

# MARBOGEN

## COMPLEX EAR DROPS SOLUTION FOR DOGS A.U.V.

**A SOLUTION FOR DOGS' OTITIS EXTERNA TREATMENT!**



**MARBOGEN  
COMPLEX**

**EAR DROPS  
SOLUTION**

**for  
dogs**

**Marboploxacin  
Gentamicin sulfate  
Ketoconazole  
Prednisolone**

**10 ml**

Each ml contains:  
Active substances:  
Marboploxacin 2,041 mg  
Gentamicin sulfate 2,044 mg  
Ketoconazole 4,081 mg  
Prednisolone 1,850 mg

**Indications for use:**  
Treatment of acute otitis externa in dogs when caused by microbological agents. Bacterial, fungal, yeast, and protozoal infections. It is also indicated for the treatment of otitis media and otitis interna. It is also indicated for the treatment of otitis externa in dogs with allergic reactions. It is also indicated for the treatment of otitis externa in dogs with allergic reactions. It is also indicated for the treatment of otitis externa in dogs with allergic reactions.

**For drops use:**  
Auricular use: 2-3 drops 3-4 times a day. Rub the drops into the ear.

**Storage:**  
Store at room temperature (15-25°C).

**For animal use:**  
See the package leaflet for more information.

**Caution:**  
Keep out of the sight and reach of children.

**MARBOGEN COMPLEX**  
ear drops solution for dogs

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## SYNERGISTIC COMBINATION: WHEN 1+1 IS MORE THAN 2!

Otitis externa: why is it so frequent in dogs?

Canine otitis externa is among the top 10 diagnosis in small animal practice. According to data of Banfield small animal hospital chain it was present in 12,9% of the 2,5 million treated dogs in 2015.

It is very common in hanging-eared dogs like Cocker spaniel. In certain breeds, particularly Golden Retrievers: 1 in 4 is affected and Labrador Retrievers 1 in 5 receiving the diagnosis.

Because dogs' ear canals are L-shaped, fluid does not drain easily from canal openings. Additionally, the lining of the ear can become inflamed and thickened, blocking air and fluid flow in and out of the canal. Animals with otitis externa can also develop otitis media.

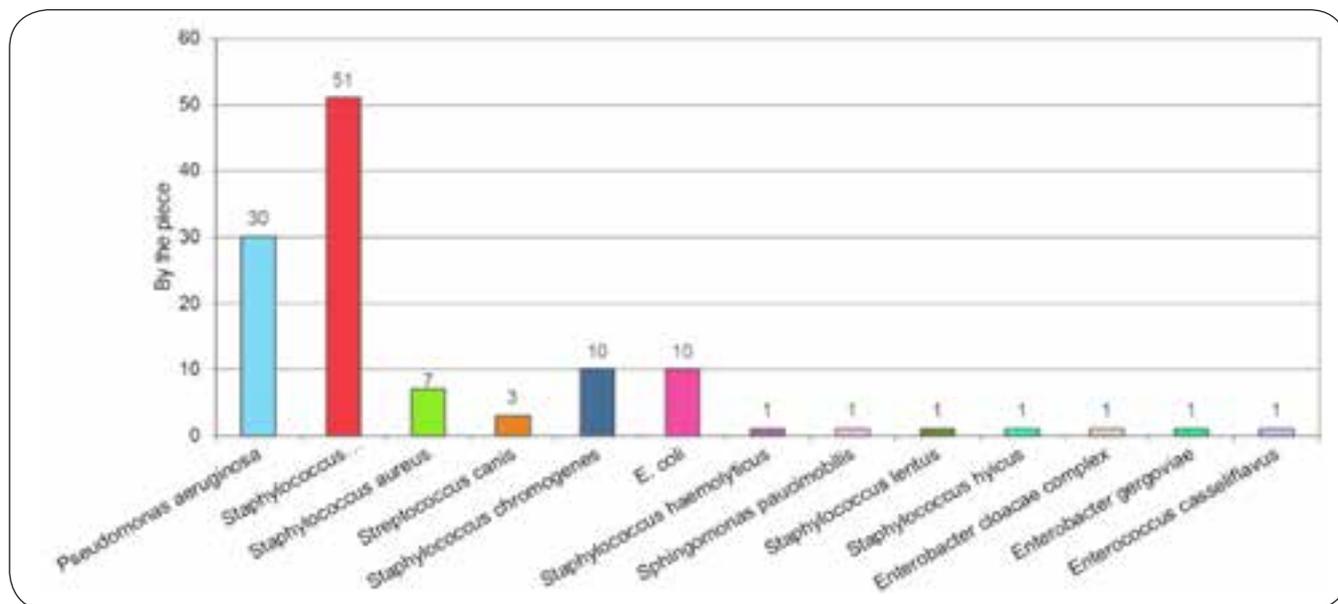
Other predisposing causes can be allergy, inflammation of anal gland, foreign bodies (such as grass seeds), or small ear canals (often seen in Shar peis) or long floppy ear flaps (for example, Basset hounds) that prevent air flow. Hormonal problems, such as poor thyroid function, or other underlying skin disorders may also be present.

Secondary bacterial and fungal infections are common, but primary infection is also possible.

Otitis externa is inflammation of the skin of the ear canal – it is similar to dermatitis of the dog – the difference is that the skin is thinner here, and the ventilation is poor.

