

Date of Approval: January 25, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-448

THYRO-TABS CANINE

levothyroxine sodium tablets

Tablet

Dogs

For replacement therapy for diminished thyroid function in dogs.

Sponsored by:

Lloyd, Inc.

Table of Contents

I. GENERAL INFORMATION	3
II. EFFECTIVENESS.....	4
A. Dosage Characterization	4
B. Substantial Evidence	5
III. TARGET ANIMAL SAFETY.....	10
A. Margin of Safety Study	10
B. Other Safety Information	13
IV. HUMAN FOOD SAFETY	13
V. USER SAFETY	13
VI. AGENCY CONCLUSIONS.....	13
A. Marketing Status.....	13
B. Exclusivity.....	13
C. Patent Information:	13

I. GENERAL INFORMATION

A. File Number

NADA 141-448

B. Sponsor

Lloyd, Inc.
604 W. Thomas Ave.
Shenandoah, IA 51601

Drug Labeler Code: 061690

C. Proprietary Name

THYRO-TABS CANINE

D. 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

THYRO-TABS CANINE (levothyroxine sodium tablets), USP is available as scored, color-coded ovoid tablets in 9 strengths: 0.1 mg–yellow; 0.2 mg–pink; 0.3 mg–green; 0.4 mg–maroon; 0.5 mg–white; 0.6 mg–purple; 0.7 mg–orange; 0.8 mg–blue; and 1.0 mg–tan, in bottles of 120 and 1,000 tablets.

I. Dispensing Status

Rx

J. Dosage Regimen

The initial daily dose is 0.1 mg/10 pounds (0.01 mg/lb; 0.022 mg/kg) body weight as a single dose every 24 hours or as a divided dose every 12 hours. The dose may then be adjusted by monitoring the serum total thyroxine (TT4) concentrations 4 to 6 hours post-tablet administration, along with clinical response, of the dog every 4 to 8 weeks until an adequate maintenance dose is established. Due to potential differences in bioavailability, monitor serum TT4

concentrations and clinical response when switching from another levothyroxine sodium formulation to THYRO-TABS CANINE.

To minimize day-to-day variations in serum TT4 concentrations, owners should consistently administer THYRO-TABS CANINE either with or without food.

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:

The pharmacokinetics of oral levothyroxine sodium are highly dependent on the individual dog. Bioavailability of oral tablet formulations range from 10%-20%, and is further decreased when taken with food.¹ Peak serum total thyroxine (TT4) concentrations are expected 4-6 hours after dosing.² Levothyroxine sodium is highly (> 99%) protein bound, with < 1% available as free thyroxine (fT4).³ In most dogs, the estimated half-life is approximately 10-14 hours.^{1,3} Levothyroxine sodium is excreted in the feces.⁴

2. Dose Selection:

A starting dose of 0.1-0.2 mg/10 pounds body weight/day of levothyroxine sodium in a solid dose oral formulation became established in the veterinary literature by the early 1990s.^{3,4} In order to verify that the low end of this dose range was effective, an initial starting dose of 0.1 mg/10 pounds body weight/day was selected for further investigation in the field effectiveness and safety study.

References

¹ Le Traon G, Burgaud S, and Horspool LJ. Pharmacokinetics of total thyroxine in dogs after administration of an oral solution of levothyroxine sodium. *J Vet Pharmacol Ther* 2008; 31:95-101.

² Nachreiner RF, Refsal KR. Radioimmunoassay monitoring of thyroid hormone concentrations in dogs on thyroid replacement therapy: 2674 cases (1985-1987). *JAVMA* 1992; 201: 623-629.

³ Rosychuk RA. Thyroid hormones and antithyroid drugs. *Vet Clin North Am Small Anim Pract* 1982; 12:111-148.

⁴ Peterson ME, Ferguson DC. Thyroid Diseases: Canine Hypothyroidism-Treatment. In: Ettinger SJ, ed. *Textbook of Veterinary Internal Medicine*. Philadelphia: W.B. Saunders Company, 1989; 1649-1653.

