1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Easotic ear drops, suspension for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:

Hydrocortisone aceponate	1.11 mg/ml
Miconazole as nitrate	15.1 mg/ml
Gentamicin as sulphate	1,505 IU/ml.

Excipient:

Qualitative composition of excipients and other constituents
Liquid paraffin.

A white suspension.

3. CLINICAL INFORMATION

3.1 Target species

Dogs.

3.2 Indications for use for each target species

Treatment of acute otitis externa, and acute exacerbation of recurrent otitis externa associated with bacteria susceptible to gentamicin and fungi susceptible to miconazole in particular *Malassezia pachydermatis*.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substances or to any of the excipients, to corticosteroids, to other azole antifungal agents and to other aminoglycosides.
Do not use if the eardrum is perforated.
Do not use concurrently with substances known to cause ototoxicity.
Do not use in dogs with generalised demodicosis.

3.4 Special warnings

Bacterial and fungal otitis is often secondary in nature and appropriate diagnosis should be used to determine the primary factors involved.

3.5 Special precautions for use

Special precautions for safe use in the target species:

If hypersensitivity to any of the components occurs, treatment should be discontinued and appropriate therapy instituted.
Use of the veterinary medicinal product should be based on identification of infecting organisms and susceptibility testing and take into account official and local antimicrobial policies.
Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria and fungi resistant to gentamicin and miconazole respectively and may

decrease the effectiveness of treatment with aminoglycosides and azole antifungal agents, due to the potential for cross-resistance.
In case of parasitic otitis, an appropriate acaricidal treatment should be implemented.
Before the veterinary medicinal product is applied, the external auditory canal must be examined thoroughly to ensure that the ear drum is not perforated in order to avoid the risk of transmission of the infection to the middle ear and to prevent damage to the cochlear and vestibular apparatus.
Gentamicin is known to be associated with ototoxicity when administered by the systemic route at higher doses.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

In case of accidental skin contact, it is recommended to wash thoroughly with water.
Avoid contact with eyes. In case of accidental contact, rinse with abundant quantities of water. In case of eye irritation, seek medical advice.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dogs:

Common (1 to 10 animals / 100 animals treated):	Application site reddening (ear) [1,2]
Uncommon (1 to 10 animals / 1,000 animals treated):	Application site papule [2]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Impaired Hearing [3,4], Deafness [3,4] Hypersensitivity reactions (facial swelling, allergic pruritus) [4]

[1] Mild to moderate.
[2] Recovering without specific therapy.
[3] Primarily in geriatric dogs.
Complete recovery was confirmed in 70% of post marketing cases with an adequate follow-up, otherwise hearing improvement was observed in most dogs.
Recovery has been observed between one week and up to two months after onset of signs.
[4] If the adverse reaction occurs, treatment should be stopped.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Systemic absorption of hydrocortisone aceponate, gentamicin sulphate and miconazole nitrate being negligible, it is unlikely for teratogenic, foetotoxic or maternotoxic effects to occur at the recommended dosage in dogs.
Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

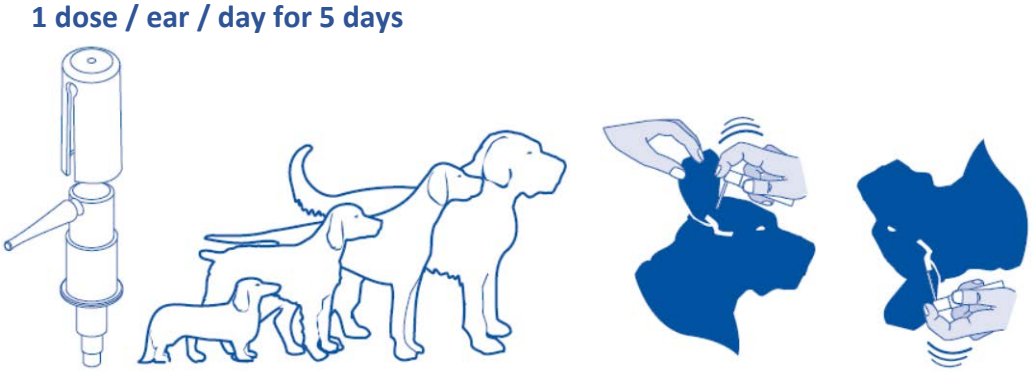
3.8 Interaction with other medicinal products and other forms of interaction

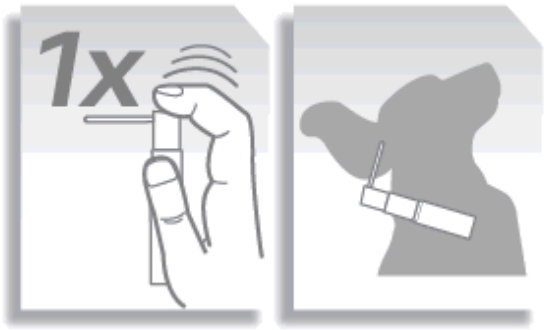
Compatibility with ear cleaners has not been demonstrated.

3.9 Administration routes and dosage

Auricular use.
One ml contains 1.11 mg hydrocortisone aceponate, 15.1 mg miconazole (as nitrate) and 1,505 IU gentamicin (as sulphate).
It is recommended that the external ear canal should be cleaned and dried before treatment and excess hair around the treatment area be cut.
The recommended dosage is 1 ml of the veterinary medicinal product per infected ear once a day for five consecutive days.

