ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DuOtic 10 mg/1 mg ear gel for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (1.2 g) contains:

Active substances:
Terbinafine 10 mg
Betamethasone acetate 1 mg
(equivalent to betamethasone base 0.9 mg)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Butylhydroxytoluene (E321)	1 mg
Oleic acid	
Lecithin	
Hypromellose	
Propylene carbonate	
Glycerol formal	

Off-white to slightly yellow translucent gel.

3. CLINICAL INFORMATION

3.1 Target species

Dogs.

3.2 Indications for use for each target species

Treatment of otitis externa associated with *Malassezia pachydermatis.*

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substances, to other corticosteroids or to any of the excipients.
Do not use if the eardrum is perforated.
Do not use in dogs with generalised demodicosis.

3.4 Special warnings

Clean the ears before the initial treatment is applied. In clinical trials, saline only was used for ear cleaning before the first application of the veterinary medicinal product and ears were not cleaned again during the duration of the study (45 days).

If treatment with this veterinary medicinal product is discontinued, the ear canals should be cleaned before treatment with an alternative product is initiated.

Transient wetness of the inner and outer pinna may be observed after administration. This observation is attributed to presence of the veterinary medicinal product and is not of clinical concern. Fungal otitis is often secondary to other conditions. Appropriate diagnosis should be used, and therapy of causative conditions should be investigated before antimicrobial treatment is considered.

In animals with a history of chronic or recurrent otitis externa, efficacy of the veterinary medicinal product may be affected if the underlying causes of the condition such as allergy or anatomical conformation of the ear are not addressed.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Safety has not been established in dogs less than 2 months of age or weighing less than 1.4 kg.

Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogen. If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at the local/regional level.

Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.

Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of fungi resistant to terbinafine and may decrease the effectiveness of treatment with other antifungal agents.

In case of parasitic or bacterial otitis externa, an appropriate acaricidal or antibiotic treatment should be implemented as appropriate.

Before the veterinary medicinal product is applied, the external auditory canal must be examined thoroughly to ensure that the ear drum is not perforated (see section 3.3).

Prolonged and intensive use of topical corticosteroid preparations is known to trigger systemic effects, including suppression of adrenal function (see section 3.10).

Decreased cortisol levels were observed after product instillation in tolerance studies using a related product (before and after ACTH stimulation), indicating that betamethasone is absorbed and enters the systemic circulation. The finding was not correlated with pathological or clinical signs and was reversible.

Additional concurrent corticosteroid treatments should be avoided.

Use with caution in dogs with a suspected or confirmed endocrine disorder (i.e. diabetes mellitus; hypo- or hyper-thyroid disease, etc.).

The veterinary medicinal product may be irritating to eyes. Avoid accidental contact with the dog's eyes. If accidental ocular exposure does occur, the eyes should be flushed thoroughly with water for 10 to 15 minutes. If clinical signs develop, seek veterinary advice.

In very rare cases, eye disorders such as keratoconjunctivitis sicca and corneal ulcers have been reported in dogs treated with a related product, in the absence of eye contact with the product.

Although a causal relationship with the product was not definitively established, owners should be recommended to monitor for ocular signs (such as squinting, redness and discharge) in the hours and

days following the veterinary medicinal product application, and to promptly consult a veterinarian in case such signs appear.

The safety and efficacy of the veterinary medicinal product in cats has not been evaluated. Post-marketing surveillance of a related product shows that the use of the product in cats can be associated with neurological signs (including Horner's syndrome with protrusion of membrane nictitans, miosis, anisocoria, and internal ear disorders with ataxia and head tilt) and systemic signs (anorexia and lethargy). The use of the veterinary medicinal product in cats should therefore be avoided.

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

The veterinary medicinal product may be irritating to eyes. Accidental eye exposure may occur when the dog shakes its head during or just after administration. To avoid this risk for the owners, it is recommended that this veterinary medicinal product is administered only by veterinarians or under their close supervision. Appropriate measures (e.g. wearing safety glasses during administration, massaging the ear canal well after administration to ensure even distribution of the veterinary medicinal product, restraining the dog after administration) are needed to avoid exposure to the eyes.

Avoid hand-to-eye contact. In case of accidental ocular exposure, flush the eyes thoroughly with water for 10 to 15 minutes. If symptoms develop, seek medical advice and show the package leaflet or the label to the physician.

