[Version 9,03/2022] corr. 11/2022

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ototop Ear Drops and Cutaneous Suspension for Dogs, Cats and Guinea Pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:

Miconazole nitrate	23.0	mg (equivalent to 19.98 mg miconazole)
Prednisolone acetate	5.0	mg (equivalent to 4.48 mg prednisolone)
Polymyxin B sulfate	5 500	IU (equivalent to 0.5293 mg polymyxin B sulfate)

Excipients:

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

Whitish to slightly yellowish suspension.

3. CLINICAL INFORMATION

3.1 Target species

Dogs, cats, guinea pigs.

3.2 Indications for use for each target species

For the treatment of infection of external auditory canal (otitis externa) in dogs and cats as well as primary and secondary infections of the skin and skin adnexa (hair, nails, sweat glands) in dogs, cats and guinea pigs, caused by the following miconazole and polymyxin B susceptible pathogens:

- Fungi (including yeasts)
  - *Malassezia pachydermatis*
  - *Candida* spp.
  - *Microsporum* spp.
  - *Trichophyton* spp.

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

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

- For the adjunct treatment of an infestation with *Otodectes cynotis* (ear mites) associated with Otitis externa.

3.3 Contraindications

Do not use:

- in cases of hypersensitivity to the active substances, as well as to other corticosteroids, to other azole agents, or to any of the excipients.
- in cases of large skin lesions and on poorly healing or fresh wounds.
- in cases of viral skin infections.
- in animals with perforated ear drums.

For the use in pregnant or lactating animals please refer also to section 3.7.

3.4 Special warnings

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 microbiological sampling and susceptibility testing of the bacteria and/or fungi isolated from the animal. If this is not possible, therapy should be based upon local (regional) epidemiological information about susceptibility of the target pathogens.
Systemic corticosteroid effects are possible, especially when the veterinary medicinal product is used under an occlusive dressing, 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.
Do not use in animals where resistance of causative agents to polymyxin B and/or miconazole is known.

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

The veterinary medicinal product may cause hypersensitivity reactions. People with known hypersensitivity to any of the ingredients should avoid contact with the veterinary medicinal product.
The veterinary medicinal product may cause skin or eye irritation. Avoid contact with skin or eyes.
Always wear single use disposable gloves when applying the veterinary medicinal product to animals.
Wash hands after use.
In case of accidental spillage, skin or eyes should be rinsed immediately with plenty of water.
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, cats, guinea pigs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Deafness[1]
Undetermined frequency (cannot be estimated from the available data):	Local immunosuppression[2,3], skin thinning[2], delayed healing[2], Teleangiectasia[2], increased vulnerability of the skin to bleeding[2] Systemic disorder[4]

[1] Especially in older dogs; in this case treatment should be discontinued.
[2] After prolonged and extensive use of topical corticosteroid preparations.
[3] With increased risk of infections.
[4] Suppression of adrenal function.

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 is low, no teratogenic/embryotoxic/foetotoxic and maternotoxic effects are expected in dogs and cats.

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. Application in the area of the mammary band in suckling dams should be avoided due to the possible direct drug intake by the offspring.
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

Auricular and cutaneous use.
Dogs, Cats: For instillation in the external auditory canal or for cutaneous application.
Guinea Pigs: For cutaneous application.

Shake well before use.

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 applying the veterinary medicinal product are essential for the therapeutic success.

Infections of the external auditory canal (otitis externa):
Clean the auricle and external ear canal and place 3 to 5 drops (0.035 ml per drop) of the veterinary medicinal product into the external auditory canal twice a day. Massage the ear and the auditory canal gently 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, at least for 7 days up to 14 days. The success of the treatment should be verified by a veterinarian before discontinuing treatment.

Infections of the skin and skin adnexa:
Apply the veterinary medicinal product in thin film 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 up to 14 days.

In some persistent cases, treatment may need to be continued for up to 2 to 3 weeks.
In cases where prolonged treatment is necessary repeated clinical examinations including a re-assessment of the diagnosis are required.
If necessary, antifungal therapy without glucocorticoid should be continued.

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

No other symptoms than those mentioned in section 3.6 (Adverse events) are expected.

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 like *Pseudomonas* spp. and *Escherichia coli*. The development of resistance is chromosomal in nature and the development of resistant Gram-negative pathogens is a relatively rare event. However, all *Proteus* species share a natural resistance to polymyxin B.
Polymyxin B binds to phospholipids in the cytoplasmic membrane to disturb membrane permeability. This results in autolysis of the bacteria, thus achieving bactericidal activity.

