Osurnia™
(florfenicol-terbinafine-betamethasone acetate)

Otic gel
Antibacterial, antifungal, anti-inflammatory

For Otic Use in Dogs Only

Caution:
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:
OSURNIA contains 10 mg florfenicol, 10 mg terbinafine and 1 mg betamethasone acetate per mL and the inactive ingredients propylene carbonate, glycerol formal, hypromellose, phospholipid, oleic acid and BHT in an off-white to slightly yellow translucent gel.

Indication:
OSURNIA is indicated for the treatment of otitis externa in dogs associated with susceptible strains of bacteria (Staphylococcus pseudintermedius) and yeast (Malassezia pachydermatis).

Dosage and Administration:
OSURNIA should be administered in the clinic. Clean and dry the external ear canal before administering the initial dose of the product. Administer one dose (1 tube) per affected ear(s) 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. 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. Open tube by twisting the soft tip. Insert the flexible tip into the affected external ear canal(s) and squeeze entire tube contents into the external ear canal(s). After application, gently massage the base of the ear to allow the gel to penetrate to the lower part of the ear canal.

Contraindications:
Do not use in dogs with a hypersensitivity to florfenicol, terbinafine or corticosteroids.

Warnings:
Not for use in humans. Keep this and all medications out of reach of children. Consult a physician prior to use in pregnant or lactating females.

Precautions:
Do not administer orally. Do not use in dogs with known tympanic perforation (see Precautions). Do not use in dogs with a hypersensitivity to florfenicol, terbinafine or corticosteroids.

Clinical Pharmacology:
OSURNIA is a fixed combination of three active substances: florfenicol (antibacterial), terbinafine (antifungal) and betamethasone acetate (steroidal anti-inflammatory). Florfenicol is a bacteriostatic antibiotic which acts by inhibiting protein synthesis. Its spectrum of activity includes Gram-positive and Gram-negative bacteria. Terbinafine is an antifungal which selectively inhibits the early synthesis of ergosterol. Betamethasone acetate is a glucocorticosteroid with anti-inflammatory activity. OSURNIA dissolves in ear wax and is slowly eliminated from the ear mechanically. Ear inflammation can increase the percutaneous absorption of active substances in OSURNIA. In a laboratory study conducted in healthy dogs (see 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.

Microbiology:
The compatibility and additive effect of each of the components in OSURNIA was demonstrated in a component effectiveness and non-interference study. An in vitro study of organisms collected from clinical cases of otitis externa in dogs determined that florfenicol and terbinafine inhibit the growth of Staphylococcus pseudintermedius and yeast* commonly associated with otitis externa in dogs. No clinical synergistic or antagonistic effect of the two antimicrobials was demonstrated. The addition of betamethasone acetate to the combination did not impair antimicrobial activity to any clinically significant extent.

In a field study (see Effectiveness), the minimum of 10 isolates from successfully treated cases with OSURNIA was met for Staphylococcus pseudintermedius, Malassezia pachydermatis, and Pseudomonas aeruginosa. However, there were only three dogs where P. aeruginosa was the only pathogen cultured and they were all treatment failures. Therefore, OSURNIA may not be effective in treating otitis externa in which P. aeruginosa is the only pathogen present.

Effectiveness:
Effectiveness was evaluated in 235 dogs with otitis externa. The study was a double-masked field study with a placebo control (vehicle without the active ingredients). One hundred and fifty-nine dogs were treated with OSURNIA and seventy-six dogs were treated with the placebo control. All dogs were evaluated for safety. Treatment (1 mL) was administered to the affected ear(s) and repeated 7 days later. Prior to the first administration, the ear(s) were cleaned with saline but not prior to the Day 7 administration. Six clinical signs associated with otitis externa were evaluated: pain, erythema, exudate, swelling, odor and ulceration. Total clinical scores were assigned for a dog based on the severity of each clinical sign on Days 0, 7, 14, 30 and 45. Success was determined by clinical improvement at Day 45. The success rates of the two groups were significantly different (p=0.0094; 64.78% of dogs administered OSURNIA were successfully treated, compared to 43.42% of the dogs in the placebo control group.

Animal Safety:
In a target animal safety study, 24 mixed breed dogs (4 dogs/sex/group) were aurally administered 0X, 1X (1 mL/ear) and 5X (5 mL/ear) with repeated administration in 7 days. OSURNIA was applied to 1X and 5X groups, and placebo control to 0X group. The highest administered dose of OSURNIA was met for Staphylococcus pseudintermedius, Malassezia pachydermatis, and Pseudomonas aeruginosa.

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 acetate resulting in a likely reversible suppression of the hypothalamic-pituitary-adrenal axis as seen with administration of exogenous corticosteroids.

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 OSURNIA with 1 tube per affected ear(s) and repeated after 7 days:

Frequency of Adverse Reaction by Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OSURNIA (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Alkaline Phosphatase</td>
<td>15 (7.9%)</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (3.7%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Elevated AST, ALT, ALP*</td>
<td>2 (1.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Weight loss (&gt;10% body weight)</td>
<td>1 (0.53%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hearing Decrease/Loss</td>
<td>1 (0.53%)</td>
<td>1 (1.1%)</td>
</tr>
</tbody>
</table>

*Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP). Two dogs with pre-existing elevations in ALP were reported to have an increase in liver enzymes (ALT, ALP and/or AST) at study exit. Subsequent clinical chemistry returned to pre-treatment levels in one dog, while no follow up was performed for the second dog.

Storage Conditions:
OSURNIA should be stored under refrigerated conditions between 36° - 46° F (2° - 8° C). To facilitate comfort during administration, OSURNIA may be brought to room temperature and stored for up to three months.

How Supplied:
OSURNIA is a gel in a single use tube with a flexible soft tip, supplied in cartons containing 2 or 20 tubes.

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Manufactured for:
Elanco US Inc. Greenfield, IN 46140, USA

Product of Great Britain

10/16