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clinicalnotes™

Otitis Treatment: Some Welcome Relief

Otitis externa is a major reason for insurance claims for dogs.[1] It is also fraught with management difficulties, not the least of which are the pain and hassle of medicating the dog. For years, veterinarians have had to rely on once- to twice-daily otic products, making compliance a challenge. More recently ear packs containing an antibiotic, antifungal, and topical corticosteroid have become available; however, there have been anecdotal concerns regarding these lanolin-based products causing deafness.

Osurnia®, an innovative adaptable gel product from Elanco, offers veterinarians an easily administered alternative to traditional otitis treatments without the need for an owner to remember, and be able, to insert daily or twice-daily drops into the dog's inflamed ears. Containing the antibiotic florfenicol, the antifungal terbinafine, and the steroid betamethasone acetate, Osurnia is indicated for the treatment of canine otitis externa associated with susceptible strains of bacteria (*Staphylococcus pseudintermedius*) and yeast (*Malassezia pachydermatis*).[2]

Osurnia requires only 2 doses, applied one week apart. Each dose comes premeasured in an easy-to-use applicator with a flexible tip. The first dose is applied in the clinic, alleviating owners of the stress of medicating the painful and inflamed ears of their dog. After the ear has been cleaned, Osurnia is deposited into the ear, and gentle massage allows the gel formulation to coat and adhere to the ear canal surface. A second dose is then administered 7 days later at a medical progress examination. The need for only 2 doses of Osurnia, and in-clinic administration, make the treatment of the condition convenient for pet owners. The ingredients in the gel provide up to 45 days of efficacy and owners do not need to, in fact should NOT clean their dog's ears during this time. This regimen allows the dog to recover without the repeated application of medications, cleaners, wipes, and cotton.

Approaching an Otitis Case

Taking a thorough history is an important first step in determining the cause of otitis. Important information can be gleaned including seasonality, recurrence, possible triggers, concurrent or previous dermatologic signs, other pets affected, etc. It is important when working up an otitis case to have 2 goals: 1) to identify and treat the primary cause, and 2) to identify and manage concurrent perpetuating causes. (see ***Table***) Treating only the infection, for example, without addressing the primary factor will most likely result in treatment failure or recurrence.

KEY POINTS

- Otitis is a multi-component disorder that requires investigation of primary, predisposing, and perpetuating factors.
- Pain and discomfort make compliance with veterinary recommendations problematic for even diligent pet owners.
- The 2-time-only application method for Osurnia® provides up to 45 days of efficacy to bring relief for pet and owner and a route to successful treatment.

Important Safety Information
OSURNIA (florfenicol/terbinafine/betamethasone acetate) is for otic use only under veterinary supervision. Do not use in dogs with known tympanic perforation or a hypersensitivity to florfenicol, terbinafine or corticosteroids. Adverse reactions observed during clinical trials include vomiting, increased liver enzymes and transient loss of hearing. Please see accompanying product insert for full prescribing information.

TABLE

COMMON PREDISPOSING, PRIMARY, AND PERPETUATING FACTORS IN OTITIS

Predisposing Factors*	Conformation Excessive moisture Excessive cerumen Systemic disease
Primary Causes	**Parasites (*Otodectes* spp, *Demodex* spp)** **Atopy** **Food allergy** **Endocrine disease** **Foreign bodies** **Immune-mediated disease (such as pemphigus foliaceus)**
Perpetuating Factors†	Bacteria/yeast Otitis media Ruptured tympanic membrane†† Chronic disease

*Create risk
†Impede resolution
††Do not use Osurnia in dogs with known tympanic perforation.

Once a thorough history has been obtained, both the external ear canals and pinnae should be thoroughly examined for the presence of erythema, exudate, discharge, odor, crusting, scaling, and swelling/stenosis. Evaluation of the cartilage to determine if it is soft and pliable or firm, the latter suggesting fibrosis or calcification, should be conducted. Both ears should be examined, including otoscopically, even if only unilateral disease is present. A full dermatologic examination of the patient should also be performed to assess for concurrent dermatologic disease/clinical signs.

An Important Key to Treating Otitis

Cytologic evaluation of the otic exudate, collected using a cotton-tipped applicator,[3] is a simple and inexpensive test that can help the veterinarian to successfully treat an individual case. Both ears can be evaluated on the same slide by separating the samples to opposite ends. The slide is heat fixed and treated with Romanowsky stain (eg, Diff-Quik) and then examined under the microscope for numbers and types of bacteria, yeast, and inflammatory cells. This information generates immediate guidance in the design of a treatment plan as well as immediate feedback to owners as to what type of infection may be present. In addition, taking cytology at medical progress examinations helps the clinician assess response to treatment. The failure to do an initial cytologic examination may result in use of an ineffective treatment, resulting in perpetuation of the problem.[4] In some refractory cases, especially those involving rod-shaped organisms, culture and susceptibility testing may be needed.

