Date of Approval: March 15, 2024

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-579

DuOtic™

(terbinafine and betamethasone acetate otic gel)

Dogs

DuOtic™ is indicated for the treatment of otitis externa in dogs, associated with susceptible strains of yeast (*Malassezia pachydermatis*).

Sponsored by:

Dechra, Ltd.

Executive Summary

DuOtic™ (terbinafine and betamethasone acetate otic gel) is approved for the treatment of otitis externa in dogs, associated with susceptible strains of yeast (*Malassezia pachydermatis*). The otic gel is a combination of an antifungal (terbinafine) and an anti-inflammatory (betamethasone acetate). It comes in a single-use tube and should be administered in the clinic to the dog's affected ear. The dose should be repeated in 7 days.

Safety and Effectiveness

The sponsor conducted a field study to demonstrate the effectiveness of the two-dose regimen of DuOtic™ to treat yeast-related otitis externa in client-owned dogs. The dogs were both male and female and represented a variety of ages, weights, and breeds (both purebred and mixed breed). The study evaluated four clinical signs associated with otitis externa: erythema, edema/swelling, erosion/ulceration, and exudate. The affected ear was assigned an Overall Severity Score (OSS) based on the sum of the severity of each clinical sign. To be enrolled, dogs had to have an OSS of ≥ 6 in at least one ear and evidence of a yeast infection on cytology in that same ear. On Day 0, the affected ear was cleaned with saline and then treated with either DuOtic™ or placebo control. Ears were not cleaned or flushed again during the study. On Day 7, each dog received the same treatment as on Day 0.

The primary endpoint was treatment success or failure on Day 45. A dog was considered a treatment success if the affected ear had an OSS of ≤ 3 with no worsening of any clinical sign compared to Day 0. Dogs in the treated group had a higher success rate compared to dogs in the placebo control group (62.31% versus 17.84%). In addition, more dogs in the treated group had a better clinical response than dogs in the placebo control group on Day 45, as ranked by both veterinarians and owners. Four dogs in the treated group had increased alanine aminotransferase on Day 45. The levels returned to normal in three dogs on subsequent bloodwork, and no follow-up was performed on the fourth dog.

Osurnia® (florfenicol, terbinafine, betamethasone acetate) otic gel is already approved for dogs under a different new animal drug application (NADA 141-437). Osurnia® and DuOtic™ have similar formulations and concentrations of terbinafine and betamethasone, and removing florfenicol from the formulation should not affect the safety of either active ingredient. Therefore, the target animal safety for DuOtic™ is supported by the target animal safety study conducted for the approval of Osurnia®. The sponsor also used the *in vitro* non-interference study conducted for the approval of Osurnia® to demonstrate that betamethasone does not have activity against *M. pachydermatis,* and that betamethasone does not interfere with the activity of terbinafine against the yeast isolates. Refer to the Freedom of Information Summary for Osurnia®, dated November 4, 2014, for detailed information about these studies.

User Safety

DuOtic™ may cause eye injury and irritation in people and dogs. People who administer DuOtic™ in the clinic should wear eye protection and the dog should be restrained to minimize post-application head shaking. This will help prevent accidental eye exposure in both people and dogs.

Conclusion
Based on the data submitted by the sponsor for the approval of DuOtic™, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-579

B. Sponsor

Dechra, Ltd.
Snaygill Industrial Estate
Keighley Rd.
Skipton, North Yorkshire
BD23 2RW, United Kingdom

Drug Labeler Code: 043264

U.S. Agent Name and Address:

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Dechra Ltd
7015 College Blvd, Suite 510
Overland Park, KS 66211

C. Proprietary Name

DuOtic™

D. Drug Product Established Name

terbinafine and betamethasone acetate otic gel

E. Pharmacological Category

Antifungal and anti-inflammatory

F. Dosage Form

Gel

G. Amount of Active Ingredient

10 mg terbinafine and 1 mg betamethasone acetate per mL

H. How Supplied

It is available in a single use tube with a flexible soft tip, supplied in cartons containing 2 or 20 tubes.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

DuOtic™ should be administered by a veterinary professional. Clean and dry the external ear canal before administering the initial dose of the product. Administer one dose (1 tube) per affected ear and repeat administration in 7 days. Do not clean the ear canal for 45 days after the initial administration to allow contact of the gel with the ear canal.

K. Route of Administration

Otic

L. Species/Class

Dogs

M. Indication

DuOtic™ is indicated for the treatment of otitis externa in dogs, associated with susceptible strains of yeast (*Malassezia pachydermatis*).

