[Version 8.1,01/2017]

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 0.5293mg polymyxin B sulfate)

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ear drops and cutaneous suspension.
Whitish to slightly yellowish suspension

4. CLINICAL PARTICULARS

4.1 Target species

Dogs, Cats, Guinea Pigs

4.2 Indications for use, specifying the 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.

4.3 Contraindications

Do not use:
- in cases of known hypersensitivity to the active substances of the veterinary medicinal product, as well as to other corticosteroids, to other azole agents, or to any of the excipients.
- in animals where resistance of causative agents to polymyxin B and/or miconazole is known
- 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 4.7.

4.4 Special warnings for each target species

Bacterial and fungal otitis is often secondary in nature. The underlying cause should be identified and treated.

4.5 Special precautions for use

Special precautions for use in animals

Use of the 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 product is used under an occlusive dressing, with increased skin blood flow, or if the product is ingested by licking.

Oral ingestion of the product by treated animals or animals having contact with treated animals should be avoided.

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 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.

4.6 Adverse reactions (frequency and seriousness)

Use of this veterinary medicinal product may very rarely be associated with the occurrence of deafness (especially in older dogs), in this case treatment should be discontinued.

Prolonged and extensive use of topical corticosteroid preparations is known to lead to local immunosuppression with increased risk of infections, thinning of the epidermis and delayed wound healing, teleangiectasia and increased vulnerability of the skin to bleeding and systemic effects, including suppression of adrenal function.

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 product has not been assessed 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 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 veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

No data available.

4.9 Amounts to be administered and administration route

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.

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.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

No other symptoms than those mentioned in section 4.6 are expected.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Otologicals, Corticosteriods and antiinfectives in combination.
ATC vet code: QS02CA01.

5.1 Pharmacodynamic properties

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 *E. 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.

5.2 Pharmacokinetic particulars

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Silica colloidal anhydrous
Paraffin, liquid

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

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: 6 months

6.4. Special precautions for storage
Do not store above 25 °C

6.5 Nature and composition of immediate packaging
LDPE bottles closed with screw cap and separate drop dispenser.
Pack sizes.
Cardboard box containing 1 bottle of 15 ml
Cardboard box containing 1 bottle of 30 ml
Cardboard box containing 1 bottle of 100 ml

Not all pack sizes may be marketed.

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

LIVISTO Int'l, S.L.
Av. Universitat Autònoma, 29
08290 Cerdanyola del Vallès (Barcelona)
Spain

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation:> <{DD/MM/YYYY}><{DD month YYYY}.>
<Date of last renewal:> <{DD/MM/YYYY}> <{DD month YYYY}.>

10 DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE
Not applicable.