Otitis news
ausrichter animal health

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Aurizon® Ear Drop Suspension for treatment of otitis externa in dogs

- Marbofloxacin, an antibiotic ***reserved exclusively for veterinary use***
- Registered for ***once-a-day*** treatment[1]
- ***Modern formulation*** for the treatment of otitis externa in dogs
- Marbofloxacin – fluroquinolone antibiotic ***indicated for gram-negative bacteria***[1]
- ***Unique product***, Marbofloxacin – clotrimazole – dexamethasone
- ***Superior*** clinical results compared with currently used treatments
- ***Faster***, observable clinical response to treatment by owners

The registration data that supports the registration of Aurizon:

Aurizon Ear Drops Suspension is an effective, safe treatment of acute and chronic canine otitis externa. Target pathogens include bacteria – *Staphylococcus intermedius* (now classified as *Staphylococcus pseudointermedius*) *Pseudomonas aeruginosa*, *Escherichia coli*, and *Proteus mirabilis* – and the yeast, *Malassezia pachydermatis*. The recommended label dose is 10 drops per ear once daily for 7 to 14 days. The data package included a laboratory study, a field study, three safety/tolerance studies and published literature to support this claim and use pattern.

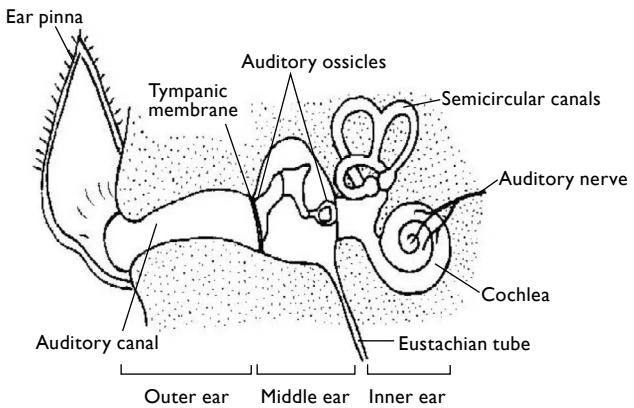
An External Reviewer assessed these studies: a 14-day pivotal laboratory study in dogs evaluated the clinical and microbiological efficacy of Aurizon Ear Drops Suspension. Inflammation, pain at palpation, pruritis and exudate quantity were assessed and compared with untreated controls. Also, microbiological examinations were conducted. Treatment with Aurizon Ear Drops Suspension reduced inflammation, pain and exudates over the time of the study. Pruritis was not noted. Overall, there was an effective reduction of infection.

A multi-centre comparative randomised blind pivotal field study evaluated Aurizon in the treatment of otitis externa in dogs. Dogs with either ceruminal or suppuratives otitis were treated with 10 drops of Aurizon per ear once a day, or 5 drops of Surolan per ear twice a day. Both treatments continued for 14 days depending on the clinical outcome. Investigators assessed each treated subject for improvements in general condition, skin erythema, skin oedema, pruritis, pain, skin ulcerations, state of tympanum, and the quantity and smell of cerumen or pus. Post-treatment microbiology and mycology was conducted on all animals.

The bacteriology results provided MIC values for marbofloxacin against strains of the target bacteria which were identified as being sensitive, resistant or intermediate. ***Marbofloxacin appeared to exhibit a greater efficacy in sensitivity testing of the isolated bacteria than polymyxin B.*** There appeared to be a trend towards greater efficacy against Pseudomonas spp.

Aurizon produced higher pain relief [than Surolan] on days 7 and 14. Similarly, there were significant differences between the two groups in terms of pus quantity and smell at days 7 and 14, with a better return to normal for both measures. ***Response rate at the end of treatment was greater for Aurizon, regardless of the type of otitis.***[4]

Fluroquinolones – and the tympanic membrane



There are many dogs presented with otitis externa where the tympanic membrane is difficult to define or cannot be visualised. The issue for the clinician is that a number of antibiotics, particularly aminoglycosides have been reported as ototoxic or potentially ototoxic.

