis, dehydration, increased ALT, abdominal distention, and anorexia. There were no deaths despite exposures as high as 8.6 mg/kg. One dog with a history of seizure activity had one seizure after a single exposure of 0.3 mg/kg levothyroxine sodium (7X the initial ThyroKare™ daily dose).

D. Conclusions

A range of sources was evaluated to support the safety of ThyroKare™. Published literature included prospective field studies, experimental studies, pharmacokinetic studies, retrospective studies on therapeutic use and acute overdoses of levothyroxine sodium, and case reports. Dogs of both genders

(intact and neutered) of varying ages, breeds, body weight, and health status were represented in the studies. Reported oral exposure to levothyroxine sodium, even at high-dose multiples, was well tolerated in the dogs included in these studies. Adverse reactions reported in experimental studies that evaluated parenteral exposures to levothyroxine were more severe. The pharmacovigilance and animal poison control center information support a wide margin of safety for a single exposure to thyroid hormone medications in dogs and the prognosis for recovery from thyrotoxicosis resulting from acute or chronic exposure to levothyroxine sodium is good to excellent. Based on the evaluated information, ThyroKare™ is safe to administer to dogs for replacement therapy for diminished thyroid function at the initial dose of 0.1 mg per 10 pounds body weight (0.01 mg/lb, 0.02 mg/kg) twice daily.

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

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

Not for human use. Keep out of reach of children. In the event of accidental ingestion, seek medical advice immediately and show the product label to the physician. Wash hands after handling.

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 ThyroKare™, when used according to the label, is safe and effective for replacement therapy for diminished thyroid function in dogs.

A. Marketing Status

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

B. Exclusivity

ThyroKare™, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of ThyroKare™.

C. Patent Information

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