B. Substantial Evidence

1. Field Effectiveness and Safety Study

a. Title and Study Number:

NADA-Oriented THYRO-TABS* Field Efficacy Study
Sponsor Study Number: V29B

b. Study Dates:

14 December 2010 to 07 January 2013

c. Investigators and Locations:

Eric Christensen, DVM	New Providence, NJ
Douglas Santen, DVM, DACVIM	Denver, CO
Samuel Geller, VMD	Quakertown, PA
Roger Sifferman, DVM	Springfield, MO
Edward Jezbera, DVM	Riverside, CA
Melissa Wiest, DVM	O'Fallon, MO
James Rierson, DVM	New Braunfels, TX
Brenda Witzel, DVM	Omaha, NE
Howard Robinson, DVM	Fort Collins, CO

d. Study Design:

(1) Objective:

This study assessed the field safety and effectiveness of two dosing regimens of levothyroxine sodium tablets for replacement therapy for diminished thyroid function in client-owned dogs.

(2) Study Animals:

Client-owned dogs, newly diagnosed with hypothyroidism, were enrolled in the study. Diagnosis of hypothyroidism was based on clinical signs and laboratory indices of thyroid gland function. To be diagnosed as hypothyroid, a dog needed to meet the following criteria:

i. Thyroid function tests:

- TT4 < 15 nmol/L OR fT4 < 8 pmol/L; AND
- Thyroid Stimulating Hormone (TSH) > 37 mU/L OR Thyroglobulin Autoantibody (TgAA) > 35%

* During product development, the proprietary name was changed from THYRO-TABS to THYRO-TABS CANINE.

- ii. Signs of sufficient severity in two of the following clinical variables:
- Dermatologic condition
 - a. At least one sign with a score ≥ 4 on a scale of 0 (no signs) to 6 (widely distributed and severe) for the following signs: alopecia, seborrhea, hyperpigmentation, and scaling; OR
 - b. Composite score (sum of the individual sign scores) ≥ 6
 - Condition of ear canals: Score ≥ 3 on a scale of 0 to 6
 - Purina Body Condition Score: Score ≥ 7 on a scale of 1 to 9
 - Heart rate: classification of bradycardia (< 70 bpm)
 - Serum cholesterol: value > 343 mg/dL
 - Activity level: score ≤ 1 on a scale of 0 to 3

Specifically excluded from enrollment were dogs that did not meet the inclusion criteria; pregnant or lactating bitches; dogs intended for breeding; dogs uncooperative with study procedures; dogs that had a general anesthetic or surgical procedure within 14 days prior to prescreening Visit 1; or dogs that received the following drugs that may affect thyroid function test results, including thyroxine and analogues, tricyclic antidepressants, diuretics, amiodarone, iodides, phenobarbital, propranolol, sulfonamides, ipodate and iopanoic acid, glucocorticoids, non-prescription non-steroidal anti-inflammatory drugs (NSAIDs), and heparin within drug-specific time periods prior to the study.

A total of 502 dogs were screened for the study, with 92 enrolled. There were 43 spayed females, 1 intact female, 42 neutered males, and 6 intact males enrolled. Ages ranged from 1-13 years, with a median of 6 years. Body weight at the start of the trial ranged from 19 to 150 pounds, with a median of 80 pounds. Breeds with ≥ 10 dogs enrolled included large mixed-breed, Golden Retriever, and Labrador Retriever.

(3) Experimental Design:

The study did not include an untreated control group. Dogs were randomized to one of two treatment groups based on initial dose of levothyroxine sodium tablets administered:

Group 1: 0.1 mg/10 lb (0.022 mg/kg) body weight administered every 24 hours (q 24 hr)

Group 2: 0.05 mg/10 lb (0.011 mg/kg) body weight administered every 12 hours (q 12 hr)

Owners and Investigators were unmasked to dose and frequency of administration. Individuals performing and reporting clinic pathologic analyses were masked to the treatment group of the dog.

(4) Drug Administration:

Levothyroxine sodium tablets were administered for 182 ± 5 days. Dose adjustments of $\frac{1}{2}$ - to 2-times the current dose were allowed following scheduled study visits based on clinical signs, physical examination findings, and thyroid panel results. The frequency of dosing could not be changed.