Miconazole
Miconazole belongs to the group of N-substituted imidazole derivatives. Its most important mode of action is the inhibition of the synthesis of ergosterol. Ergosterol is an essential membrane lipid and must be synthesised *de novo* by fungi. Ergosterol deficiency impedes numerous membrane functions, thus leading to the cell's 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 topically used for its anti-inflammatory, anti-pruritic, anti- exudative, and anti-proliferative effects. This quickly leads to an improvement in inflammatory skin diseases, which is in any case purely symptomatic.
The effectiveness is about 4 – 5 times higher than that of natural cortisol.
Like other glucocorticoids, prednisolone binds to intracellular cytoplasmic receptors in the target organs. After translocation of the receptor complex into the nucleus, the DNA is derepressed which subsequently results in an increased mRNA synthesis and ultimately in protein synthesis. Formation of catabolic enzymes for gluconeogenesis and inhibitory proteins, such as phospholipase A2-inhibiting lipocortin, is increased. Due to this course of the reaction, the typical glucocorticoid effects and the associated effects occur only after a latency period and remain beyond the disappearance of the glucocorticoid out of the bloodstream, as long as there are receptor-glucocorticoid complexes in the cell nucleus.

Ear mites
The exact mechanism of the acaricidal effect is unclear. It is assumed that the mites are suffocated or immobilised by the oily excipients.

4.3 Pharmacokinetics

Polymyxin B
Following topical application of polymyxin B, there is very low absorption of the compound through intact skin and mucous membranes, but significant absorption via wounds.

Miconazole
After topical application of miconazole nitrate, there is very low absorption of the compound through intact skin or mucous membranes.

Prednisolone
When applied topically to intact skin, prednisolone is subject to limited and delayed absorption. Greater absorption of prednisolone should be expected 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: 3 years.
Shelf life after first opening the immediate packaging: 6 months.

5.3 Special precautions for storage

Do not store above 25 °C.

5.4 Nature and composition of immediate packaging

LDPE bottles closed with screw cap and separate drop dispenser in a cardboard box.

Pack sizes:
Bottle of 15 ml
Bottle of 30 ml
Bottle of 100 ml

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

LIVISTO Int'l, S.L.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}.

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).

ANNEX III

LABELLING AND PACKAGE LEAFLET

2. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

{Cardboard box}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ototop Ear Drops and Cutaneous Suspension

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:

Miconazole nitrate	23.0	mg (equivalent to 19.98 mg miconazole)
Prednisolone acetate	5.0	mg (equivalent to 4.48 mg prednisolone)
Polymyxin B sulfate	5 500	IU (equivalent to 0.5293 mg polymyxin B sulfate)

3. PACKAGE SIZE

15 ml, 30 ml, 100 ml

4. TARGET SPECIES

Dogs, cats, guinea pigs.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Auricular and cutaneous use.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

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

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C.

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

LIVISTO Int'l, S.L.

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

{Label bottle 100 ml}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ototop Ear Drops and Cutaneous Suspension

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:

Miconazole nitrate	23.0	mg (equivalent to 19.98 mg miconazole)
Prednisolone acetate	5.0	mg (equivalent to 4.48 mg prednisolone)
Polymyxin B sulfate	5 500	IU (equivalent to 0.5293 mg polymyxin B sulfate)

3. TARGET SPECIES

Dogs, cats, guinea pigs.

(Target species may be replaced by pictogram)

4. ROUTES OF ADMINISTRATION

Auricular and cutaneous use.
Read the package leaflet before use.

5. WITHDRAWAL PERIODS

6. EXPIRY DATE

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

7. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C.

8. NAME OF THE MARKETING AUTHORISATION HOLDER

LIVISTO Int'l, S.L.

9. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{Label bottle 15 ml, 30 ml}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ototop

(Target species in form of pictogram)

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Miconazole nitrate	23.0	mg/ml
Prednisolone acetate	5.0	mg/ml
Polymyxin B sulfate	5 500	IU/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

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

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Ototop Ear Drops and Cutaneous Suspension for Dogs, Cats and Guinea Pigs

2. Composition

Each ml contains:

Active substances:

Miconazole nitrate	23.0	mg (equivalent to 19.98 mg miconazole)
Prednisolone acetate	5.0	mg (equivalent to 4.48 mg prednisolone)
Polymyxin B sulfate	5 500	IU (equivalent to 0.5293mg polymyxin B sulfate)

Whitish to slightly yellowish suspension.