"However some of the antibacterials contained in ear drops are potentially ototoxic if used in the presence of a ruptured tympanum and/or otitis media, particularly if use is prolonged. They include polymyxin B. Moreover, otitis media is considered to be concomitant with acute otitis externa in 16% of dogs. In this instance, if a tympanum rupture is suspected, topical application of fluoroquinolone is recommended.[1]"

"Marbofloxacin is a third generation fluoroquinolone developed for veterinary use and is an antibacterial with potent bactericidal activity against Gram-positive and Gram-negative organisms. Like other fluoroquinolones, it is not associated with ototoxicity and can achieve high local concentrations when used. It is thus a potentially interesting drug for treatment of canine otitis externa."

In general, aminoglycosides are potentially ototoxic and should be avoided when the integrity of the tympanic membrane is in question.

The ototoxic potential of polymyxin B has been well described experimentally in several species of animals, both in vivo and in vitro.[2]

Corticosteroids are important in the treatment of otitis externa

Corticosteroids are common in topical treatments of otitis for their anti-phlogistic, anti-inflammatory effects.

Corticosteroids not only reduce the inflammation but also lessen the viscosity of the ear contents, thus facilitating their expulsion. (Gustavo Machicote Goth DVM – 08/07/2012)

In general, the potency of topical steroids is assumed to concur with their biologic activities. Relative potencies compared with hydrocortisone are:

hydrocortisone (1);

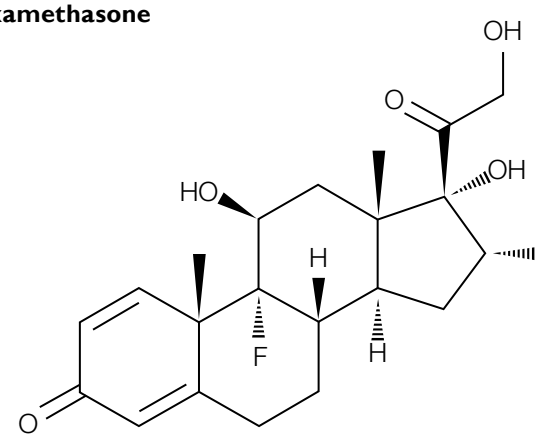
prednisolone (5);

triamcinolone (5);

dexamethasone (25); and

betamethasone (25).

Dexamethasone



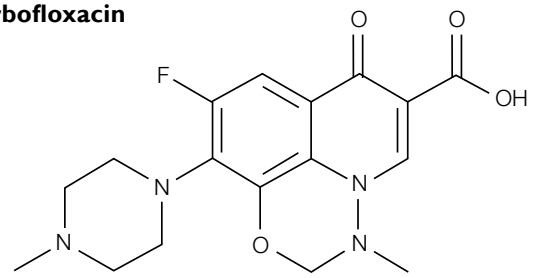
The ear canals of dogs with otitis externa are frequently stenotic. It is essential to open the canals to allow penetration of the topical treatments. This can be accomplished through systemic and/or topical corticosteroids. Often the systemic steroids are administered initially with the idea that topical steroids will maintain the ear canal open.[5]

Dexamethasone injection helps decrease otic inflammation with less side effects. If the ear canal is patent then a potent topical corticosteroid such as dexamethasone or betamethasone may be used to relieve the intense pain and itching.[9]

Concurrent parenteral corticosterioids are indicated for dogs with severe inflammation of the ear canal.[6]

In terms of steroid stength, mometasone is more potent than hydrocortisone, and less potent than dexamethasone.[10]

Marbofloxacin



Marbofloxacin is a carboxylic acid derivative third generation fluoroquinolone antibiotic. It is used in veterinary medicine only. A formulation of marbofloxacin combined with clotrimazole and dexamethasone is available under the name Aurizon Ear Drops.

Its mechanism of action is similar to the other fluoroquinolones by impairing the bacterial DNA gyrase which results in rapid bactericidal activity. The another proposed mechanisms include that it acts against non-dividing bacteria and does not require protein and RNA synthesis, which block protein and RNA synthesis respectively.

It exhibits a broad spectrum of activity against Gram-positive bacteria (e.g. *Staphylococcus intermedius**) and against Gram-negative organisms (*Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus mirabilis*).