If the primary causes are not handled properly the otitis become chronic or relapses.

Species distribution of bacterial isolates from canine otitis externa

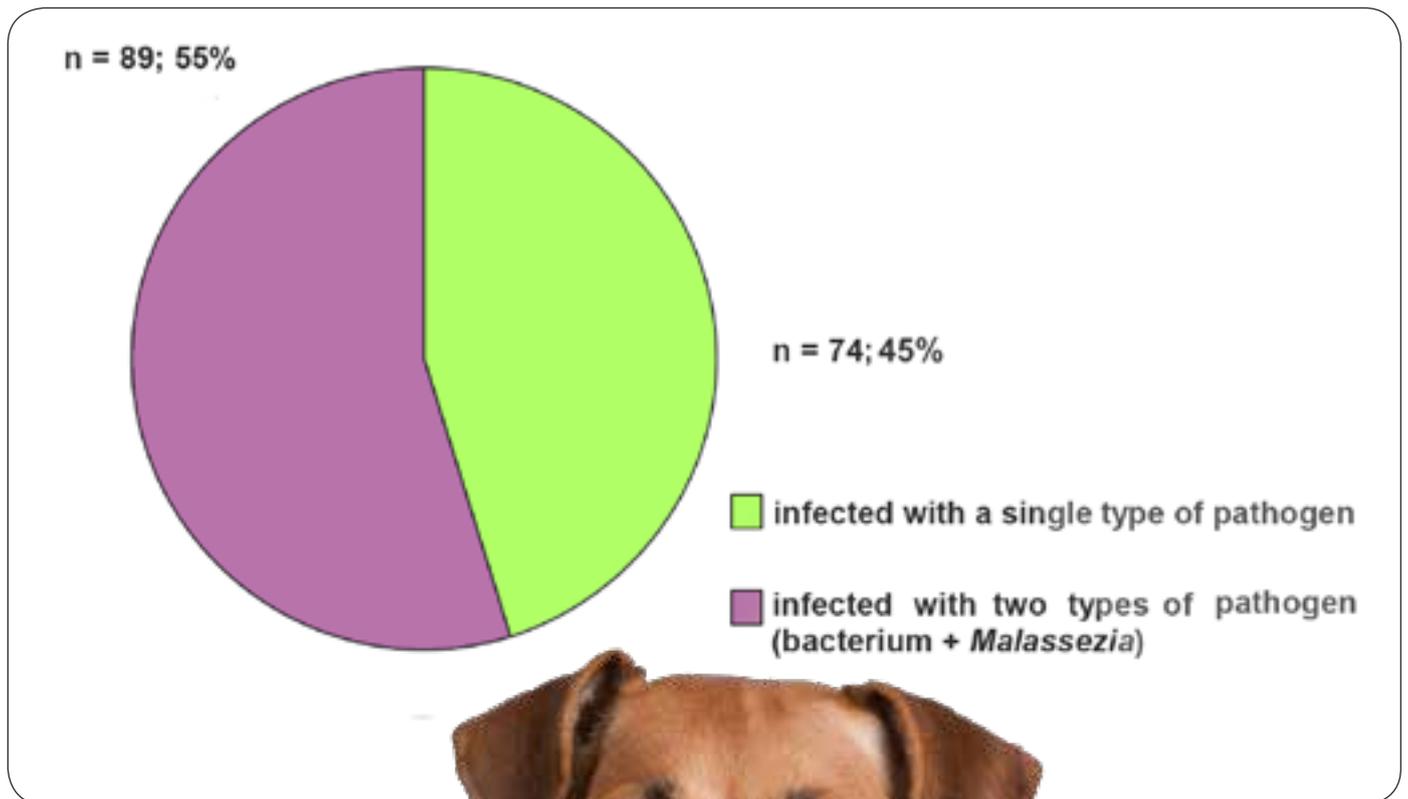




## PATHOGENS IN OTITIS EXTERNA

In our study we analysed canine otitis externa isolates from 7 different geographical areas of Central Europe. In majority of cases (in 55%) mixed fungal and bacterial infection – *Malassezia* and *Staphylococcus* or *Pseudomonas* were detected.