Once cytology indicates whether and what type of infection is present, a treatment plan should be instituted. Ear cleaning is an important component of managing otitis externa, as it can help facilitate examination of the ear canal; remove microbes, small foreign bodies, and debris; and increase exposure of the lining of the ear canal to topical agents. Often the first cleaning can be done in the clinic and then a cleanser can be sent home for use in subsequent ear maintenance once the infection is cleared. In cases of severe otitis, including otitis media, it may be necessary to do a deep ear cleaning and evaluation under anesthesia.

In the presence of either *Staphylococcus pseudintermedius* or *Malassezia pachydermatis*, using Osurnia® allows the practitioner the freedom to treat the ear while investigating for the underlying triggers. Meanwhile, the simplified, 2-time-only application eliminates the issue of owner compliance.

Osurnia is also a good choice in patients that are being treated for atopy or food allergy but occasionally flare with otitis externa during allergy season. The residual activity of its active ingredients remains up to 45 days, which helps prevent recurrence. The clinician may meanwhile adjust the allergy therapy to avoid those occasional flares.

If cytology is the first key, determining *why* the dog has otitis is the next. As mentioned earlier, the 2 goals in treating otitis are, first, to identify and treat the primary cause, and then to identify and manage concurrent perpetuating causes. If only the infectious cause is determined and treated, the clinician is setting the scenario for failure and more frequent recurrence. Utilizing the findings from the history, physical/otic/dermatologic examinations, and cytology can help uncover the possible underlying causes. Since allergy is so often a trigger, it is often prudent to begin the dog on a food trial and/or perform a workup for atopic dermatitis while treatment has begun.

References

1. Nationwide Pet Insurance. Top 10 Canine Claims in 2016 List. Nationwide Website. https://press8.petinsurance.com/articles/2016/march/nationwide-reveals-the-10-most-common-medical-conditions-for-dogs-and-cats
2. Elanco, Osurnia® product label.
3. Muller WH, Griffin CE, Campbell KL. *Muller and Kirk's Small Animal Dermatology*, 7th ed. St. Louis: Elsevier. 2013;83.
4. Angus JC. Otic cytology in health and disease. *Vet Clin North Am Small Anim Pract*. 2004; 34:411-424.

Osurnia®
(florfenicol·terbinafine·betamethasone acetate)

Elanco™

USCACOSU00084

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 known tympanic perforation (see **Precautions**).
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 in case of accidental ingestion by humans. In case of accidental skin contact, wash area thoroughly with water. Avoid contact to the eyes.

Precautions:
Do not administer orally.
The use of OSURNIA in dogs with perforated tympanic membranes has not been evaluated.
The integrity of the tympanic membrane should be confirmed before administering this product.
Reevaluate the dog if hearing loss or signs of vestibular dysfunction are observed during treatment.
Use of topical otic corticosteroids has been associated with adrenocortical suppression and iatrogenic hyperadrenocorticism in dogs (see **Animal Safety**).
Use with caution in dogs with impaired hepatic function (see **Animal Safety and Adverse Reactions**).
The safe use of OSURNIA in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

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

Adverse Reaction		
	OSURNIA (n=190)	Placebo (n=94)
Elevated Alkaline Phosphatase	15 (7.9%)	3 (3.2%)
Vomiting	7 (3.7%)	1 (1.1%)
Elevated AST, ALT, ALP*	2 (1.1%)	0 (0.0%)
Weight loss (>10% body weight)	1 (0.53%)	0 (0.0%)
Hearing Decrease/Loss	1 (0.53%)	1 (1.1%)

*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 (ALP, ALT and/or AST) at study exit. Subsequent clinical chemistries returned to pre-treatment levels in one dog, while no follow up was performed for the second dog.

To report suspected adverse drug events, contact Elanco US Inc. at 1-888-545-5973.
For additional information about adverse drug experience reporting for animal drugs, contact the FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth
For technical assistance, contact Elanco US Inc. at 1-888-545-5973.

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 bacteria and yeast commonly associated with otitis externa in dogs. No consistent 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 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:
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.

NADA # 141-437, Approved by FDA

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

Product of Great Britain

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