In case of accidental skin contact, wash exposed skin thoroughly with water.
In case of accidental ingestion by humans, 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:

Uncommon (1 to 10 animals / 1,000 animals treated):	Elevated liver enzymes[a]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Deafness, impaired hearing[b] Application site reactions (i.e. erythema, pain, pruritus, oedema, ulcer) Hypersensitivity reactions (including facial oedema, urticaria, shock)[c]

[a] Mainly transient elevation of alanine aminotransferase
[b] Usually temporary. Mainly in elderly animals
[c] If hypersensitivity to any of the components occurs, the ear should be thoroughly washed

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 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:

Betamethasone is known to be teratogenic in laboratory species.

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

Do not use during pregnancy and lactation.

Fertility:

Do not use in breeding animals.

3.8 Interaction with other medicinal products and other forms of interaction

Compatibility with ear cleaners, other than saline, has not been demonstrated.

3.9 Administration routes and dosage

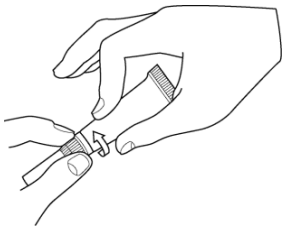
Auricular use.

Administer one tube per affected ear. Repeat the administration after 7 days. The maximum clinical response may not be seen until 21 days after the second administration (28 days after the start of treatment).

Instructions for proper use:

It is recommended to clean and dry the external ear canal before the first administration of the veterinary medicinal product.

1. Open the tube by twisting the soft tip.



2. Introduce this flexible soft tip into the ear canal.
3. Apply the veterinary medicinal product into the ear canal by pressing it between two fingers.

After application, the base of the ear may be massaged briefly and gently to facilitate even distribution of the veterinary medicinal product into the ear canal.

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

In a study using a related, similar product, auricular administration of five times the recommended dose, one week apart, for 5 consecutive weeks (a total six administrations of 5 tubes per ear or 10 tubes per dog) to mixed breed dogs weighing 10 to 14 kg resulted in clinical signs of wetness of the inner and outer pinna (attributed to presence of the product). There were no clinical signs associated with unilateral vesicle formation within the epithelium of the tympanic membrane (also observed after six administrations, one week apart, of 1 tube per ear or 2 tubes per dog), unilateral mucosal ulceration in the lining of the middle ear cavity, or decrease in serum cortisol response below normal reference range in ACTH stimulation testing. The decreased adrenal and thymus weights accompanied by

atrophy of the adrenal cortex and lymphoid depletion of the thymus correlated with the decreased cortisol levels, and were consistent with the pharmacologic effects of betamethasone. These findings are considered reversible. Reversibility of the epithelial tympanic membrane blistering is also likely through epithelial migration, a natural self-cleaning and self–repair mechanism for the tympanic membrane and ear canal. Additionally, dogs showed slightly elevated red blood cell count, haematocrit, total protein, albumin and alanine aminotransferase. These findings were not associated with clinical signs.

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: QS02CA90

4.2 Pharmacodynamics

The veterinary medicinal product is a fixed combination of two active substances (a corticosteroid and an antifungal):

Terbinafine is an allylamine with a pronounced fungicidal activity. It selectively inhibits the early synthesis of ergosterol, which is an essential component of the membrane of yeasts and fungi including *Malassezia pachydermatis*. Resistance to terbinafine and other allylamines is rare and is usually associated with point mutations in the squalene epoxidase gene that cause amino acid changes in the enzyme necessary for the ergosterol synthesis pathway, impairing the binding of the allylamines. An MIC_{50} of 0.12 µg/mL and an MIC_{90} of 0.25 µg/mL have been calculated based on isolates collected from dogs with yeast predominant otitis externa in several European countries between 2021 and 2023. Terbinafine has a different mode of action than azole antifungals, therefore there is no cross resistance with azole antifungals. Cross-resistance with other antifungals has not been reported.

Betamethasone acetate belongs to the diesters class of glucocorticosteroids with a potent intrinsic glucocorticoid activity which relieves both inflammation and pruritus leading to an improvement of clinical signs observed in otitis externa.

4.3 Pharmacokinetics

The formulation dissolves in ear wax and is slowly eliminated from the ear mechanically.

Systemic absorption of the active substances was determined in multiple-dose studies using a related, similar product. After placing this veterinary medicinal product into both ear canals of healthy mixed breed dogs, absorption occurred primarily during the first two to four days after administration, with low peak plasma concentrations of betamethasone and terbinafine (1.5 and 3.7 ng/ml respectively). The extent of percutaneous absorption of topical medications is determined by many factors including the integrity of the epidermal barrier. Inflammation can increase the percutaneous absorption of veterinary medicinal products.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

Single-use multi-layered aluminium and polyethylene tube with a polypropylene screw cap and bonded thermoplastic elastomer applicator tip.

