ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Otomicol ear drops and cutaneous suspension for dogs, cats and guinea pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of suspension contains:

Active substances:

Miconazole nitrate	23.00 mg (equivalent to 19.98 mg miconazole)
Prednisolone acetate	5.00 mg
Polymyxin B sulfate	5500 IU (equivalent to 0.5293 mg polymyxin B sulfate).

Excipients:

Qualitative composition of excipients and other constituents
Silica, colloidal anhydrous
Paraffin, liquid

White suspension.

3. CLINICAL INFORMATION

3.1 Target species

Dogs, cats and guinea pigs.

3.2 Indications for use for each target species

For the treatment of primary and secondary infections of skin (eczema, dermatitis, pyoderma) and skin adnexa (hair, claws, sweat glands) in dogs, cats and guinea pigs, as well as for the treatment of otitis externa in dogs and cats, caused by infections with the following miconazole and polymyxin B susceptible pathogens:

Gram-positive bacteria
- *Staphylococcus* spp.
- *Streptococcus* spp.

Gram-negative bacteria
- *Pseudomonas* spp.
- *Escherichia coli*

Yeasts and fungi
- *Malassezia pachydermatis*
- *Candida* spp.
- *Microsporum* spp.
- *Trichophyton spp.*

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Do not use on large wounds.

Do not use in dogs or cats suffering from perforation of the tympanic membrane.

3.4 Special warnings

Do not use in cases of known resistance against polymyxin B or miconazole.
Cross-resistance has been shown between polymyxin B and colistin. Use of the product should be carefully considered when susceptibility testing has shown resistance to colistin because its effectiveness may be reduced.
Bacterial and fungal otitis is often secondary in nature. The underlying cause should be identified and treated.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at local/regional level.
Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.
An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.
In case of otitis externa, before treatment with the veterinary medicinal product is initiated, the integrity of the tympanic membrane must be verified.
Systemic corticosteroid effects are possible, especially when the veterinary medicinal product is used under an occlusive dressing, on skin lesions with increased skin blood flow, or if the veterinary medicinal product is ingested by licking.
Oral ingestion of the veterinary medicinal product by treated animals or animals having contact with treated animals should be avoided.
The veterinary medicinal product should not be used on the mammary glands of lactating animals due to the possible oral intake by the offspring.

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

People with known hypersensitivity to prednisolone, polymyxin B or miconazole should avoid contact with the veterinary medicinal product.
The veterinary medicinal product may cause irritation to skin and eyes. Avoid contact with skin or eyes. Personal protective equipment consisting of single use disposable gloves should be worn when applying the veterinary medicinal product to animals. In case of accidental spillage, skin or eyes should be rinsed immediately with plenty of water.
Take care to avoid accidental ingestion, especially by a child. In case of accidental ingestion, seek medical advice immediately and show the leaflet or the label to the physician.
Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dog, cat, guinea pig:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Deafness[1]

Undetermined frequency (cannot be estimated from the available data):	Local immune deficiency[2,3] Skin thinning[2] Delayed healing[2] Teleangiectasia[2] Increased vulnerability of the skin (with bleeding)[2]

[1]In animals treated for otitis externa, especially in older dogs. Treatment should be discontinued.
[2]With prolonged use due to the contained glucocorticoid.
[3]Associated with increased susceptibility to infection.

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

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Absorption of miconazole, polymyxin B and prednisolone through the skin being low, no teratogenic/ embryotoxic/foetotoxic and maternotoxic effects are expected.
Oral ingestion of the active substances by treated animals when grooming can possibly occur and appearance of the active ingredients in blood and milk can be expected.
The veterinary medicinal product should not be used on the mammary glands of lactating animals.
Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

No data available.

3.9 Administration routes and dosage

For auricular and cutaneous use.

Shake well before use (10 seconds).

Routes of administration:
Dogs, Cats: For instillation in the external auditory canal or for cutaneous application.
Guinea Pigs: For cutaneous application.

Infections of the external auditory canal (otitis externa):
Clean the auricle and external auditory canal and place 3 to 5 drops of the veterinary medicinal product into the external auditory canal twice a day. Massage the auricle and the external auditory canal gently to avoid causing pain to the animal, but thoroughly to ensure proper distribution of the active substances.
Treatment should be continued without interruption until a few days after complete disappearance of the clinical symptoms.

Infections of the skin and skin adnexa:
Apply a thin film of the veterinary medicinal product to the skin lesions to be treated twice a day and rub well.
At the beginning of treatment, hair surrounding or covering the lesions must be clipped; this should be repeated during treatment if necessary. Hygienic measures such as cleaning the skin to be treated before the use of the product are essential for successful therapy.

Treatment should be continued without interruption until a few days after complete disappearance of the clinical symptoms.

In persistent cases (otitis externa or skin infections), treatment may be required for 2 to 3 weeks. If necessary, antimycotic therapy without glucocorticoid should be continued.