Multi-dose container:
Shake the bottle thoroughly before first administration and prime the pump by pressing it.
Introduce the atraumatic canula in the ear canal. Administer one dose (1 ml) of the product in each affected ear. This dose is adequately delivered by one pump activation. The airless pump allows the product to be administered whatever the position of the bottle is.





The product as presented allows treating a dog suffering from bilateral otitis.

Single-dose container:
To administer one dose (1 ml) of the product in the affected ear:

- Take out one pipette from the box.
- Shake the pipette thoroughly before use.
- To open: hold up the pipette upright and break the top of the cannula.
- Introduce the atraumatic cannula in the ear canal. Squeeze gently but firmly in the middle of the body of the pipette.

After application, the base of the ear may be massaged briefly and gently to allow the preparation to penetrate to the lower part of the ear canal.

The veterinary medicinal product should be used at room temperature (i.e. do not instil cold product).

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

At 3 and 5 times the recommended dose, no local or general adverse reactions were observed with the exception of some dogs showing erythema and papulae in the ear canal.
In dogs treated at the therapeutic dose for ten consecutive days, serum cortisol levels decreased from five days onward and returned to normal values within ten days after the end of treatment. However, serum cortisol response levels post ACTH stimulation remained in the normal range during the extended treatment period, indicating a preserved adrenal function.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QS02CA03

4.2 Pharmacodynamics

The veterinary medicinal product is a fixed combination of three active substances (corticosteroid, antifungal and antibiotic):

Hydrocortisone aceponate belongs to the diester class of the glucocorticosteroids with a potent intrinsic glucocorticoid activity which means a relief of both inflammation and pruritus leading to an improvement of clinical signs observed in otitis externa.

Miconazole nitrate is a synthetic imidazole derivative with a pronounced antifungal activity. Miconazole selectively inhibits the synthesis of ergosterol, which is an essential component of the membrane of yeasts and fungi including *Malassezia pachydermatis*. Mechanisms of resistance to azoles consist of either failure in antifungal accumulation or modification of target enzyme. No standardised *in-vitro* susceptibility breakpoints have been defined for miconazole; however, using the method by Diagnostics Pasteur, no resistant strains were found.

Gentamicin sulphate is an aminoglycoside bactericidal antibiotic which acts by inhibiting protein synthesis. Its spectrum of activity includes Gram-positive and Gram-negative bacteria, such as the following pathogenic organisms isolated from the ears of dogs: *Staphylococcus intermedius*, *Pseudomonas aeruginosa*, *Proteus mirabilis, Escherichia coli*, etc.

Since many bacterial strains may be involved in otitis externa in dogs, the mechanisms of resistance can vary. The bacterial resistance phenotypes to gentamicin are mainly based on three mechanisms: enzymatic modification of aminoglycosides, failure of intracellular penetration of the active substance and alteration of the aminoglycoside target.
Cross-resistance is mainly linked with efflux pumps which confer resistance to β-lactams, quinolones and tetracyclines depending on the specificity of the pump with its substrate.
Co-resistance has been described, i.e. gentamicin resistance genes are found to be physically linked to other antimicrobial resistance genes that are transferred between pathogens due to transferable genetic elements such as plasmids, integrons and transposons.
Gentamicin resistant bacteria isolated from the field between 2008 and 2010 in canine otitis before treatment (determined according to CLSI guideline breakpoint ≥ 8 for all isolates except for

Staphylococci ≥ 16 µg/ml) were low: 4.7%, 2.9% and 12.5% for *Staphylococcus* spp., *Pseudomonas* and *Proteus* spp. respectively. All *Escherichia coli* isolates were fully susceptible to gentamicin.

4.3 Pharmacokinetics

After application of the veterinary medicinal product into the ear canal, absorption of miconazole and gentamicin through the skin is negligible.
Hydrocortisone aceponate belongs to the diesters' class of glucocorticosteroids. The diesters are lipophilic components ensuring an enhanced penetration into the skin associated with low systemic bioavailability. The diesters are transformed inside the skin structures in C17 monoesters responsible for the potency of the therapeutic class. In laboratory animals, hydrocortisone aceponate is eliminated the same way as hydrocortisone (other name for endogenous cortisol) through urine and faeces.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Do not mix with any other veterinary medicinal product.

5.2 Shelf life

Multi-dose container:
Shelf life of the veterinary medicinal product as packaged for sale: 18 months.
Shelf life after first opening the immediate packaging: 10 days.

Single-dose container:
Shelf life of the veterinary medicinal product as packaged for sale: 18 months.

5.3 Special precautions for storage

Do not store above 25°C.

5.4 Nature and composition of immediate packaging

Multi-dose container:
Multi-dose container composed of two extruded parts, one external white polypropylene rigid tube and one internal (ethylene-methacrylic acid)-zinc copolymer (Surlyn) flexible pouch containing a steel ball, closed with a 1 ml dosing airless pump equipped with a flexible atraumatic cannula and covered by a plastic cap.
Box containing 1 multi-dose container (the content of 10 ml is equivalent to 10 doses).

Single-dose container:
Pipette composed of high density polyethylene (body and cannula) containing a steel ball.
Cardboard box containing 5, 10, 50, 100 or 200 pipettes.

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

VIRBAC

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/08/085/001–006

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 20/11/2008.

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (*https://medicines.health.europa.eu/veterinary*).