*Until a few years ago *Staphylococcus intermedius* was considered a canine commensal species and a frequent cause of pyoderma, wound infections, otitis externa and other body tissue infections in dogs and cats (Morris et al., 2006). However, two independent molecular studies by Bannoehr et al. (2007) and Sasaki et al. (2007b) have recently demonstrated that *S. intermedius* is associated with pigeons, whereas the most common staphylococcal species isolated from dogs is *Staphylococcus pseudointermedius*.[8]

Marbofloxacin is a synthetic, broad spectrum bactericidal agent. The bactericidal activity of marbofloxacin is concentration dependent, with susceptible bacteria cell death occurring within 20-30 minutes of exposure. Like other fluoroquinolones, marbofloxacin has demonstrated a significant post-antibiotic effect for both gram-positive and gram-negative bacteria and is active in both stationary and growth phases of bacterial replication.[3]

It has good activity against many gram-negative bacilli and cocci, is effective against: *Pseudomonas aeruginosa*, *Klebsiella* spp, *Escherichia coli*, *Enterobacter*, *Campylobacter*, *Shigella*, *Salmonella*, *Aeromonas*, *Haemophilus*, *Proteus*, *Yersinia*, *Serratia*, *Vibrio*, *Brucella*, *Chlamydia trachomatis*, *Staphylococci* (including penicillinase-producing and methicillin-resistant strains) and *Mycobacterium*.

Review of published literature and studies confirms the superior efficacy of Aurizon.

The External Reviewer for the APVMA advised that the published literature comprehensively documented the efficacy of marbofloxacin as an antibacterial agent, clotrimazole as an antifungal agent and dexamethasone as a corticosteroid. The Reviewer accepted the literature as strong evidence for the potential efficacy of the combination product.

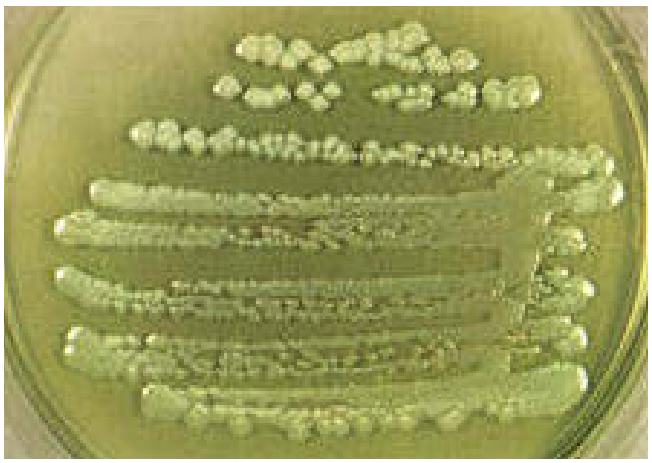
In particular, both pharmacodynamic and pharmacokinetic experimental data were presented to confirm the efficacy of marbofloxacin and clotrimazole in Aurizon.

Their efficacy in relation to other members of the fluoroquinolone and imidazole antifungal groups was well documented and a lack of antagonism between the two compounds was evident. Similarly, adverse effects were documented as largely absent with marbofloxacin. Pharmacological, toxicological and toxicokinetic studies were also presented to support conclusions regarding the absorption and effects of dexamethasone.[4]

"When large numbers of Malassezia are noted, we may look for the superior antifungal effect of clotrimazole."

Because of the frequency with which we encounter resistant strains, it has become difficult to select effective antibiotics for some patients. In small animals the most common bacteria producing resistant infections are *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus* species, and *Enterococcus* species.[6]

Polymixin B is potentially ototoxic. It is contraindicated in the presence of a perforated tympanum.[6]



Pseudomonas aeruginosa colonies on agar. There is a high level of sensitivity of *P aeruginosa* to antibiotic marbofloxacin.

The review of Aurizon registration documentation and data indicates the benefits of otitis externa treatment with Marbofloxacin – clotrimazole – dexamethasone.