Ratio of single and mixed infections in otitis externa cases





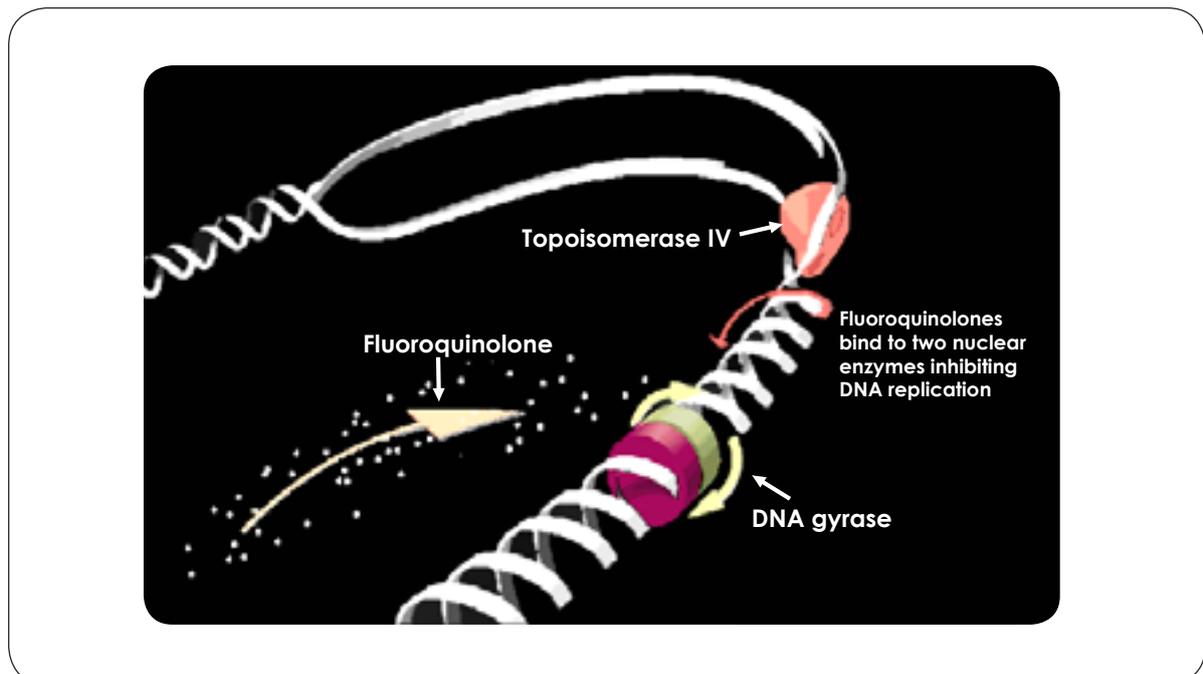
## ABOUT MARBOGEN COMPLEX EAR DROP SOLUTION

Marbogen Complex ear drop solution was developed for treatment of canine otitis externa. Its active ingredients are marbofloxacin, gentamicin-sulfate, ketoconazole and prednisolone. It is a water-based mixture.

Besides antimicrobials Marbogen Complex contains prednisolone as well. Prednisolone is a well-known corticosteroid anti-inflammatory drug. By inhibition of phospholipase A2 it decreases inflammation, pain and irritation. This effect is supplemented by DMSO, an excipient, which also has prompt anti-itching effect.

Marbofloxacin is a second-generation fluoroquinolone antibiotic which is widely used in veterinary medicine for treatment of dermatological and other infections. It is effective against a wide range of bacteria causing dermatitis and otitis externa, especially against *Staphylococcus* and *Pseudomonas aeruginosa*. Marbofloxacin is a concentration-dependent, bactericide antibiotic.

Marbofloxacin acts by blocking bacterial gyrase enzymes

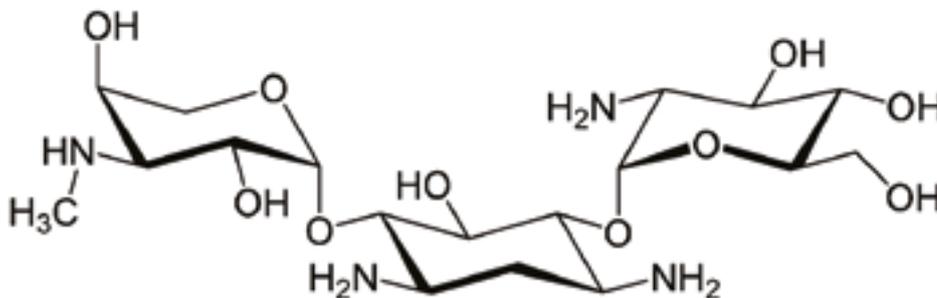




# GENTAMICIN: A POPULAR ANTIBIOTIC FOR OTITIS EXTERNA TREATMENT

Gentamicin is an aminoglycoside antibiotic, which is also often used in everyday veterinary praxis for topical and systemic treatment.

Stereo formula of gentamicin



Ketoconazole is an imidiazol derivate, one of the most effective, broad spectrum antimycotic. It is effective against a wide range of yeasts and Dermatophytions which cause dermatitis: Malassezia, Candida albicans, Trichophyton and Microsporium spp. are usually very sensitive to ketoconazole.



## BIOFILM PRODUCING STRAINS:

WE HAVE A SOLUTION  
FOR THE PROBLEM!

Certain yeast species – similarly to *Pseudomonas* – produce biofilm. The consequence is that in case of certain drugs there can be even thousand fold difference between in vitro and in vivo MIC values. In our studies we found that the biofilm producing *Malassezia pachydermatis* strains isolated from dogs did not grow in presence of 0,008 µg/ml ketoconazole if the biofilm was not present.

On the other hand 0,2-1 µg/ml ketoconazole concentration was necessary to inhibit growth of the same strains if they could develop biofilm on steady surfaces. That is the explanation of the general rule that in a topical dermatological preparation the recommended concentration of an imidazole derivate is much more than the in vitro MIC 90 value of *Malassezia pachydermatis* if the infection is expected. By this way the product will kill biofilm producing strains as well, and prevents development of resistant strains.