II. EFFECTIVENESS

A. Dosage Characterization

Dosage characterization for DuOtic™ was based on Osurnia® (florfenicol, terbinafine, betamethasone acetate; NADA 141-437). The presentation and concentrations of terbinafine and betamethasone acetate in DuOtic™ are identical to those in Osurnia®.

An ear-swab study conducted in 33 beagle dogs evaluated the depletion of florfenicol, terbinafine, and betamethasone acetate after the administration of two 1 mL doses of Osurnia® seven days apart. Based on confidence intervals calculated around predicted individual values, therapeutic concentrations in normal ears may be expected to persist 45 days after the initial dose. Faster depletion is assumed to occur in ears affected with otitis externa due to increased absorption through the disrupted skin barrier and drug degradation secondary to inflammation. A pilot clinical field study of 121 dogs affected by canine otitis externa associated with susceptible strains of bacteria and yeast evaluated the effectiveness of Osurnia® administered as a single dose or with a second dose repeated seven days later. The effectiveness of Osurnia®, administered twice, 7 days apart, was greater compared to administration once, an active control, and placebo.

Together, these two studies justified the selection of the dose of 1 mL of DuOtic™ to be administered per affected ear, with a repeat dose after seven days, for the treatment of canine otitis externa associated with susceptible strains of yeast (*Malassezia pachydermatis)*.

B. Substantial Evidence

Substantial evidence of effectiveness was demonstrated in an *in vitro* non-interference study and a field effectiveness study. The non-interference study demonstrated that betamethasone does not have activity against, and does not interfere with the activity of terbinafine against, *M. pachydermatis*. The field study, conducted in the United States (US) and Spain, established the effectiveness of the two-dose regimen of DuOtic™ (terbinafine, betamethasone acetate otic gel) for treatment of otitis externa in dogs, associated with susceptible strains of yeast (*M. pachydermatis*). Four clinical signs associated with otitis externa were evaluated: erythema, edema/swelling, erosion/ulceration, and exudate. Overall Severity Scores (OSS) were assigned to each dog based on the sum of the severity of each clinical sign on Days 0, 7, 14, 28, and 45 in the evaluable ear. The primary endpoint of the field study was treatment success or failure as assessed by the OSS in the evaluable ear on Day 45.

1. Non-Interference study

   Non-interference of terbinafine and betamethasone for the DuOtic™ formulation was based on the results of an *in vitro* Fractional Inhibitory Concentration Index (FICI) study. Study 10-003 demonstrated there was no activity of betamethasone alone against *M. pachydermatis* isolates and the two-way combination of terbinafine and betamethasone resulted in no negative effect on the activity of terbinafine against *M. pachydermatis* isolates. Refer to the Freedom of Information (FOI) Summary for Osurnia® (NADA 141-437), dated November 4, 2014, for detailed information on this study.

2. Field Study

   Title: A Pivotal Field Study to Evaluate the Efficacy and Safety of DuOtic™ in the Treatment of Yeast-Related Canine Otitis Externa. (Study No. D20028)

   Study Dates: August 16, 2021 to July 21, 2023

   Study Locations: Veterinary clinics in the US and Spain from the following locations participated in this study:

Fort Collins, CO	Harrisburg, PA
Manistee, MI	Hendersonville, NC
Dallas, TX	Franklin, IN
Quakertown, PA	Springfield, MO
Raleigh, NC	Logrono, Spain
Shippensburg, PA	Redondela, Spain
Elgin, SC	Bertola – Vilaboa, Spain
Bartlesville, OK	San Sebastian, Spain
Memphis, TN	

Study Design: A randomized, double-masked, placebo-controlled, multi-center field study.

Objective: A clinical study conducted in client-owned dogs intended to demonstrate the field effectiveness and safety of DuOtic™ in comparison to a placebo control for the treatment of yeast-related otitis externa.

Study Animals: Two hundred thirty-nine client-owned dogs with otitis externa were enrolled in sites in the US (n = 174; 73%) and Spain (n = 65; 27%). Dogs were randomized to treatment with DuOtic™ (120) or placebo control (119). Fifty-nine different breeds were represented, and enrolled dogs were between 5 months to 16.2 years of age, and weighed 4.6 lbs to 210.6 lbs, at the start of the study. The otitis externa in the dogs at presentation was classified as sub chronic (43.1%), chronic (31.0%), and acute (25.9%). Most of the dogs (84.5%) presented with non-recurrent otitis and 84.1% required bilateral treatment.

Experimental Design: This study was conducted in compliance with good laboratory practice (GLP) regulations. The dogs in the study were randomized in a 1:1 ratio to the DuOtic™ or the placebo control groups. Table II.1 details the number of dogs enrolled in each treatment group.