- Marbofloxacin exhibits a greater efficacy in sensitivity testing
- Marbofloxacin trends towards greater efficacy against *Pseudomonas* spp
- Dexamethasone produces a higher level of pain relief on 7 and 14 days
- Response rate at the end of treatment was greater for Aurizon, regardless of the type of otitis.[4]

Diagnosis and treatment of otitis externa in dogs – another view

Otitis externa is a common presenting complaint in veterinary and referral practice. The prevalence of otitis externa in dogs is 10-20%, perhaps as high as 30-40% in tropical and subtropical environments. Often, character and smell of the discharge, along with bacterial culture and sensitivity testing are common procedures used in the diagnosis of otitis externa, and as such veterinarians frequently rely on them to select antibiotic therapy for bacterial otitis externa and anti-yeast therapy for Malassezia otitis externa.

Unfortunately, these findings are often unreliable and inconsistent.

Determining what you are treating

In this day of communicable/zoonotic, methicillin-resistant and other bacteria, it is advisable to AVOID sniffing infected ears, as it does not provided accurate information. The visual character of the discharge may also be misleading. For example, candidiasis can result in a mucopurulent discharge with ulcerative aural lesions similar to that of Pseudomonas. Diagnostically, I tend to rely primarily on otic examination and ear cytology.

Otic examination provides a rapid means of diagnosing ear mites, tumours and foreign bodies, as well as providing a clinical baseline from which to correlate laboratory diagnostics with clinical relevance (e.g. purulent ulcerated ear would be consistent with rod-shaped bacteria oncytology and *Pseudomonas aeruginosa* on otic culture). Use of video-otoscopy enhances the clinician's ability to visualize the entire ear canal, magnifying the image 22 times over that of a hand-held otoscope. As well, video-otoscopy provides a wide-angled view that the clinician, technician and client can appreciate on a monitor, enforcing the need for treatment and owner compliance.

Otic cytology is quantitative, giving the clinician a rapid indication of the relative number of morphologically different species present in the ear, which may aid in empirical selection of otic therapy. Discordance between cytology and otic cultures has been reported by Graham-Mize et al., and for this reason, it must be emphasized that otic cultures should always be interpreted with reference to concurrent cytology done by the clinician at the time of sampling, and the results of both these diagnostic tests should be interpreted in light of the otic examination. As well, otic cultures are fraught with many challenges and controversies, hence I tend to only pursue otic bacterial culture and sensitivity when:

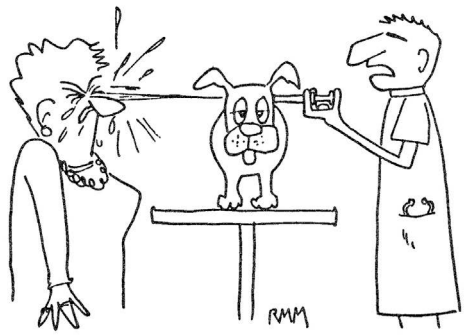
1. The infection has failed to respond to appropriate medication despite good owner compliance indicative of resistant bacteria (MRSA, MRSS, MRSI).
2. When otitis media is present (head tilt), especially if systemic antibiotics are to be used.

NB: Stop all therapy for at least 72 hours prior to culturing for representative results.

Based on a study by Robson et al where sensitivity findings did not correlate with clinical response to topical enrofloxacin, an evaluation of Topical Otic Product Sensitivity (TOPS) testing at the Ontario Veterinary College revealed evidence that correlated these findings. Of note, 33/83 (40%) isolates of Pseudomonas aeruginosa were classified as biofilm producers.

Biofilm MICs for polymyxin B, neomycin and enrofloxacin were significantly higher than for the planktonic form ($P<0.05$) potentially leading to a lack of response to treatment. Biofilm MICs for gentamicin were not statistically different between the planktonic cells and the biofilm embedded bacteria ($P<0.05$). As a result, if polymyxin B, neomycin or enrofloxacin are to be used for topical treatment of a *Pseudomonas* otitis, concentrations of the medications should be increased in particular if addressing chronic otitis as biofilms may have developed.