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

None known.
Adverse events as stated in section 3.6 may be observed.

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: QS02CA01

4.2 Pharmacodynamics

Polymyxin B
Polymyxin B belongs to the polypeptide antibiotics which are isolated from bacteria. It is only active against Gram-negative bacteria, such as *Pseudomonas* spp. and *E. coli*. The mechanism of action is damage of the microbial cytoplasmic membrane, because polypeptides act as cationic detergents. This results in a bactericidal effect.
Resistance of Gram-negative bacteria to polymyxin may result from chromosomal mutations or horizontal transfer of the *MCR* gene. All *Proteus* species have a natural resistance to polymyxin.

Miconazole
Miconazole belongs to the group of N-substituted imidazole derivatives. Their most important mechanism of action is the inhibition of ergosterol biosynthesis. Ergosterol is an essential membrane lipid and must be synthesised *de novo* by fungi. The lack of ergosterol impedes numerous membrane functions and ultimately leads to cell death. The spectrum of activities covers nearly all fungi and yeasts of relevance to veterinary medicine as well as Gram-positive bacteria.
Practically no development of resistance has been reported. Miconazole has a fungistatic mode of action, but high concentrations are also observed to produce fungicidal effects.

Prednisolone
Prednisolone is a synthetic corticosteroid and is used for its anti-inflammatory, anti-pruritic, anti-exudative and anti-proliferative effects.
This quickly leads to a symptomatic relief in inflammatory skin diseases.
Its anti-inflammatory activity is approx. 4 - 5 times more potent than that of natural cortisol.
Like other glucocorticoids, prednisolone binds to intracellular cytoplasmic receptors in the target organs. After the translocation of the receptor complex into the nucleus it causes derepression of the DNA and subsequently an increase in mRNA synthesis and ultimately protein synthesis. This increases the number of catabolic enzymes for gluconeogenesis. Inhibitory proteins, such as the phospholipase A2-inhibiting lipocortin, are formed. Consequently, the typical glucocorticoid effects and the associated effects are observed. Effects are noticeable only after a latency period. They persist

beyond the elimination of the glucocorticoid from the bloodstream as long as there are receptor-glucocorticoid complexes in the nucleus present.

4.3 Pharmacokinetics

Polymyxin B
After topical application of polymyxin B, there is virtually no absorption of the ingredient through intact skin and mucous membranes, but significant absorption via wounds.

Miconazole
After topical application of miconazole, there is virtually no absorption of the ingredient through intact skin or mucous membranes.

Prednisolone
After topical application of prednisolone to intact skin, the ingredient is subject to limited and delayed absorption. Greater proportion of the applied ingredient can be absorbed in cases of compromised skin barrier function (e.g. skin lesions).

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 6 months

5.3 Special precautions for storage

Store below 25 °C. Store in the original container in order to protect from light.

5.4 Nature and composition of immediate packaging

Folding box consist of:
- white bottle 15 ml, made of low density polyethylene (LDPE)
- white dropper, made of low density polyethylene (LDPE)
- white screw closure with tamper proof ring, made of high density polyethylene (HDPE)

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

KRKA, d.d., Novo mesto

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation:

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

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).

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

{Box}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Otomicol ear drops and cutaneous suspension

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml of suspension contains:

Miconazole nitrate	23.00 mg (equivalent to 19.98 mg miconazole)
Prednisolone acetate	5.00 mg
Polymyxin B sulfate	5500 IU (equivalent to 0.5293mg polymyxin B sulfate)

3. PACKAGE SIZE

15 ml

4. TARGET SPECIES

dogs, cats and guinea pigs

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

For auricular and cutaneous use.
Shake well before use (10 seconds).

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}
Once opened use within 6 months.

9. SPECIAL STORAGE PRECAUTIONS

Store below 25 °C. Store in the original container in order to protect from light.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

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

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

14. MARKETING AUTHORISATION NUMBERS

EU/0/00/000/000

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{Label}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Otomicol

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

15 ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

KRKA

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Otomicol ear drops and cutaneous suspension for dogs, cats and guinea pigs

2. Composition

Each ml of suspension contains:

Active substances:

Miconazole nitrate	23.00 mg (equivalent to 19.98 mg miconazole)
Prednisolone acetate	5.00 mg
Polymyxin B sulfate	5500 IU (equivalent to 0.5293mg polymyxin B sulfate).

White suspension.

3. Target species

Dogs, cats and guinea pigs

4. Indications for use

For the treatment of primary and secondary infections of skin (eczema, dermatitis, pyoderma) and skin adnexa (hair, claws, sweat glands) in dogs, cats and guinea pigs, as well as for the treatment of otitis externa in dogs and cats, caused by infections with the following miconazole and polymyxin B susceptible pathogens:

Gram-positive bacteria
- *Staphylococcus* spp.
- *Streptococcus* spp.