Cardboard box containing 2, 20 or 40 tubes (each tube containing 2.05 g of the veterinary medicinal product of which a single dose of 1.2 g can be extracted).

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

Dechra Regulatory B.V.

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/24/327/001-003

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 22/11/2024.

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

{DD month 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 II

OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

None

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DuOtic 10 mg/1 mg ear gel for dogs

2. STATEMENT OF ACTIVE SUBSTANCES

One dose contains 10 mg terbinafine and 1 mg betamethasone acetate (equivalent to 0.9 mg betamethasone base)

3. PACKAGE SIZE

2 tubes
20 tubes
40 tubes

4. TARGET SPECIES

Dogs.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Auricular use.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

This veterinary medicinal product does not require any special storage conditions.

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

Dechra Regulatory B.V.

14. MARKETING AUTHORISATION NUMBERS

EU/2/24/327/001 (2 tubes)
EU/2/24/327/002 (20 tubes)
EU/2/24/327/003 (40 tubes)

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Tube

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DuOtic

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

10 mg terbinafine + 1 mg betamethasone acetate / 1.2 g

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

DuOtic 10 mg/1 mg ear gel for dogs

2. Composition

One dose (1.2 g) contains:

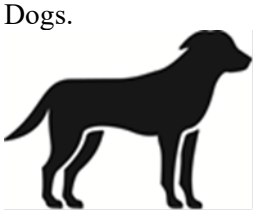
Active substances:
10 mg terbinafine and 1 mg betamethasone acetate (equivalent to 0.9 mg betamethasone base).

Excipient:
1 mg butylhydroxytoluene (E 321).

Off-white to slightly yellow translucent gel.

3. Target species

Dogs.



4. Indications for use

Treatment of otitis externa associated with *Malassezia pachydermatis.*

5. Contraindications

Do not use in cases of hypersensitivity to the active substances, to other corticosteroids or to any of the excipients.
Do not use if the eardrum is perforated.
Do not use in dogs with generalised demodicosis.

6. Special warnings

Special warnings:
Clean the ears before the initial treatment is applied. In clinical trials, saline only was used for ear cleaning before the first application of the veterinary medicinal product and ears were not cleaned again during the duration of the study (45 days).

If treatment with this veterinary medicinal product is discontinued, the ear canals should be cleaned before treatment with an alternative product is initiated.

Transient wetness of the inner and outer pinna may be observed after administration. This observation is attributed to presence of the veterinary medicinal product and is not of clinical concern. Fungal

otitis is often secondary to other conditions. Appropriate diagnosis should be used, and therapy of causative conditions should be investigated before antimicrobial treatment is considered.

In animals with a history of chronic or recurrent otitis externa, efficacy of the veterinary medicinal product may be affected if the underlying causes of the condition such as allergy or anatomical conformation of the ear are not addressed.

Special precautions for safe use in the target species:
Safety has not been established in dogs less than 2 months of age or weighing less than 1.4 kg.
Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogen. If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at the local/regional level.
Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.
Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of fungi resistant to terbinafine and may decrease the effectiveness of treatment with other antifungal agents.
In case of parasitic or bacterial otitis externa, an appropriate acaricidal or antibiotic treatment should be implemented as appropriate.
Before the veterinary medicinal product is applied, the external auditory canal must be examined thoroughly to ensure that the ear drum is not perforated (see 'contraindications' section).
Prolonged and intensive use of topical corticosteroid preparations is known to trigger systemic effects, including suppression of adrenal function (see 'overdose' section).
Decreased cortisol levels were observed after product instillation in tolerance studies using a related product (before and after ACTH stimulation), indicating that betamethasone is absorbed and enters the systemic circulation. The finding was not correlated with pathological or clinical signs and was reversible.
Additional concurrent corticosteroid treatments should be avoided.
Use with caution in dogs with a suspected or confirmed endocrine disorder (i.e. diabetes mellitus; hypo- or hyper-thyroid disease, etc.).

The veterinary medicinal product may be irritating to eyes. Avoid accidental contact with the dog's eyes. If accidental ocular exposure does occur, the eyes should be flushed thoroughly with water for 10 to 15 minutes. If clinical signs develop, seek veterinary advice.
In very rare cases, eye disorders such as keratoconjunctivitis sicca and corneal ulcers have been reported in dogs treated with a related product, in the absence of eye contact with the product. Although a causal relationship with the product was not definitively established, owners should be recommended to monitor for ocular signs (such as squinting, redness and discharge) in the hours and days following the veterinary medicinal product application, and to promptly consult a veterinarian in case such signs appear.