Table II.1. Treatment Groups and Dose.

Treatment Group	Dose	Administration Schedule	Number of Dogs Enrolled
DuOtic™	DuOtic™ (1 mL) per affected ear(s)	Day 0 and Day 7	120
Placebo Control	Saline (1mL) per affected ear(s).	Day 0 and Day 7	119

Inclusion criteria: For enrollment, a minimum OSS of ≥ 6 (a score of 12 being the worst possible OSS) was required in at least one ear and evidence of a yeast infection on cytology. Yeast infection was defined as a mean count (from 5 random oil immersion fields – 1000X) of ≥ 15 yeast in at least one ear AND < 15 cocci, ≤ 1 rod, and ≤ 1 neutrophil in both ears. In addition, dogs needed to have a positive yeast culture from the evaluable ear to be considered for evaluation of effectiveness.

Exclusion criteria: Dogs that were pregnant, lactating, or intended for breeding, were owned by the sponsor or by study site employees involved in the conduct of the study, or living in the same household as another dog which was currently participating in this study were not eligible. The dogs could not have an autoimmune disease, clinical signs of uncontrolled hyperadrenocorticism, sex hormone abnormality, hypothyroidism, an otic foreign body in either ear, clinical signs of inner or middle ear disease, ruptured tympanic membrane, an active auricular hematoma, or ear polyps. Prior to study start, dogs were withdrawn

from other drugs or treatments that might have interfered with the assessment of effectiveness.

Drug Administration: Prior to treatment administration on Day 0, for both treatment groups, the affected ear canal(s) was cleaned with saline. Ears were not cleaned or flushed at any time during the study after the initial administration of treatment on Day 0. DuOtic™ or the placebo control was administered by a dedicated dispenser on Days 0 and 7. Treatment was applied topically to the ear canal, followed by massaging of the base of the ear to ensure distribution of the formulation. Bilateral application was allowed if both ears were affected but effectiveness was based on the evaluation of one ear only.

Measurements and Observations: The right ear was considered the evaluable ear by default; if, the right ear did not qualify (i.e., it did not meet all eligibility criteria) the left ear was considered to be the evaluable ear.

Physical examination, body weight, general otic examination, and hearing tests were completed at baseline (Day 0) and at each subsequent visit on Days 7, 14, 28, and 45. Hematology, serum chemistry, urinalysis, and ear cytology were completed at baseline (Day 0) and at Study Exit. Ear culture of the evaluable ear was performed on Day 0 for all dogs, and at Study Exit in dogs with a final OSS 3.

The primary clinical effectiveness endpoint was the determination of Success/Failure, based on the OSS of the evaluable ear on Day 45. Additional secondary endpoints included success rate per classification of otitis (chronic, sub-chronic, acute), success rate over time, and the overall clinical response assessed by the examining veterinarians and the owners on Days 14 and 45.

Definition of Success/Failure: Each case was considered a treatment success if it achieved an OSS ≤ 3 on Day 45 in the evaluable ear with no worsening of any individual parameters compared to baseline (Day 0). A case was considered a failure if the criteria for success were not met, or the dog exited the study prior to Day 45.

Statistical Methods:
All analyses were performed using Statistical Analysis System (SAS; SAS Institute, Cary, NC, V9.4). For the analysis of effectiveness, a two-sided test was used at a significance level of 0.05. The model included the fixed effect ‘treatment’ and random effects ‘site’ and the interaction ‘treatment-by-site’. A generalized linear mixed model was used to assess the effect of treatment on the evaluable outcome variable (treatment success), assuming a binomial distribution and using a logit link. Back-transformed least squares means, and standard errors of the means were used to summarize the results. The odds-ratio for the DuOtic™ versus placebo control treatment groups was also computed, along with the associated 95% confidence interval.

Results:
A total of 197 dogs (102 DuOtic™ and 95 placebo control) were included in the effectiveness evaluation. The success rate on Day 45 in the DuOtic™ treated group was 62.31% versus 17.84% for the placebo control group (back-transformed least squares estimates). The difference in success rates between the treatment groups was statistically significant (p = 0.0001). The observed success rates for DuOtic™ versus placebo control on Day 45 were similar across all classifications of otitis at presentation: acute (63% versus 16%), sub chronic (63% versus 23%), and chronic (62% versus 16%). The peak success rate for DuOtic™ was observed on Day 28 (73% success rate) and on Day 14 for the placebo control group (28% success rate). At Study Exit, the percent of cases that were considered to have a "*good"* or "*excellent*" clinical response to treatment by the examining veterinarians was 62% for the DuOtic™ group and 13% for the placebo control group. Similarly, owners ranked 71% of DuOtic™-treated dogs and 24% of the placebo control dogs as having a "*good"* or *"excellent*" clinical response on Day 45.