A range of papers states that topical antimicrobials should contain the active ingredients on the concentration which is at least 10-12 times higher than the MIC values of less sensitive strains. Around 10% of field isolates of *P. aeruginosa* showed moderate in vitro susceptibility to the 1:1 marbofloxacin : gentamicin combination, that was the basis of determination of Marbogen Complex' active ingredient content. It is not easy to completely remove hair from ear canal before treatment which hampers the product to reach skin surface – that was an other reason to choose relatively high doses of active ingredients.

*Pseudomonas aeruginosa*





# MARBOGEN COMPLEX: THE POWER OF SYNERGY

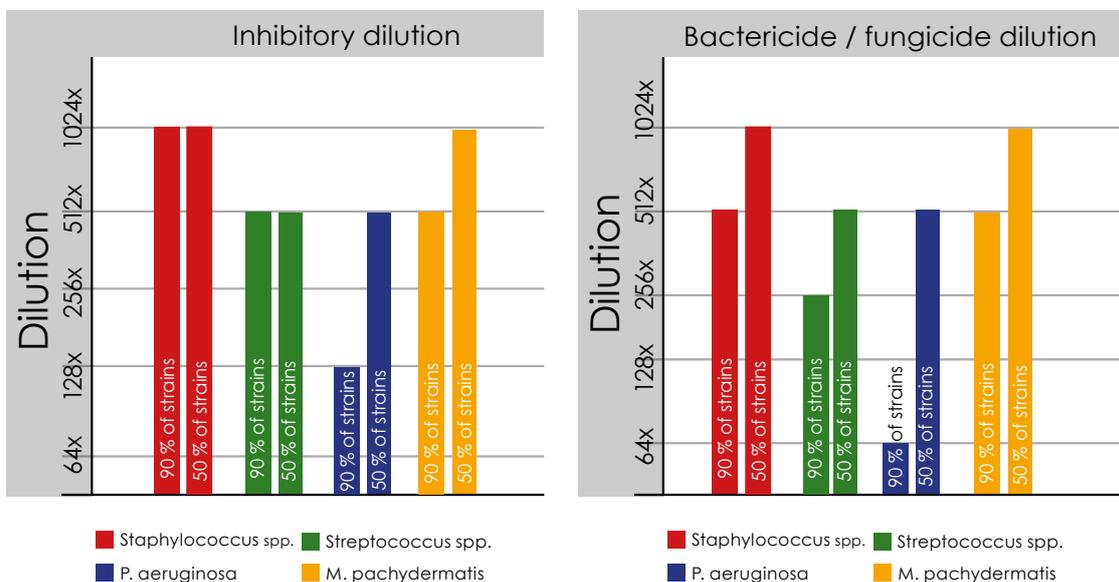
It is a basic principle of modern antibiotic therapy that you have to choose a drug by bacterial resistance profile instead of using several different antibiotics in parallel to widen antibacterial spectrum during the treatment.

In case of Marbogen Complex however the situation is completely different. Antibacterial spectra of marbofloxacin and gentamicin is overlapping, the product contains these antibiotics because there is synergism between them. It has been proven in case of a range of bacteria: *Pseudomonas aeruginosa*, several *Staphylococcus* spp., and *Streptococcus canis*. It results in improved clinical efficacy, and decreasing development of resistance in these mutable pathogens.

Low MIC values are important in particular in case of biofilm producing bacteria, like *Pseudomonas*. This biofilm prevents antibiotic molecules to reach the bacterial cell wall, high drug concentration may be necessary to penetrate through them.

In vitro activity of Marbogen Complex was tested on bacteria isolated from canine otitis externa cases. *Pseudomonas aeruginosa* strains proved to be the less susceptible – still Marbogen Complex was bactericide even in 64x dilution against them.

*In vitro* sensitivity of bacteria and fungi for different dilutions of Marbogen Complex ear drops.



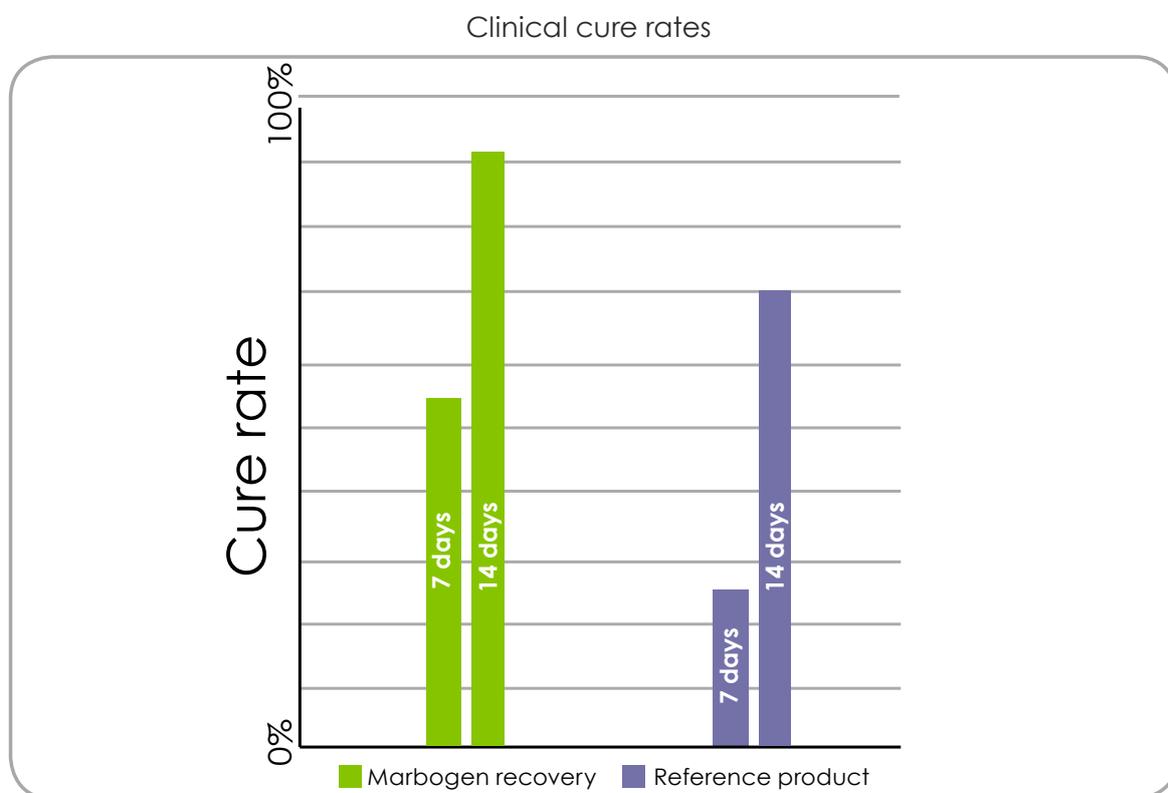


## CLINICAL STUDY RESULTS

Efficacy and safety of Marbogen Complex solution was evaluated in the treatment of naturally occurring canine otitis externa cases in a multicentre, randomised, blinded and blocked field trial performed in 7 Central-European study sites.

The active control was a suspension registered for A.U.V. use containing miconazole, polymyxin-B and prednisolone in paraffin as excipient.

143 dog received Marbogen Complex solution during the study, 94% showed complete recovery till the 14th day of the treatment which was the end point of the study. Average healing times were 8,75 and 8,44 days for right and left ears respectively if Marbogen Complex was used, while in case of control product it has taken 9,87 and 10,14 days (Figure 6). This 1,5 days quicker recovery times is due to marbofloxacin / gentamicin synergistic effect and the unique water soluble formulation.



Marbogen Complex was well tolerated, none of the treatments had to be interrupted because of adverse reactions.

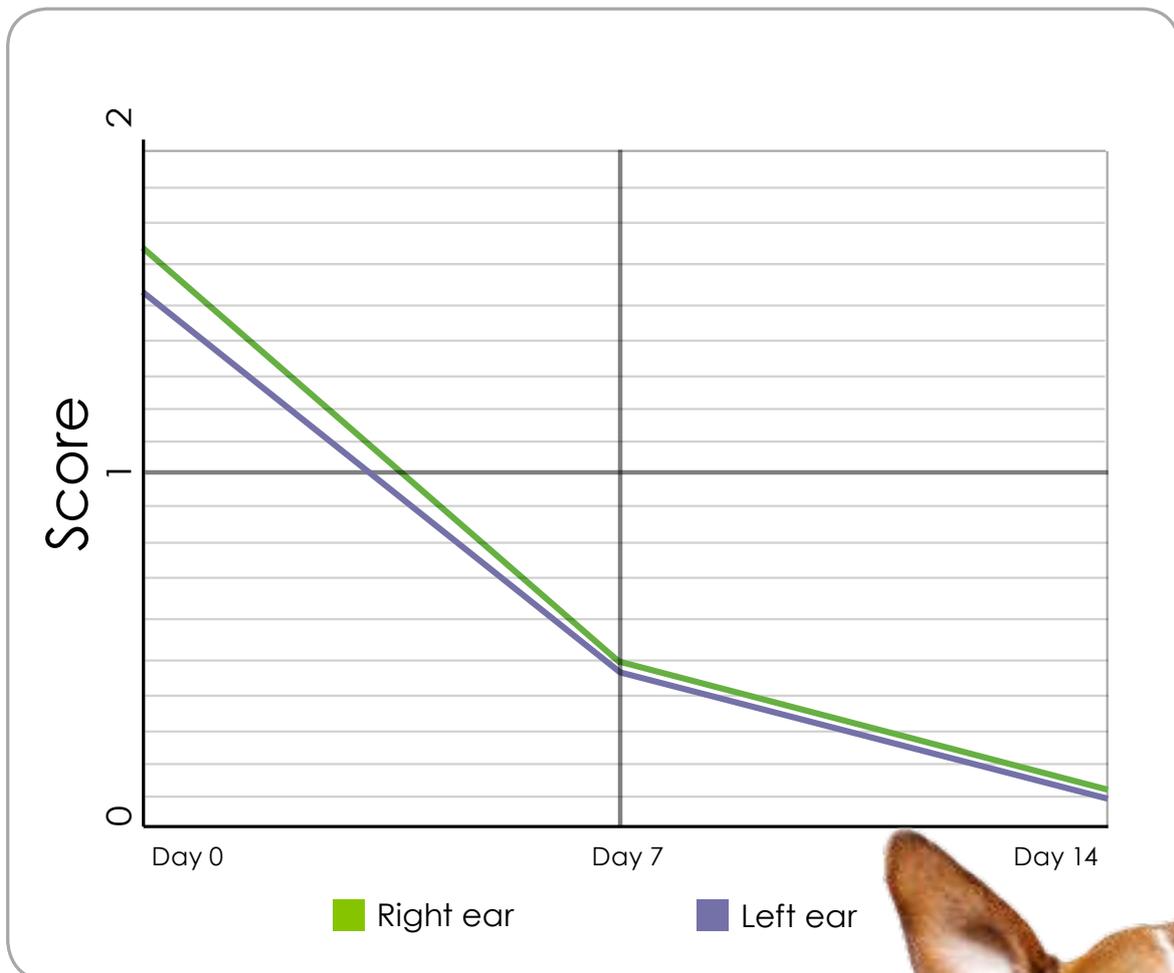


# ITCHING: THE MAIN SOURCE OF REINFECTION DURING OE TREATMENT

Itching time was also measured during the study.