Gram-negative bacteria
- *Pseudomonas* spp.
- *Escherichia coli*

Yeasts and fungi
- *Malassezia pachydermatis*
- *Candida* spp.
- *Microsporum* spp.
- *Trichophyton spp.*

5. Contraindications

Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Do not use on large wounds.
Do not use in dogs or cats suffering from perforation of the tympanic membrane.

6. Special warnings

Special warnings:
Do not use in cases of known resistance against polymyxin B or miconazole.

Cross-resistance has been shown between polymyxin B and colistin. Use of the product should be carefully considered when susceptibility testing has shown resistance to colistin because its effectiveness may be reduced.
Bacterial and fungal otitis is often secondary in nature. The underlying cause should be identified and treated.

Special precautions for safe use in the target species:
Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at local/regional level.
Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.
An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.
In case of otitis externa, before treatment with the veterinary medicinal product is initiated, the integrity of the tympanic membrane must be verified.
Systemic corticosteroid effects are possible, especially when the veterinary medicinal product is used under an occlusive dressing, on skin lesions with increased skin blood flow, or if the veterinary medicinal product is ingested by licking.
Oral ingestion of the veterinary medicinal product by treated animals or animals having contact with treated animals should be avoided.
The veterinary medicinal product should not be used on the mammary glands of lactating animals due to the possible oral intake by the offspring.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to prednisolone, polymyxin B or miconazole should avoid contact with the veterinary medicinal product.
The veterinary medicinal product may cause irritation to skin and eyes. Avoid contact with skin or eyes. Personal protective equipment consisting of single use disposable gloves should be worn when applying the veterinary medicinal product to animals. In case of accidental spillage, skin or eyes should be rinsed immediately with plenty of water.
Take care to avoid accidental ingestion, especially by a child. In case of accidental ingestion, seek medical advice immediately and show the leaflet or the label to the physician.
Wash hands after use.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Absorption of miconazole, polymyxin B and prednisolone through the skin being low, no teratogenic/ embryotoxic/foetotoxic and maternotoxic effects are expected.
Oral ingestion of the active substances by treated animals when grooming can possibly occur and appearance of the active ingredients in blood and milk can be expected.
The veterinary medicinal product should not be used on the mammary glands of lactating animals.
Use only according to the benefit-risk assessment by the responsible veterinarian.

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

Overdose:
None known.
Adverse events as stated in section »Adverse events« may be observed.

Major incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

7. Adverse events

Dog, cat, guinea pig:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Deafness[1]
Undetermined frequency (cannot be estimated from the available data):	Local immune deficiency[2,3] Skin thinning[2] Delayed healing[2] Teleangiectasia[2] Increased vulnerability of the skin (with bleeding)[2]

[1]In animals treated for otitis externa, especially in older dogs. Treatment should be discontinued.
[2]With prolonged use due to the contained glucocorticoid.
[3]Associated with increased susceptibility to infection.

Reporting adverse events is important. It allows continuous safety monitoring of a product. 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 contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder <or the local representative of the marketing authorisation holder> using the contact details at the end of this leaflet, or via your national reporting system: <{national system details}>.

8. Dosage for each species, routes and method of administration

For auricular and cutaneous use.

Routes of administration:
Dogs, Cats: For instillation in the external auditory canal or for cutaneous application.
Guinea Pigs: For cutaneous application.

Infections of the external auditory canal (otitis externa):
Clean the auricle and external auditory canal and place 3 to 5 drops of the veterinary medicinal product into the external auditory canal twice a day. Massage the auricle and the external auditory canal gently to avoid causing pain to the animal, but thoroughly to ensure proper distribution of the active substances.
Treatment should be continued without interruption until a few days after complete disappearance of the clinical symptoms.

Infections of the skin and skin adnexa:
Apply a thin film of the veterinary medicinal product to the skin lesions to be treated twice a day and rub well.
Treatment should be continued without interruption until a few days after complete disappearance of the clinical symptoms.

In persistent cases (otitis externa or skin infections), treatment may be required for 2 to 3 weeks. If necessary, antimycotic therapy without glucocorticoid should be continued.

9. Advice on correct administration

Shake well before use (10 seconds).

At the beginning of treatment, hair surrounding or covering the lesions must be clipped; this should be repeated during treatment if necessary. Hygienic measures such as cleaning the skin to be treated before the use of the product are essential for successful therapy.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.

Store below 25 °C. Store in the original container in order to protect from light.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after Exp. The expiry date refers to the last day of that month.

Shelf life after first opening the immediate packaging: 6 months

12. Special precautions for disposal

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 applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Folding box consist of:
- white bottle 15 ml, made of low density polyethylene (LDPE)
- white dropper, made of low density polyethylene (LDPE)
- white screw closure with tamper proof ring, made of high density polyethylene (HDPE)

15. Date on which the package leaflet was last revised

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

16. Contact details

Marketing authorisation holder and manufacturer responsible for batch release and contact details to report suspected adverse reactions:
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

Local representatives and contact details to report suspected adverse reactions:

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

<17. Other information>