DuOtic™

(terbinafine and betamethasone acetate otic gel)
Antifungal, anti-inflammatory
For Otic Use in Dogs Only
Do not use in cats

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

DESCRIPTION:
DuOtic™ contains 10 mg terbinafine and 1 mg betamethasone acetate per mL and the inactive ingredients propylene carbonate, glycerol formal, hypromellose, phospholipid, oleic acid and butylated hydroxytoluene in an off-white to slightly yellow translucent gel.

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

DOSAGE AND ADMINISTRATION:
DuOtic™ should be administered by a veterinary professional. Wear eye protection when administering DuOtic™ (see **Human Safety Warnings, Precautions, Post-approval Experience,** and **Target Animal Safety**).
Splatter may occur if the dog shakes its head following administration.
Persons near the dog during administration should also take steps to avoid ocular exposure.

1. Clean and dry the external ear canal before administering the initial dose of the product.
2. **Verify the tympanic membrane is intact prior to each administration** (see **Precautions, Contraindications, Target Animal Safety** and **Post-approval Experience**).
3. Administer one dose (1 tube) per affected ear.
   Repeat administration in 7 days.
4. Open tube by twisting the soft tip. Insert the flexible tip in the affected external ear canal and squeeze entire tube contents into the external ear canal. After application, gently massage the base of the ear to allow the gel to penetrate the lower part of the ear canal.
5. **Restrain dog to minimize post-application head shaking** to reduce potential for splatter of product, and accidental eye exposure in people and dogs (see **Post-Approval Experience** and **Target Animal Safety**).
6. Do not clean the ear canal for 45 days after the initial administration to allow contact of the gel with the ear canal. Cleaning the ear may affect product effectiveness (see **Effectiveness**). If alternative otic therapies are required, it is recommended to clean the ear(s) before application of those therapies.

CONTRAINDICATIONS:
Do not use in dogs with known tympanic perforation (see **Precautions**). Do not use in dogs with a hypersensitivity to terbinafine or corticosteroids.

WARNINGS:
Human Safety Warnings:
DuOtic™ may cause eye injury and irritation (see **Precautions, Post-approval Experience** and **Target Animal Safety**).

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.

PRECAUTIONS:
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 (see **Human Safety Warnings, Post-approval Experience** and **Target Animal Safety**). Avoid hand-to-eye contact.

Proper patient selection is important when considering the benefits and risks of using DuOtic™. The use of DuOtic™ in dogs with perforated tympanic membranes has not been evaluated. The integrity of the tympanic membrane should be confirmed before administering each dose of this product. Reevaluate the dog if hearing loss or signs of vestibular dysfunction are observed during treatment.

Changes to the middle ear, such as ulceration of the mucosal lining, have been associated with administration of Osurnia® (florfenicol, terbinafine, betamethasone acetate). The presentation and concentrations of terbinafine and betamethasone acetate in DuOtic™ are identical to the concentrations of these active ingredients in Osurnia® (see **Target Animal Safety**).

Signs of tympanic membrane rupture, internal ear disease such as head tilt, ataxia, nystagmus, facial paralysis, and keratoconjunctivitis sicca have also been reported in relation to the administration of Osurnia® (see **Post-approval Experience**).

Do not administer orally.

Use of topical otic corticosteroids has been associated with adrenocortical suppression and iatrogenic hyperadrenocorticism in dogs (see **Target Animal Safety**).

Use with caution in dogs with impaired hepatic function (see **Target Animal Safety** and **Adverse Reactions**).

The safe use of DuOtic™ has not been evaluated in dogs that are pregnant, lactating or intended for breeding.

ADVERSE REACTIONS:
The following adverse reactions were reported during the course of a US field study for treatment of otitis externa in dogs treated with DuOtic™ with 1 tube per affected ear(s) and repeated after 7 days:

Number (%) of dogs with Adverse Reactions by Treatment

Adverse Reaction	DuOtic™ (n=120)	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.

Post-Approval Experience:
The following adverse events are based on post-approval adverse drug experience reporting for Osurnia® (florfenicol, terbinafine, betamethasone acetate). The presentation and concentrations of terbinafine and betamethasone acetate in DuOtic™ are identical to the concentrations of these active ingredients in Osurnia®. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using this data.

In humans, accidental exposure leading to corneal ulcers and other ocular injuries such as eye irritation, burning, stinging, and itchiness have been reported to occur when the dog shook its head after application of Osurnia®.

In dogs, the adverse events reported for Osurnia® are presented below in decreasing order of reporting frequency:

Deafness, ear discharge, pinnal irritation and ear pain, emesis, head shaking, internal ear disorder (head tilt and vestibular), ataxia, vocalization, corneal ulcer, keratoconjunctivitis sicca, nystagmus, tympanic rupture, and cranial nerve disorder (facial paralysis).

Osurnia® is not approved for use in **cats**. The adverse events reported following extra-label use in cats are presented below in decreasing order of reporting frequency:

Ataxia, anorexia, Horner's syndrome (third eyelid prolapse and miosis), internal ear disorder (head tilt and vestibular), anisocoria, lethargy, head shake, emesis, nystagmus, deafness, and tympanic rupture.

CONTACT INFORMATION:
To report suspected adverse drug events and/or to obtain a copy of the Safety Data Sheet (SDS) or for technical assistance, contact Dechra at 1-866-933-2472.

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

INFORMATION FOR DOG OWNERS:
Owners should be aware that adverse reactions may occur following administration of DuOtic™ and should observe their dog for signs such as deafness, ear pain and irritation, vomiting, head shaking, head tilt, incoordination, eye pain and ocular discharge (see **Animal Safety** and **Post-approval Experience**). Owners should be advised to contact their veterinarian if any of the above signs are observed.