Marbogen Complex decreased itching time with more than one day compared to the control product, which is particularly important: scratching is the main source of reinfection during otitis externa treatment.

*Average itching scores during the treatment*

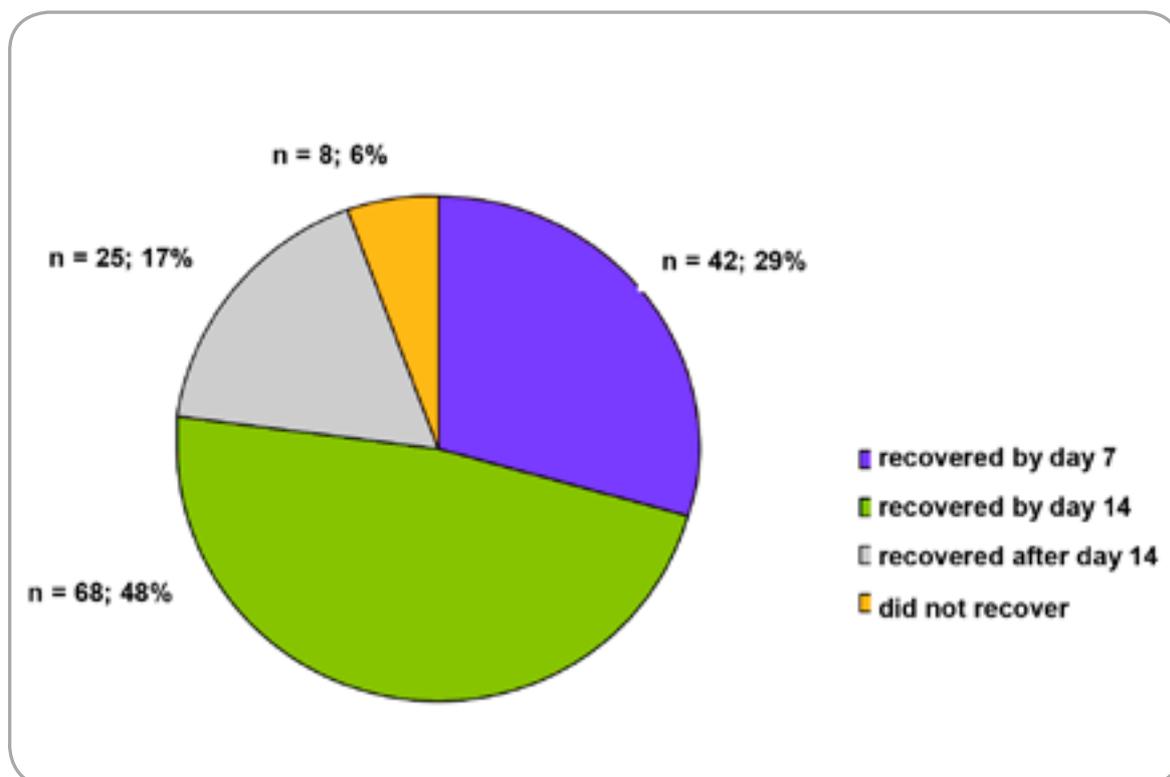




## PROVEN EFFICACY AGAINST PATHOGENS

Microbiological laboratory tests were performed at day 7 and 14 of the study besides clinical healing - 94% of the patients' samples were negative at day 14. Marbogen Complex Solution could eliminate the pathogens in the large majority of cases.

Bacteriological recovery times determined by the testing of Marbogen Complex samples





# MARBOGEN COMPLEX PRODUCT INFORMATION

1 ml contains:

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Marbofloxacin: 2,041 mg

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Gentamicin-sulfate 2,044 mg

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Ketoconazole 4,081 mg

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Prednisolone 1,850 mg

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Indications: Treatment of acute canine otitis externa caused by *Staphylococcus pseudintermedius*, *Pseudomonas aeruginosa* and *Malassezia pachydermatis*, sensitive to ketoconazole.

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Dosage and administration: Drop 5 drops (0,1 ml) twice daily into the ear canal. Maximal recommended treatment time is 14 days.

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Package: 10 ml in plastic (LDPE) drop bottle, in cartoon.