3. Target species

Dogs, cats, guinea pigs.

4. Indications for use

For the treatment of infection of external auditory canal (otitis externa) in dogs and cats as well as primary and secondary infections of the skin and skin adnexa (hair, nails, sweat glands) in dogs, cats and guinea pigs, caused by the following miconazole and polymyxin B susceptible pathogens:

- Fungi (including yeasts)
  - *Malassezia pachydermatis*
  - *Candida* spp.
  - *Microsporum* spp.
  - *Trichophyton* spp.

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

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

- For the adjunct treatment of an infestation with *Otodectes cynotis* (ear mites) associated with Otitis externa.

5. Contraindications

Do not use:
- in cases of hypersensitivity to the active substances, as well as to other corticosteroids, to other azole agents, or to any of the excipients.
- in cases of large skin lesions and on poorly healing or fresh wounds.
- in cases of viral skin infections.
- in animals with perforated ear drums.

For the use in pregnant or lactating animals please refer also to section “Special warnings”.

6. Special warnings

Special warnings:
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 microbiological sampling and susceptibility testing of the bacteria and/or fungi isolated from the animal. If this is not possible, therapy should be based upon local (regional) epidemiological information about susceptibility of the target pathogens.
Systemic corticosteroid effects are possible, especially when the veterinary medicinal product is used under an occlusive dressing, 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.
Do not use in animals where resistance of causative agents to polymyxin B and/or miconazole is known.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
The veterinary medicinal product may cause hypersensitivity reactions. People with known hypersensitivity to any of the ingredients should avoid contact with the veterinary medicinal product.
The veterinary medicinal product may cause skin or eye irritation. Avoid contact with skin or eyes.
Always wear single use disposable gloves when applying the veterinary medicinal product to animals.
Wash hands after use.
In case of accidental spillage, skin or eyes should be rinsed immediately with plenty of water.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
The use on the mammary gland of lactating bitches and queens should be avoided.
Use only according to the benefit-risk assessment by the responsible veterinarian.

Overdose:
No other symptoms than those mentioned in section “Adverse events” are expected.

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

7. Adverse events

Dogs, cats, guinea pigs:

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

Undetermined frequency (cannot be estimated from the available data):
Local immunosuppression[2,3], skin thinning[2], delayed healing[2], Teleangiectasia[2], increased vulnerability of the skin to bleeding[2]
Systemic disorder[4]

[1] Especially in older dogs; in this case treatment should be discontinued.

[2] After prolonged and extensive use of topical corticosteroid preparations.
[3] With increased risk of infections.
[4] Suppression of adrenal function.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal 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

Auricular and cutaneous use.
Dogs, Cats: For instillation in the external auditory canal or for cutaneous application.
Guinea Pigs: For cutaneous application.

Shake well before use.

Infections of the external auditory canal (otitis externa):
Clean the auricle and external ear canal and place 3 to 5 drops (0.035 ml per drop) of the veterinary medicinal product into the external auditory canal twice a day. Massage the ear and the auditory canal gently 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, at least for 7 days up to 14 days. The success of the treatment should be verified by a veterinarian before discontinuing treatment.

Infections of the skin and skin adnexa:
Apply the veterinary medicinal product in thin film 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 up to 14 days.

In some persistent cases, treatment may need to be continued for up to 2 to 3 weeks.
In cases where prolonged treatment is necessary repeated clinical examinations including a re-assessment of the diagnosis are required.
If necessary, antifungal therapy without glucocorticoid should be continued.

9. Advice on correct administration

Shake well before use.

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 applying the veterinary medicinal product are essential for the therapeutic success.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.
Do not store above 25 °C.
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

Xxx

Pack sizes:
Bottle of 15 ml
Bottle of 30 ml
Bottle of 100 ml

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{MM/YYYY}

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 contact details to report suspected adverse reactions:
LIVISTO Int'l, S.L.
Av. Universitat Autònoma, 29
08290 Cerdanyola del Vallès (Barcelona)
Spain
Tel: +34 934 706 270

Manufacturer responsible for batch release:

aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	aniMedica Herstellungs GmbH Im Südfeld 9 48308 Senden-Bösensell Germany

Industrial Veterinaria S.A.
Esmeralda 19
08950 Esplugues de Llobregat (Barcelona)
Spain

Local representatives and contact details to report suspected adverse reactions: