**IPAR**

**Publicly Available Assessment Report for a**
**Veterinary Medicinal Product**

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Doxycare Flavour 200 mg Tablets for Cats and Dogs

**PRODUCT SUMMARY**

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| **EU Procedure number** | IE/V/0645/002/DC |
| **Name, strength and pharmaceutical form** | Doxycare Flavour 200 mg Tablets for Cats and Dogs |
| **Active substances(s)** | Doxycycline hyclate |
| **Applicant** | Ecuphar NV<br>Legeweg 157-I<br>8020 Oostkamp<br>Belgium |
| **Legal basis of application** | Hybrid application (Article 13(3) of Directive No 2001/82/EC) |
| **Date of completion of procedure** | 26/10/2019 |
| **Target species** | Cats,Dogs |
| **Indication for use** | Treatment of bacterial respiratory tract infections in cats and dogs, due to organisms sensitive to doxycycline including: *Staphylococcus aureus* and other *Staphylococcus* spp., *Streptococcus* spp., *Bordetella bronchiseptica*, and *Pasteurella* spp.<br>Treatment of tick - borne *Ehrlichia canis* infection in dogs. |
| **ATCvet code** | QJ01AA02 |
| **Concerned Member States** | Austria, Belgium, Cyprus,Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Romania,Slovakia, Spain, Sweden, United Kingdom (Original RMS) |

**PUBLIC ASSESSMENT REPORT**

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

**I. SCIENTIFIC OVERVIEW**

Doxycare Flavour 40 mg Tablets for Cats and Dogs and Doxycare Flavour 200 mg Tablets for Cats and Dogs contain 40 mg or 200 mg doxycycline (as doxycycline hyclate) per tablet.

The proposed indications are:
Treatment of respiratory tract infections in cats and dogs, including rhinitis, tonsillitis, bronchopneumonia and feline respiratory disease, due to organisms sensitive to doxycycline including; *Pasteurella spp., Bordetella bronchiseptica, Staphylococcus aureus* and other *Staphylococcus spp.* and *Streptococcus spp.*

Treatment of arthropod-borne *Ehrlichia canis* infections in cats and dogs.

The proposed dosing regimen for respiratory tract infections is 10 mg doxycycline per kilogram of bodyweight (1 tablet per 4 kg bodyweight for Doxycare 40 mg Tablets and 1 tablet per 20 kg bodyweight for Doxycare 200 mg Tablets), administered daily for up to five days. For treatments of infections caused by *Ehrlichia canis,* the proposed dosing regimen is 10 mg doxycycline per kilogram of bodyweight per day for 28 days.

These were Generic-Hybrid applications, submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended, due to the quantitative changes to the active substance, the addition of cats as a target species and a change in therapeutic

indications as compared to the reference product.

The reference products are Ronaxan 20 mg Tablets (for the 40 mg product), and Ronaxan 100 mg Tablets (for the 200 mg product), which have been authorised in the UK since June 1991. Additional data justified efficacy, in the form of extrapolated dissolution studies, performed in order to link the full range of reference and proposed products. Bioequivalence studies were additionally provided, along with bibliographical data. Bibliographical data was submitted to support the claim for the treatment of respiratory disease in cats. Bioequivalence, and thus efficacy as described in the Summary of Product Characteristics (SPC), was accepted on the basis of all the composite data.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC. The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy {1} of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

{1} Efficacy – The production of a desired or intended result.

## II. QUALITY ASPECTS

### *II.C. Control of Starting Materials*

The active substance is doxycycline hyclate, an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.
Current versions of the relevant EDQM certificates of suitability were provided for the manufacturers and suppliers of doxycycline hyclate.
The excipients are sodium starch glycolate type A, cellulose microcrystalline, magnesium stearate and meat flavour (yeast extract). The excipients are compliant with the European pharmacopeia and a declaration of compliance with EU flavouring regulation 1334/2008 was supplied for the meat flavour.

*The container/closures for the active substance are described in the certificates of suitability as double polyethylene bags placed in a fibre drum.*
The finished product is packed in formed and sealed Alu/Alu blisters made of oriented polyamide (25 µm)/Aluminium (45 µm)/PVC (60 µm) and aluminium (20 µm) with heat seal lacquer.

### *II.C.4. Substances of Biological Origin*
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

### *II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process*
Not applicable.

### *II.E. Control Tests on the Finished Product*
The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product include those for: appearance, identification (doxycycline base), impurities, average tablet weight, uniformity of mass, subdivision of tablets (1/4 tablets), uniformity of dosage units, disintegration time, friability, resistance to crushing, dissolution rate and microbiological purity. Additional dissolution studies were performed to support the efficacy of the products.

### *II.F. Stability*
The retest periods for the active substance are stated on the European certificates of suitability and in both cases are 4 years when stored under the approved conditions.
Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

***G. Other Information***

A declaration of compliance of the finished product with VICH GL18(R) was provided.
Shelf-life as packaged for sale: 2 years.
Shelf-life of tablet portions: 72 hours.
The tablets do not require any special storage conditions.

## III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

***Pharmacological & Toxicological Studies***

The applications were submitted in accordance with Article 13(3) of Directive 2001/82/EC, as amended, due to the products containing a greater amount of active substance than the reference product. The omission of pharmacological and toxicological data was justified as the applicant claimed bioequivalence.

***User Safety***

A user risk assessment was provided in compliance with the relevant guideline which shows that highlighted the risk of hypersensitivity reactions from tetracyclines. A literature review of over dose symptoms of doxycycline in humans suggests there are no specific adverse effects to be expected over and above the typical adverse effects seen at the standard dose. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- Tetracyclines may cause hypersensitivity (allergy) reactions.
- People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product.
- If you develop symptoms following exposure such as skin rash, seek medical advice immediately and show package leaflet to the physician.
- Doxycycline may cause gastrointestinal disturbances after accidental ingestion, especially by children. To avoid accidental ingestion, particularly by a child, unused tablet parts should be returned to the open blister space and inserted back into the carton. In case of accidental ingestion, particularly by children, seek medical advice.
- Keep out of sight and reach of children.

***Environmental Safety***

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

**Phase I:**

The applicant performed and submitted a Phase I ERA, the disposal advice on the SPC and product literature was acceptable and therefore the products are not expected to pose a risk to the environment when used as recommended.
The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

## IV. CLINICAL ASSESSMENT

***IV.I. Pre-Clinical Studies***

***Pharmacology***

Pharmacodynamics

Doxycycline is a second generation, broad spectrum tetracycline.
It is active against a large number of Gram positive and Gram-negative pathogens, including strains resistant to first generation tetracyclines.
In general, bacteriostatic, it inhibits the bacterial protein synthesis.
Resistance is mainly mediated by efflux pumps or ribosomal protection proteins. Cross-resistance among tetracyclines is common but depends on resistance mechanisms.
(See also 'Resistance' below).

Pharmacokinetics

After oral administration in dogs and cats at the recommended dose of 10 mg/kg, doxycycline reaches the maximal plasma concentration ($T_{max}$) within 24 hours. The peak concentration ($C_{max}$) is 1.4 µg/ml and 4.3 µg/ml in dogs and cats respectively.

The oral bioavailablilty of doxycycline after repeated administration is approximately 45% in both species and is not affected by the presence of food.
The volume of distribution of doxycycline is high, demonstrating that doxycycline is broadly distributed in organs and tissues. This is due to high liposolubility of doxycycline. Doxycycline is mainly excreted as unchanged drug and eliminated in faeces and urine.

***Tolerance in the Target Species***
Tolerance studies were not required because suitable data were provided to justify bioequivalence, (see Section IV.II). Data in the SPC refer to avoiding leaving the products in reach of animals as they are palatable, administration of the product with food to avoid oesophageal administration, avoiding use of the product in animals with liver disease and caution when using the product in young animals. The product should additionally not be used in cases of hypersensitivity to the active substance, other tetracyclines or the excipients, in cases of dysphagia or disease accompanied by vomiting, or in cases of vomiting, oesophagitis and oesophageal ulcerations.

***Resistance***
Due to the likely variability (time, geographical) in the occurrence of resistance of bacteria for doxycycline, bacteriological sampling and susceptibility testing are recommended. Official, national and regional antimicrobial policies should be taken into account when the product is used. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to doxycycline and may decrease the effectiveness of treatment with other tetracyclines, due to the potential for cross-resistance.

***IV.II. Clinical Documentation***
***Laboratory Trials***

The applicant conducted bioequivalence studies, the results of which when linked with suitable dissolution studies, provided the data required for efficacy of the products to be accepted.

Bioequivalence Studies Dogs

This was a single dose, two-period, two-sequence crossover study of the proposed product and the reference product, administered orally to dogs. There was a washout period of seven days between treatments. The proposed product was Doxycare 200 mg Tablets for Dogs and Cats, and the reference product was Ronaxan 100 mg Tablet.
A dose rate of 10 mg/kg bodyweight was used, equating to half of one tablet of the proposed product, and one tablet of the reference product. Suitable assessment was made of the health and weight of the animals. A small amount of food was provided. Appropriate blood samples were taken and analysed.

Pharmacokinetic parameters were suitably assessed using suitable software. Parameters assessed included the key parameters $C_{max}$[1], $T_{max}$[2] and $AUC_{last}$[3], ($C_{max}$ and $AUC_{last}$ being pivotal), for which 90% confidence intervals were confirmed, being within agreed limits of 70-143% for the formed and 80-125% for the latter. Bioequivalence was therefore established.

Cats
This was a single dose, two-period, two-sequence crossover study of the proposed product and the reference product, administered orally to cats. There was a washout period of four weeks between treatments. The proposed product was Doxycare 40 mg Tablets for Dogs and Cats, and the reference product was Ronaxan 20 mg Tablet.

A dose rate of 10 mg/kg bodyweight was used, equating to one 40 mg tablet of the proposed product, and one tablet of the reference product, with suitable assessment made of the health and weight of the animals. A small amount of food was provided. Appropriate blood samples were taken and analysed.

Pharmacokinetic parameters were suitably assessed using suitable software. Parameters assessed included key parameters $C_{max}$, $T_{max}$ and $AUC_{last}$, ($C_{max}$ and $AUC_{last}$ being pivotal), for which 90% confidence intervals were suitably confirmed. Bioequivalence was therefore established.

***Field Trials***

Due to the nature of the application, no data were required in this section.

[1] $C_{max}$ – Maximum concentration of active substance in the blood plasma.
[2] $T_{max}$ – Time at which $C_{max}$ achieved.
[3] $AUC_{last}$ – Total, directly measurable active substance in the blood plasma during exposure to a dose of a drug.

## V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics the benefit/risk profile of the products is favourable.

## VI. POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the HPRA website.
This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

**Changes:**
None.