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## References:

1. Banfield: State of Pet Health@2016 Report
2. <https://www.acvs.org/small-animal/otitis-externa>
3. Lajos Zoltán: AZ OTITIS EXTERNA MÁSKÉPPEN: MIKROBIOLÓGIA ÉS ANTIBIOTIKUM-KEZELÉS Bőrgyógyászat fakultáció 2014.05.09.
4. Jerzsele and Gál: Activity of Ketoconazole Against biofilm producing and planctonic *Malassezia pachydermatis* strains – a comparative study. Study code: AU-04/2014
5. Jerzsele and Gál: Pharmacokinetics-pharmacodynamics (PK/PD) analysis for topical products containing marbofloxacin, gentamicin and marbofloxacin:gentamicin in a 1:1 ratio. Study code: AU-05/2014
6. Vandeputte P. et al. Antifungal resistance and new strategies to control fungal infections. *International Journal of Microbiology*. 2012.
7. Kroemer et al.: Antibiotic susceptibility of bacteria isolated from infections in cats and dogs throughout Europe (2002–2009). *Comparative Immunology, Microbiology and Infectious Diseases* 37 (2014) 97–108
8. Csere István: Final study report. Study No: 001/ED/A003
9. MARBOGEN COMPLEX ear drops solution for dogs SUMMARY OF PRODUCT CHARACTERISTICS

# MARBOGEN

## COMPLEX EAR DROPS SOLUTION FOR DOGS A.U.V.

### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MARBOGEN COMPLEX ear drops solution for dogs  
<in AT, BG, CY, EL, HR, HU, IT, LT, LV, MT, PT, RO, SK>  
GENAURIS ear drops solution for dogs<in SI>

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:

Marbofloxacin	2.041 mg
Gentamicin sulfate	2.044 mg
Ketoconazole	4.081 mg
Prednisolone	1.850 mg

Excipients:

For a full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Ear drops, solution

Yellowish, clear to almost clear solution

#### 4. CLINICAL PARTICULARS

##### 4.1 Target species

Dogs

##### 4.2 Indications for use, specifying the target species

Treatment of acute otitis externa in dogs when based on microbiological testing *Staphylococcus pseudintermedius* and *Pseudomonas aeruginosa* and ketoconazole-sensitive *Malassezia pachydermatis* infections are present at the same time and based on the susceptibility testing, due to the different resistance patterns, both marbofloxacin and gentamicin application is deemed necessary against the above bacteria.

##### 4.3 Contraindications

Do not use in case of hypersensitivity to the active substances or to any of the excipients. Do not use in dogs suffering from perforation of the tympanic membrane. See also 4.7.

##### 4.4 Special warnings for each target species

Unnecessary use of the product in terms of any active substance should be avoided. Treatment is indicated only if mixed infection with *Pseudomonas aeruginosa* and *Staphylococcus pseudintermedius* and *Malassezia pachydermatis* has been proved. If one of the active substances is no longer indicated due to the different characteristics of bacterial and fungal infections, the application of the product should be discontinued and replaced by an appropriate treatment option. Bacterial and fungal otitis is often secondary in nature. The underlying cause should be identified and treated.

Eye contact should be avoided during the application of the product. In case of accidental eye contact, immediately flush eyes with plenty of water.

##### 4.5 Special precautions for use

###### Special precautions for use in animals

Use of the veterinary medicinal product should be based on identification of infecting organisms and susceptibility testing, taking into account official and local antimicrobial policies. Care should be taken that diagnostic procedures are not neglected due to the wide spectra of the antimicrobial components.

Diagnostic procedure should include physical examination, cytology examination, and taking swab samples. Samples should be cultured, pathogen microbes and their resistance pattern should be determined.

Heavy reliance on a single class of antibiotic may result in the induction of resistance in a bacterial population. It is prudent to reserve fluoroquinolones for the treatment of clinical conditions, which have responded poorly or are expected to respond poorly to other classes of antibiotics.

Prolonged and intensive use of topical corticosteroids preparation is known to trigger local and systemic effects, including suppression of adrenal function, thinning of the epidermis and delayed healing.

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

People with known hypersensitivity to any of the ingredients should avoid contact with the product.

Personal protective equipment consisting of impermeable gloves should be worn when handling the product.

Do not eat, drink or smoke when administering the product.

In case of skin exposition clean the contaminated area with a water-soap solution.

In case eye contact, wash immediately with abundant water.

Seek medical advice if signs of cutaneous erythema, exanthema, or persistent ocular irritation appear after exposure. Swelling of face, lips and eyes, or respiratory difficulties are more serious signs that need urgent medical action.

##### 4.6 Adverse reactions (frequency and seriousness)

Mild erythematous lesions may be observed following the application. The frequency of adverse reactions is very rare (less than 1 animal in 10,000 animals, including isolated reports)

No adverse reactions were observed after recommended dosage. If hypersensitivity to any of the components occurs, treatment should be discontinued and appropriate therapy instituted.

##### 4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation. The use is not recommended during pregnancy and lactation.

##### 4.8 Interaction with other medicinal products and other forms of interaction

No data are available.

##### 4.9 Amounts to be administered and administration route

Auricular use. Only for external use.

The recommended dose level of the product for dogs is 5 drops (app. 0.1 ml) in the ear canal, two times per day, for 14 days. Before the application of product the hair and dirt on the surface to be treated has to be removed. Massage the base of the ear and try to prevent the dog from shaking its head for at least 5 minutes.

##### 4.10 Overdose (symptoms, emergency procedure, antidotes), if necessary

At 5 times the recommended dose, no local or general adverse reactions were observed. If hypersensitivity to any of the components occurs, treatment should be discontinued and appropriate therapy initiated.