Owners should also be informed that splatter may occur if the dog shakes its head following administration of DuOtic™ which may lead to eye exposure. As a result, eye injuries in humans and dogs have been reported including corneal ulcers following the use of a similar product (Osurnia®). Owners should be careful to avoid ocular exposure (see **Precautions** and **Post-approval Experience**).

CLINICAL PHARMACOLOGY:
DuOtic™ is a fixed combination of two active ingredients: terbinafine (antifungal) and betamethasone acetate (steroidal anti-inflammatory). Terbinafine is an antifungal which selectively inhibits the early synthesis of ergosterol. Betamethasone acetate is a glucocorticosteroid with anti-inflammatory activity.

DuOtic™ dissolves in ear wax and is slowly eliminated from the ear mechanically. Ear inflammation can increase the percutaneous absorption of active substances in DuOtic™.

In a laboratory study conducted in healthy dogs administered Osurnia® (see **Target Animal Safety**), low plasma concentrations of florfenicol, terbinafine, and betamethasone acetate were measurable during the first 2-4 days after administration of 1X dose, and during the first 2-7 days after administration of 5X dose. No quantifiable plasma concentrations of any of the three active ingredients were observed in the pre-dose samples of most dogs prior to second and third administrations. Although total and peak exposure in the blood tended to be highly variable between dogs, systemic drug concentrations tended to increase in a less than dose-proportional manner as the administered dose increased from 1X to 5X. The systemic exposure of terbinafine and betamethasone are not expected to be affected by the removal of florfenicol from the formulation.

MYCOLOGY:
The compatibility of the components of DuOtic™ was demonstrated in a non-interference study. An *in vitro* study of organisms collected from clinical cases of otitis externa in dogs determined that terbinafine inhibits the growth of *Malassezia pachydermatis,* a yeast commonly associated with otitis externa in dogs. The presence of betamethasone acetate in the formulation did not impair the antifungal effect of terbinafine to any clinically significant extent. In a field study (see **Effectiveness**), the minimum of 10 isolates from successfully treated cases with DuOtic™ was met for *Malassezia pachydermatis.*

EFFECTIVENESS:
Effectiveness was evaluated in 197 dogs with otitis externa associated with *M. pachydermatis.* The study was a placebo-controlled, randomized, double-masked, multi-center field study. One hundred and two dogs were treated with DuOtic™ and 95 dogs were treated with placebo control (saline). All dogs were evaluated for safety. Treatment (1 mL) was administered to the affected ear(s) and repeated seven days later. Prior to the first administration only, the ear(s) were cleaned with saline. Four clinical signs associated with otitis externa were evaluated: erythema, edema/swelling, erosion/ulceration, and exudate.

Total clinical scores were assigned for a dog based on the severity of each clinical sign on Days 0, 7, 14, 28, and 45.

Success was determined by clinical improvement at Day 45. The success rates of the two groups were significantly different (p=0.0001); 62.31% of dogs administered DuOtic™ were successfully treated, compared to 17.84% of the dogs in the placebo group.

TARGET ANIMAL SAFETY:
The presentation and concentrations of terbinafine and betamethasone acetate in DuOtic™ are identical to the concentrations of these active ingredients in Osurnia® (florfenicol, terbinafine, betamethasone acetate), approved under NADA 141-437. Therefore, the target animal safety for DuOtic™ is supported by the target animal safety study conducted for the approval of Osurnia®.

In a target animal safety study, 24 mixed breed dogs (4 dogs/sex/group) were aurally administered 0X, 1X (1 mL/ear or 2 mL/dog with repeated administration in 7 days) or 5X (5 mL/ear or 10 mL/dog with repeated administration in 7 days) doses of Osurnia® for a total of 6 administrations in 5 weeks. All dogs remained in good health with normal hearing throughout the study. Decreased weight gain was noted in the 1X and 5X groups compared to the control group. Clinical findings included post-administration ear wetness in 1X and 5X groups and unilateral, transient brown/red discharge from one ear each in two 5X dogs, with erythema in one dog after the 4th application. Local microscopic changes in ears (without clinical effects) included: slight or moderate unilateral vesicle formation within the epithelium of the tympanic membrane in two 1X and four 5X dogs, and unilateral mucosal ulceration in the lining of the middle ear cavity in three 5X dogs. Three 5X dogs had slightly elevated ALT activity, accompanied by minimal or mild microscopic hepatocellular vacuolation (in two dogs). Cortisol response to ACTH stimulation was decreased, but within the normal reference range, in 1X dogs. The 5X dogs had a decrease in serum cortisol levels after ACTH stimulation (below normal reference range) accompanied by decreased adrenal gland and thymic weights with minimal adrenal cortical atrophy and slight (in three dogs) or moderate (in one dog also noted with slightly lower lymphocyte counts) lymphoid depletion of the thymus. The ACTH stimulation test results are consistent with systemic absorption of betamethasone resulting in a likely reversible suppression of the hypothalamic-pituitary-adrenal axis as seen with administration of exogenous corticosteroids.

STORAGE CONDITIONS:
Store at or below 77° F (25° C), with excursions up to 104° F (40° C).

HOW SUPPLIED:
DuOtic™ is a gel in a single-use tube with a flexible soft tip, supplied in cartons containing 2 or 20 tubes.

Approved by FDA under NADA # 141-579

Manufactured for:
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Product of Great Britain

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