Considering antimicrobial sensitivities are currently reported as the concentration of drugs systemically delivered to infected tissue, TOPS testing (planktonic and biofilm) is needed to assess topically applied medications, which typically achieve concentrations well above 10 to 1000 times by avoiding the first-pass effect and need for vascular delivery of the medication to the site of infection. Ultimately, commercial distribution of TOPS testing will provide guidance regarding the appropriate selection of topical otic therapies in a patient that has already been non-responsive to 2 or 3 empirically chosen ear medications.



"I can tell you one thing, Madam. These ears have been neglected far too long. The infection is deep . . . very deep!"

Treatment of Otitis Externa

The inflamed ear is an extremely moist and warm environment with readily available nutritional sources and often with a compromised epithelium. Under these conditions, the ear canal is extremely favourable for bacterial and yeast overgrowth, including for those species that otherwise are not part of the commensal population and are simply unable to reproduce successfully in the normal ear canal (e.g. *Pseudomonas* spp., *Enterococcus* spp.). Chronicity of ear disease often worsens this problem. Hence, the three-pronged concept is key to successful treatment of ALL cases of otitis externa:

1. Identify and address the underlying etiology.
2. Calm the microenvironment such that it is not conducive for bacterial or yeast overgrowth.
3. Identify and treat the secondary infection.

My top three underlying etiologies once I have eliminated *Otodectes*, foreign body and neoplasia with the otic examination, include adverse food reactions, environmental allergies and hypothyroidism. Hypothyroidism causes a ceruminous otitis externa with alterations in cerumen lipid composition to low levels of free fatty acids in surface lipids along with increased levels of surface triglycerides, which both in turn acts as fodder for the microorganisms. The bacteria and/or yeast are also allowed to propagate and establish an infection in hypothyroid patients as a result of the compromised immune system.

Other clinical symptoms of hypothyroidism may or may not be noted, hence a thyroid profile is often used to support the clinical diagnosis and establish a basis for supplementation. Rosser reported that up to 24% of adverse food reaction patients present with otitis externa as their only clinical complaint. It behooves us therefore, to consider a dietary restriction using limited ingredient novel or hydrolyzed protein sources in patients with recurrent otitis externa.

Environmental allergies should be a serious consideration in a patient that started with a history of seasonally recurrent otitis externa. Allergy testing and immunotherapy or symptomatic medical management may result in control of the otitis externa without the need for otic therapy.

The "Routine" Otitis Externa

Many topical products contain anti-yeast, antibacterial and anti-inflammatory agents … a shotgun approach. In general, these products work well for uncomplicated first and even repeated cases of otitis externa. Knowledge of the active ingredients within these products will help with selection of the appropriate therapy for your patient. Selection is based on otic examination, otic cytology and correlation with the degree of clinical involvement.

My favourite otic treatment ingredients are as follows:

Topical anti-yeast	Topical antibiotic	Topical anti-inflammatory
Posaconazole	**Marbofloxacin***	Mometasone
Clotrimazole*	Enrofloxacin	Fluocinolone
Enilconazole	Orbifloxacin	Betamethasone
Miconazole	Polymyxin B	**Dexamethasone***
Nystatin	Gentamicin	Prednisone/Prednisolone

NB: Neomycin is a potential contact sensitizer in the ear and hence its use should be limited.

The actives in Aurizon® Ear Drops Suspension – 20 mL recently introduced to the Australian market

1. Rougier S et al; Veterinary Dermatology 2005, 16, 299-307.
2. Vet Clin Small Anim 34 (2004) 541–555.
3. Rod A.W. Rosychuk DVM, DACVIM Colorado State University, Ft. Collins, Colorado.
4. APVMA; Evaluators Review 2013.
5. The University of Tennessee; the College of Veterinary Medicine.
6. Stephen D. White, DVM, Diplomat ACVD Professor, School of Veterinary Medicine University of California, Davissdwhite@ucdavis.edu
7. N. C. Paul, A. Moodley, G. Ghibaudo and L. Guardabassi Zoonoses and Public Health.
8. Yu A DVM, MS, Diplomate ACVD University of Guelph, Guelph, Ontario Canada: Western Veterinary Conference 2013.
9. Gotthelf LN, Montgomery pet Skin and Ear Clinic, Montgomery Alabama USA.
10. Data on file.

Vétoquinol

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