##### 4.11 Withdrawal periods

Not applicable.

#### 5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group:

Otologics containing corticosteroids and anti-infectives in combination.

ATCvet code: QS02AA30

##### 5.1 Pharmacodynamic properties

Marbofloxacin is a synthetic broad-spectrum bactericidal agent. It is classified as second (formerly 3rd) generation fluoroquinolone. It has activity against wide range of Gram-positive and Gram-negative organism, as well as against mycoplasmas. The bactericidal action of marbofloxacin results from interference with the enzymes DNA topoisomerase II (DNA-gyrase) in Gram-negatives and DNA topoisomerase IV in Gram-positives which are needed for the synthesis and maintenance of bacterial DNA. Such impairment disrupts replication of the bacterial cell, leading to rapid cell death. The rapidity and extent of killing are directly proportional to the drug concentration. It consists of significant post antibiotic effect (PAE).

Gentamicin belongs to aminoglycosides and is a mixture of antibiotic substances produced by the growth of *Micromonospora purpurea*. It affects the integrity of the plasma membrane and the metabolism of RNA, but its most important effect is inhibition of protein synthesis at the level of the 30s ribosomal subunit. The mode of its action is time-dependant bactericidal. Gentamicin is often highly effective against wide variety of aerobic bacteria, including *Pseudomonas aeruginosa* and *Staphylococcus* spp..

Marbofloxacin and gentamicin together are active in vitro against a wide variety of Gram-positive and Gram-negative bacteria isolated from domestic animals, including the following organisms isolated from infected canine ears: *Staphylococcus* spp. (including *S. pseudintermedius*) and *Pseudomonas aeruginosa*.

Resistance to fluoroquinolones develops by chromosomal mutations. The primary target of fluoroquinolones in *S. aureus* is considered to be the DNA topoisomerase IV encoded by the *gIIA* gene, and first-step resistance has been associated with mutations in this gene. An efflux pump (norA in norfloxacin resistance) is also incriminated in staphylococcal resistance. Recently plasmid-mediated resistance mechanism (*qnr*-gene) has been described. The mechanisms of resistance in *S. pseudintermedius* are not yet known, but a few data have suggested they are certainly similar to those described for *S. aureus*.

Most clinically important resistance to aminoglycosides is caused by plasmid-mediated enzymes, broadly classified as phosphotransferases, acetyltransferases, and adenyltransferases. Several other mechanisms of resistance are recognized:

1) Increasing the concentration of divalent cations in the media (especially Ca<sup>++</sup> and Mg<sup>++</sup>) increases resistance in *Pseudomonas aeruginosa*.

2) Mutants of *Pseudomonas aeruginosa* produce an excess of outer cell membrane protein, called H1, that confers relative resistance to gentamicin.

Ketoconazole is a broad spectrum imidazole antifungal agent. It inhibits the ergosterol biosynthesis of the sensitive fungal species. Lower concentrations of ketoconazole are fungistatic, however higher concentrations are fungicidal. Ketoconazole exhibits a wide spectrum of in vitro antifungal activity, including against the yeast *Malassezia pachydermatis* frequently isolated from otitic ears in dogs.

Prednisolone is a synthetic corticosteroid. It inhibits the synthesis of eicosanoid molecules during the inflammatory processes due to the inhibition of phospholipase A2 enzyme. It demonstrates pronounced local and systemic anti-inflammatory properties. Corticosteroid therapy is necessary to reduce the irritation and risk of self-trauma, which exist as a result of the acute inflammatory nature of the lesion.

##### 5.2 Pharmacokinetic particulars

When the product was applied in recommended dose for 14 days in one external ear canal, the active ingredients appeared only at very low concentrations in plasma samples. The concentrations remained very low during the whole study. The highest levels of marbofloxacin, gentamicin, ketoconazole and prednisolone in plasma were 2.7 ng/ml, 4.4 ng/l, 1.6 ng/ml and 3.0 ng/ml, on days 14th, 10th, 3rd and 14th respectively. The above maximum levels declined rapidly after the cessation of application.

According to the literature data marbofloxacin, gentamicin and ketoconazole do not appear to be appreciably absorbed systemically following topical application to the skin. Percutaneous absorption of prednisolone is slow, but nearly complete. Each above active ingredient is eliminated from the body within a few days (1-3 d).

#### 6. PHARMACEUTICAL PARTICULARS

##### 6.1 List of excipients

Dimethyl sulfoxide

Polysorbate 80

Propylene glycol

Ethanol (96%)

Water for injection

##### 6.2 Incompatibilities

The bactericidal activity of fluoroquinolones and aminoglycosides is decreased in the presence of acidifying ear cleansers. Acidifying ear cleansers should be avoided.

##### 6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 28 days.

##### 6.4 Special precautions for storage

Store below 25°C.

##### 6.5 Nature and composition of immediate packaging

10 ml white LDPE bottle assembled with white LDPE dropper and closed with white HDPE cap.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

#### 7. MARKETING AUTHORISATION HOLDER

ALPHA-VET Ltd., H-1194 Budapest, Hoffer A. u. 38-40., Hungary.

##### Export Office

E-mail: [export.office@alpha-vet.hu](mailto:export.office@alpha-vet.hu)