The safety and efficacy of the veterinary medicinal product in cats has not been evaluated. Post-marketing surveillance of a related product shows that the use of the product in cats can be associated with neurological signs (including Horner's syndrome with protrusion of membrane nictitans, miosis, anisocoria, and internal ear disorders with ataxia and head tilt) and systemic signs (anorexia and lethargy). The use of the veterinary medicinal product in cats should therefore be avoided.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
The veterinary medicinal product may be irritating to eyes. Accidental eye exposure may occur when the dog shakes its head during or just after administration. To avoid this risk for the owners, it is recommended that this veterinary medicinal product is administered only by veterinarians or under their close supervision. Appropriate measures (e.g. wearing safety glasses during administration, massaging the ear canal well after administration to ensure even distribution of the veterinary medicinal product, restraining the dog after administration) are needed to avoid exposure to the eyes. Avoid hand-to-eye contact. In case of accidental ocular exposure, flush the eyes thoroughly with water

for 10 to 15 minutes. If symptoms develop, seek medical advice and show the package leaflet or the label to the physician.

In case of accidental skin contact, wash exposed skin thoroughly with water.
In case of accidental ingestion by humans, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation:
Betamethasone is known to be teratogenic in laboratory species.
The safety of the veterinary medicinal product has not been established in pregnant and lactating bitches.
Do not use during pregnancy and lactation.

Fertility:
Do not use in breeding animals.

Interaction with other medicinal products and other forms of interaction:
Compatibility with ear cleaners, other than saline, has not been demonstrated.

Overdose:
In a study using a related, similar product, administration into the ear of five times the recommended dose, one week apart, for 5 consecutive weeks (a total six administrations of 5 tubes per ear or 10 tubes per dog) to mixed breed dogs weighing 10 to 14 kg resulted in clinical signs of wetness of the inner and outer ear flap (attributed to presence of the product). There were no clinical signs associated with unilateral vesicle (blister) formation within the epithelium of the ear drum (also observed after six administrations, one week apart, of 1 tube per ear or 2 tubes per dog), unilateral mucosal ulceration in the lining of the middle ear cavity, or decrease in serum cortisol response below normal reference range in ACTH stimulation testing. The decreased adrenal and thymus weights accompanied by atrophy of the adrenal cortex and lymphoid depletion of the thymus correlated with the decreased cortisol levels, and were consistent with the pharmacologic effects of betamethasone. These findings are considered reversible. Reversibility of the epithelial are drum blistering is also likely through epithelial migration, a natural self-cleaning and self–repair mechanism for the tympanic membrane and ear canal. Additionally, dogs showed slightly elevated red blood cell count, haematocrit, total protein, albumin and alanine aminotransferase. These findings were not associated with clinical signs.

7. Adverse events

Dogs:

Uncommon (1 to 10 animals / 1,000 animals treated):	Elevated liver enzymes[a]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Deafness, impaired hearing[b] Application site reactions (i.e. erythema (redness), pain, pruritus (itching), oedema (swelling), ulcer) Hypersensitivity reactions (including facial oedema, urticaria (hives), shock)[c]

[a] Mainly transient elevation of alanine aminotransferase
[b] Usually temporary. Mainly in elderly animals
[c] If hypersensitivity to any of the components occurs, the ear should be thoroughly washed

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 using the contact details at the end of this leaflet, or via your national reporting system: {national system details}

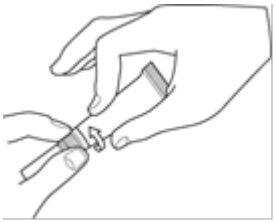
8. Dosage for each species, routes and method of administration

Auricular use.
Administer one tube per affected ear. Repeat the administration after 7 days. The maximum clinical response may not be seen until 21 days after the second administration.

9. Advice on correct administration

It is recommended to clean and dry the external ear canal before the first administration of the veterinary medicinal product.

1. Open the tube by twisting the soft tip.



2. Introduce this flexible soft tip into the ear canal.
3. Apply the veterinary medicinal product into the ear canal by pressing it between two fingers.
4. After application, the base of the ear may be massaged briefly and gently to facilitate even distribution of the veterinary medicinal product into the ear canal.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special storage conditions.

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

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

EU/2/24/327/001
EU/2/24/327/002
EU/2/24/327/003

Cardboard box containing 2, 20 or 40 tubes.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{DD month 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 events:
Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands
Tel: +31 348 563 434

Manufacturer responsible for batch release:
Genera Inc.
Svetonedeljska cesta 2
Kalinovica
10436 Rakov Potok
Croatia

17. Other information

This veterinary medicinal product is a fixed combination of two active substances: antifungal and corticosteroid.