(5) Measurements and Observations:

There were a total of six planned study visits: Visit 1 (-7 to -1), Visit 2 (Day 0), Visit 3 (Day 42 ± 5), Visit 4 (Day 70 ± 5), Visit 5 (Day 126 ± 5), and Visit 6 (Day 182 ± 5). Prescreening, enrollment, and initiation of dosing were performed at the first two visits. At each visit (except Visit 2) clinical signs were assessed and blood for laboratory tests (TT4, fT4, TSH, hematology, and biochemical profile) was collected 4-6 hours post-tablet administration. Thyroglobulin autoantibody titer was assessed at Visit 1, and urinalysis was conducted at Visits 1 and 6. Owners completed daily dosing diaries, including comments on any abnormalities observed in their dog during the study period.

e. Statistical Methods:

The primary variable for effectiveness was treatment success or failure for each dog, evaluated at Visit 6. Each dog was considered a treatment success if, at Visit 6, its thyroid panel results were in the desired treatment range:

- i. TT4 ≥ 15 nmol/L and no more than 93.8 nmol/L (1.4-times the upper reference limit of 67 nmol/L); AND
- ii. fT4 ≥ 8 pmol/L and no more than 36.4 pmol/L (1.4-times the upper reference limit of 26 pmol/L); AND
- iii. TSH ≤ 37 mU/L

Levothyroxine sodium tablets would be considered effective if the lower bound of the one-sided 95% confidence interval for the overall success rate was 66%.

The difference in the percent of treatment successes at Visit 6 (Day 182 ± 5) in the two administration schedules was evaluated by Fisher's exact test. Administration schedule was evaluated at $\alpha = 0.10$. The exact binomial confidence limit was used to compute the lower bound of the one-sided 95% confidence limit.

Serum TT4, fT4, and TSH concentrations were additionally evaluated by calculating the percentage of dogs, with 95% confidence intervals, that had values within the desired therapeutic range for each hormone at each scheduled visit.

Changes in clinical variables associated with hypothyroidism were evaluated as secondary outcome measures for effectiveness. For overall dermatologic condition and for each dermatologic lesion, the percentage of dogs with responses of worsened, none, fair, good, or excellent was

summarized at each visit. For each of the other clinical variables, the percentage of dogs with responses of worsened, none, or improved was summarized at each visit.

f. Results:

After 182 days on study, the dose ranged from 0.04 to 0.2 mg/10 lb (0.009-0.044 mg/kg) body weight with a median dose of 0.11 mg/10 lb (0.024 mg/kg) body weight. The majority (80%) of the dogs were dosed at 0.08-0.12 mg/10 lb (0.008-0.012 mg/lb; 0.018-0.026 mg/kg) by the end of the study, with the majority (69.7%) of dogs requiring one dose change.

Of the 92 dogs enrolled, 78 were included in the effectiveness evaluation. Fourteen dogs were excluded: 11 because of protocol non-compliance and 3 due to serious illness not related to the test article.

(1) Primary outcome measures for the determination of effectiveness

Of the 78 evaluable cases, 59 dogs (75.6%) were considered treatment successes. The lower bound of the one-sided 95% confidence interval (CI) was estimated as 66.3%. There was no difference in treatment success between the two treatment groups (P-value = 0.1121, Table 1).

Table 1. Treatment Success by Treatment Group

Treatment Group	N	Percent Success
Group 1 (q 24 hr)	39	66.7% (26/39)
Group 2 (q 12 hr)	39	84.6% (33/39)

(2) Secondary outcome measures for the determination of effectiveness

The percentage of dogs at 182 days with serum hormone concentrations within the desired treatment range for each hormone for each dosing schedule is provided (Table 2).

Table 2. Percentage of Dogs with Serum Hormone Concentrations within the Desired Treatment Range after 182 Days of Treatment

Hormone	Treatment Group	Least Squares Means	95% Confidence Intervals
fT4, pmol/L	Group 1 (q 24 hr)	87.2	72.6, 95.7
	Group 2 (q 12 hr)	92.1	78.6, 98.3
TSH, mU/L	Group 1 (q 24 hr)	92.3	79.1, 98.4
	Group 2 (q 12 hr)	89.5	75.2, 97.1
TT4, nmol/L	Group 1 (q 24 hr)	82.1	66.5, 92.5
	Group 2 (q 12 hr)	94.7	82.3, 99.4

Clinical signs of hypothyroidism (weight gain, lethargy, bradycardia, seborrhea, alopecia, hyperpigmentation, scaling, and hypercholesterolemia) generally improved by the end of the study (Day 182 ± 5). Respiratory rate, excluding panting dogs, increased during the study along with activity level.

g. Adverse Reactions:

All 92 of the enrolled dogs received at least one dose of the levothyroxine sodium tablets and were evaluated for safety.

