[Version 8.1,01/2017]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MARBOGEN COMPLEX ear drops solution for dogs
<in AT, BG, CY, EL, 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 the 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 pachydermatitis* 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.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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 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 7-14 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.
Bacterial and fungal infections might require different treatment schedule. After 7 days of treatment, the veterinary surgeon should evaluate if it is necessary to extend the treatment for another week or to continue the treatment with another product containing a smaller number of active substances.

4.10 Overdose (symptoms, emergency procedures, 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 period(s)
Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Otologicals containing corticosteroids and antiinfectives in combination.
ATC vet 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 ad 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 it's 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 grlA 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++ and Mg++) 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, 4.8 ng/ml, 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 Major incompatibilities

The bactericide 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 Állatgyógyászati Kft., H-1194 Budapest, Hoffherr A. u. 4238-40., Hungary.
Tel.: +36-22-516-416
Fax: +36-22-516-419
E-mail: alpha-vet@alpha-vet.hu

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2016
Date of last renewal: {DD month YYYY}.

10 DATE OF REVISION OF THE TEXT

23 September 2020

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARDBOARD BOX - SECONDARY PACKAGING

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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GENAURIS ear drops solution for dogs
<in SI>

Marbofloxacin, Gentamicin sulfate, Ketoconazole, Prednisolone

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
Active substances:

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

3. PHARMACEUTICAL FORM

Ear drops, solution

4. PACKAGE SIZE

10 ml

5. TARGET SPECIES

Dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Auricular use. Only for external use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once opened use within 28 days.
Use by: ...

11. SPECIAL STORAGE CONDITIONS

Store below 25°C.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ALPHA-VET Állatgyógyászati Kft., Hoffherr A. u. 4238-40., Budapest, H-1194, Hungary

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch {number}

NATIONAL ISSUE - ITALY

Manufacturer responsible for batch release:
ALPHA-VET Állatgyógyászati Kft., Köves János út 13., Bábolna, H-2943, Hungary

MINIMUM PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS

10 ml dropper bottle

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Active substances:

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Ketoconazole	4.081 mg
Prednisolone	1.850 mg

3. PHARMACEUTICAL FORM

Ear drops, solution

4. PACKAGE SIZE

10 ml

5. TARGET SPECIES

Dogs

6. INDICATION(S)

Read the package leaflet before use.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Superbrands Alpha-Vet Állatgyógyászati Kft.

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Batch {number}

B. PACKAGE LEAFLET

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

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
ALPHA-VET Állatgyógyászati Kft., Hoffherr A. u. 4238-40., Budapest, H-1194, Hungary

Manufacturer responsible for batch release:
ALPHA-VET Állatgyógyászati Kft., Köves János út 13., Bábolna, H-2943, Hungary

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

Marbofloxacin, Gentamicin sulfate, Ketoconazole, Prednisolone

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each ml contains:
Active substances:

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

4. INDICATION(S)

Treatment of acute otitis externa in dogs when based on microbiological testing *Staphylococcus pseudintermedius* and *Pseudomonas aeruginosa* and ketoconazole-sensitive *Malassezia pachydermatitis* 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.

5. 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 section 12.

6. ADVERSE REACTIONS

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.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))

- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

Alternatively you can report via your national reporting system {national system details}.

7. TARGET SPECIES

Dogs

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

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 7-14 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.
Bacterial and fungal infections might require different treatment schedule. After 7 days of treatment, the veterinary surgeon should evaluate if it is necessary to extend the treatment for another week or to continue the treatment with another product containing a smaller number of active substances.

9. ADVICE ON CORRECT ADMINISTRATION

Dropper should be cleaned after using with clean paper towel or tissue and the bottle should be tightly closed with cap after using.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Store below 25°C.
Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton after EXP.
Shelf life after first opening the container: 28 days.

12. SPECIAL WARNING(S)

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.

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 skin 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.

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

Interaction with other medicinal products and other forms of interaction:
No data are available.

Overdose (symptoms, emergency procedures, antidotes):
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.

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

~~23 September 2020~~

15. OTHER INFORMATION

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

Available package size: 10 ml