Table II.2. Day 45 Effectiveness Summary.

Treatment	Number of Dogs	Success Rate[1.]
DuOtic™	102	62.31%
Placebo Control	95	17.84%

[1.] Obtained by back transforming the least squares estimates from the statistical model.

Mycology:
Swabs from the evaluable ear were collected for culture from all dogs on Day 0 and from any dog with an OSS > 3 at Study Exit. A total of 373 ear swabs were collected of which 271 were from dogs in the US and 102 from dogs in Spain. *Malassezia pachydermatis* was isolated from 214 of the 239 enrolled dogs on Day 0. *Candida* spp. were isolated from two dogs, both in Spain, on Day 0.

Terbinafine susceptibility testing for *M. pachydermatis* was conducted on 338 isolates obtained from Day 0 or Study Exit. The Minimal Inhibitory Concentration (MIC) summary statistics for the isolates, evaluated separately per geography or combined (US and Spain), were identical, with an MIC_{mode} of 0.12 µg/mL, MIC_{50} of 0.12 µg/mL, and MIC_{90} 0.5 µg/mL (Table II.3). Differences in the *M. pachydermatis* susceptibility from Day 0 to Study Exit and by region were negligible, with only six US isolates showing MICs above the maximum MIC observed in the Spain isolates (1 µg /mL). Three of those US isolates had an MIC of > 16 µg/mL and were from Day 0 and Study Exit swabs from the same dog.

The terbinafine MIC of the two *Candida* spp. isolates were > 16 µg/mL, and both were from the same case. Summary statistics could not be done for *Candida* spp. due to the low number of isolates.

Table II.3. Terbinafine MIC results (µg/mL) for *M. pachydermatis* (Day 0 and Study Exit combined)

Isolates Tested	All Isolates (n = 338)	US (n = 255)	Spain (n = 83)
Min MIC (µg/mL)	0.015	0.015	0.03
Max MIC (µg/mL)	> 16	> 16	1
MIC_{mode} (µg/mL)	0.12	0.12	0.12
MIC_{50} (µg/mL)	0.12	0.12	0.12
MIC_{90} (µg/mL)	0.5	0.5	0.5

Adverse Reactions: The adverse reactions reported during the course of the field study are listed in Table II.4.

Table II.4. Number (%) of dogs with Adverse Reactions by Treatment Group.

Adverse Reactions	DuOtic™ (n = 120)	Placebo Control (n = 119)
Elevated alanine aminotransferase*	4 (3.3%)	0 (0.0%)
Conjunctivitis	1 (0.8%)	0 (0.0%)
Ocular discharge	1 (0.8%)	2 (1.7%)
Ear discharge	0 (0.0%)	1 (0.8%)
Ear pruritus	3 (2.5%)	4 (3.4%)

*Four dogs were reported to have an increase in alanine aminotransferase at Study Exit. The levels reported in subsequent clinical chemistries returned to normal in three dogs, while no follow up was performed for the fourth dog.

Conclusion: DuOtic™ administered as a single intra-auricular dose (1 tube) per affected ear with a second dose seven days later, was safe and effective for the treatment of otitis externa associated with susceptible strains of yeast (*Malassezia pachydermatis*).

III. TARGET ANIMAL SAFETY

As the presentation and concentrations of terbinafine and betamethasone acetate in DuOtic™ are identical to these active ingredients in Osurnia® (florfenicol, terbinafine, betamethasone acetate) Otic gel for dogs, and because the systemic exposure of terbinafine and betamethasone are not expected to be affected by the removal of florfenicol from the formulation, the target animal safety for DuOtic™ is supported by the target animal safety study conducted for the approval of Osurnia®. Refer to the Freedom of Information (FOI) Summary for Osurnia® (NADA 141-437), dated November 4, 2014, for detailed information on this study.

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 DuOtic™:

DuOtic™ may cause eye injury and irritation. In case of accidental eye contact, flush thoroughly with water for at least 15 minutes. If wearing contact lenses, rinse eyes first then remove contact lenses and continue to rinse. If symptoms develop, seek medical advice.

Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. In case of accidental skin contact, wash area thoroughly with water.

Wear eye protection when administering DuOtic™ and restrain the dog to minimize post-application head shaking. Reducing the potential for splatter of product will help prevent accidental eye exposure in people and dogs and help to prevent eye injury. Avoid hand-to-eye contact.

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 DuOtic™, 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 otitis externa and prescribe the appropriate treatment.

B. Exclusivity

DuOtic™, 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 DuOtic™.

C. Patent Information

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