The most commonly reported adverse reactions, by percentage of dogs experiencing the reaction included: anorexia (17%), dermatitis (15%), vomiting (15%), otitis externa (14%), lethargy (14%), polydipsia (13%), diarrhea (11%), leukocytosis (9%), pruritus (8%), tachypnea (8%), polyuria (5%), hyperactivity (4%), and seborrhea (1%).

One dog was withdrawn from the study at the owner's request because of increased water consumption and urination, which was possibly related to levothyroxine sodium tablets.

h. Clinical Pathology:

(1) Hematology:

Hematocrit and red blood cell counts exceeded the upper limit of the reference range in seven dogs by the end of the study.

(2) Serum Chemistry and Urinalysis:

Liver enzyme (alkaline phosphatase [ALP], alanine aminotransferase [ALT], or aspartate aminotransferase [AST]) elevations related to levothyroxine sodium tablet administration were reported in three dogs. In two of the dogs with elevated ALT and AST, the elevations resolved by Day 70 and Day 126, respectively. There were no clinically significant changes noted on urinalysis.

i. Concurrent Medications and Procedures:

Levothyroxine sodium tablets were used in conjunction with a wide variety of medications and procedures routinely prescribed and performed in veterinary medicine. These included vaccinations, heartworm preventatives, ectoparasite control products, antibiotics, NSAIDs, antihistamines, corticosteroids (injectable, oral, and topical), topical ear cleansers and ear ointments, medicated shampoos, anesthetic agents, and nutritional supplements.

j. Conclusions:

Levothyroxine sodium tablets were effective in maintaining serum TT4, fT4, and TSH within desired treatment ranges in dogs with diminished thyroid function. There was no difference in treatment success between the two treatment groups (daily dose q 24 hr or daily dose split and each half given q 12 hr), and the drug was well-tolerated in dogs in both groups.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

1. Title and Study Number:

NADA-Oriented THYRO-TABS* Target Animal Safety Study
Sponsor Study Number V-28

a. Investigator and Location:

Kingfisher International, Inc.
Stouffville, Ontario, Canada

b. Study Design:

(1) Objective:

To evaluate the tolerance of repeated oral administration of levothyroxine sodium tablets to dogs treated for 26 weeks. This study was conducted in accordance with the Good Laboratory Practice Regulations (GLPs; 21 CFR 58).

(2) Study Animals:

32 Beagle dogs (16 intact males and 16 intact females) aged 7 to 10 months, and weighing 5.2 to 11.0 kg.

(3) Experimental Design:

Euthyroid dogs, identified by thyroid screening (normal TT4, fT4, and TSH) and found in general good health based on physical examinations, clinical pathology results, and electrocardiography, were selected for study enrollment.

The initial dose is 0.1 mg/10 lb (0.01 mg/lb; 0.022 mg/kg) levothyroxine sodium administered once daily. Dogs were administered 0, 2, 6, or 10 times this dose as shown in Table 3 below.

Table 3. Treatment Groups

Group	Treatment	Number of Dogs
0X (control)	0 mg/kg once daily (sham dosed)	4M, 3F [†]
2X	0.044 mg/kg (0.2 mg/10 lb) levothyroxine sodium tablets once daily	4M, 4F
6X	0.132 mg/kg (0.6 mg/10 lb) levothyroxine sodium tablets once daily	4M, 4F
10X	0.220 mg/kg (1.0 mg/10 lb) levothyroxine sodium tablets once daily	4M, 4F

[†] One of the 0X female dogs was excluded from the safety analysis but remained in the study.

* During product development, the proprietary name was changed from THYRO-TABS to THYRO-TABS CANINE.

(4) Drug Administration:

Dogs were administered levothyroxine sodium tablets once daily for 26 weeks. The levothyroxine sodium tablets were administered in the morning following a 15-hour fast. Food was offered to dogs 1 hour after dosing and was removed 8 hours later.

(5) Measurements and Observations:

Clinical observations were made before and 4 and 16 hours after dosing. Food consumption was measured daily. Physical examinations, body weights, hematology, serum biochemistry, coagulation profiles, thyroid panels, urinalyses, and electrocardiology were collected twice prior to the start of dosing and at 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 22, 23, 25, and 26 weeks. All dogs were euthanized and underwent full gross necropsy. Organ weights were collected for spleen, liver, lungs, kidneys, adrenals, heart, pituitary gland, prostate, thymus, thyroids with parathyroids, uterus, ovaries/testes, and brain. Histopathological evaluation was performed on full sets of tissues from dogs in the 0X and 10X treatment groups, and from grossly abnormal tissues identified from dogs in the 2X and 6X treatment groups.

c. Statistical Methods:

(1) Single Time Point Analysis:

For variables with continuous outcomes (i.e. organ weights), analysis of covariance (ANCOVA) was used to evaluate the effects of gender, group, and the gender-by-group interaction under the assumption of normality. These effects were included as fixed effects in the statistical model. Weight block within gender was included as a random effect. Body weight was included as a covariate.

(2) Repeated Measures Analysis:

Data collected over time (hematology, clinical chemistry, urinalysis, body weight, food consumption, and various physical examination results) were analyzed by ANCOVA appropriate for a repeated measures experiment under the assumption of normality (Shapiro-Wilk test). Data were log transformed when necessary, prior to analysis to stabilize the residuals. The appropriate structure of the covariance matrix was evaluated using Akaike's Information Criterion (AIC), evaluating compound symmetric, heterogeneous compound symmetric, autoregressive type I, and heterogeneous auto regressive type I structures. Group, gender, time, all two-way interactions and the three-way interaction of the main effects were included as fixed effects. Weight block within gender was included as a random effect. Pretreatment values were included as a covariate.

d. Results:

(1) Clinical Observations:

Vomiting, diarrhea, excitation, rapid respiration, and feces with blood were observed in all treatment groups, but were seen with greater frequency in dogs in the groups administered levothyroxine sodium tablets.

(2) Electrocardiography:

Tachycardia was observed in all treatment groups, but was seen with greater frequency in dogs in the groups administered levothyroxine sodium tablets.

(3) Thyroid Panel:

The mean TSH values in the 2X, 6X, and 10X groups were lower than the untreated control group (approaching or close to the lower limit of quantitation for the assay). There was a directly proportional, dose-dependent increase in FT4 and in the TT4 values.

(4) Hematology:

Dogs administered levothyroxine sodium tablets had dose-dependent increases in hemoglobin, hematocrit, and red blood cell counts compared to control dogs. Mean red blood cell counts remained within the normal laboratory range. The mean group values for hematocrit and hemoglobin in the 2X, 6X, and 10X treatment groups were close to or just above the upper reference range.

(5) Serum Chemistry:

Dogs administered levothyroxine sodium tablets had dose-dependent increases in ALT compared to control dogs, but remained within the normal laboratory range. Lower albumin, calcium, cholesterol, globulin, and total protein values were observed in a dose-dependent manner in dogs administered levothyroxine sodium tablets compared to control dogs, but the values remained within the normal laboratory ranges.

(6) Gross Necropsy and Histopathological Examinations:

There were no treatment-related gross or histopathologic lesions observed in any treatment group.

(7) Organ Weights:

The pituitary gland and the thyroid/parathyroid glands had a dose-dependent decrease in organ weight compared to the control dogs.

e. Conclusion:

This study supports the safe use of levothyroxine sodium tablets at the labeled initial dose of 0.022 mg/kg (0.1 mg/10 lb) administered once daily to dogs.

B. Other Safety Information

The following events related to the clinical use of levothyroxine sodium tablets in dogs were reported voluntarily to Lloyd, Inc. (as of 2015): Allergic-type hypersensitivity reactions (pruritus, hives, rash, facial swelling), alopecia, anorexia, vomiting, diarrhea, polyuria, polydipsia, hyperactivity, tachypnea, lethargy, collapse, and high or low serum total thyroxine concentrations.

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 THYRO-TABS CANINE:

Not for use in humans. 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 THYRO-TABS CANINE, 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 lawful 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

THYRO-TABS CANINE, 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 Federal Food, Drug, and Cosmetic Act because this is the first time we are approving this active ingredient in a new animal drug.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.