Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Doxycare Flavour 200 mg Tablets for Cats and Dogs
Doxycare Flavour 40 mg Tablets for Cats and Dogs

Date Created: November 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure numbers	UK/V/0686/001-2/DC
Name, strength and pharmaceutical form	Doxycare Flavour 200 mg Tablets for Cats and Dogs Doxycare Flavour 40 mg Tablets for Cats and Dogs Tablet
Applicant	Ecuphar NV Legeweg 157-i B-8020 Oostkamp Belgium
Active substance(s)	Doxycycline Hyclate
ATC Vetcode	QJ01AA02
Target species	Cats and Dogs
Indication for use	Dogs For the treatment of respiratory tract infections including rhinitis, tonsillitis and bronchopneumonia caused by *Bordetella bronchiseptica* and *Pasteurella* spp. susceptible to doxycycline. For the treatment of canine ehrlichiosis (a disease transmitted by ticks) caused by *Ehrlichia canis*. Cats For the treatment of respiratory tract infections including rhinitis, tonsillitis and bronchopneumonia caused by *Bordetella bronchiseptica* and *Pasteurella* spp. susceptible to doxycycline.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic-Hybrid applications in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	29th October 2019
Concerned Member States for original procedure	Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Latvia, Lithuania, Luxembourg, Norway, Poland, Portugal, Romania, Slovakia, Spain and Sweden

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:

Dogs
For the treatment of respiratory tract infections including rhinitis, tonsillitis and bronchopneumonia caused by *Bordetella bronchiseptica*, and *Pasteurella* spp. susceptible to doxycycline.

For the treatment of canine ehrlichiosis caused by *Ehrlichia canis*.

Cats
For the treatment of respiratory tract infections including rhinitis, tonsillitis and bronchopneumonia caused by *Bordetella bronchiseptica*, and *Pasteurella* spp susceptible to doxycycline.

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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains doxycycline hyclate (as doxycycline) and the excipients cellulose microcrystalline, sodium starch glycolate (type A), yeast extract and magnesium stearate.

The container/closure system consists of formed aluminium blister packs, each blister strip contains 10 tablets. The blister strips are presented in cartons of 1 ,2, 3, 4, 5, 6 ,7 ,8 ,9, 10, 25 or 50 blisters. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of mixing, blending and compressing into tablet form. The tablets are then packed into blister strips and blister packs are secondary packed into cardboard boxes.

[1] Efficacy – The production of a desired or intended result.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

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: 30 months.
Shelf-life of tablet portions: 72 hours.
The tablets do not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

For generics, insert in the relevant sections as appropriate:

III.A Safety Documentation

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 overdose 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:

- People with known hypersensitivity to tetracyclines should avoid contact with the veterinary medicinal product and personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product.
- In case of skin irritation, seek medical advice immediately and show the package leaflet or the label to the physician.
- Accidental ingestion, especially by children, may cause adverse reactions such as emesis.
- To avoid accidental ingestion, blisters should be inserted back into the outer packaging and kept in a safe place. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

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 DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Doxycycline is a broad-spectrum tetracycline-class antibiotic active against a large number of gram positive and gram-negative bacteria including both aerobic and anaerobic species.

Doxycycline inhibits bacterial protein synthesis and has a predominantly bacteriostatic activity.

The penetration of doxycycline into the bacterial cell takes place by both active transport and passive diffusion.
The main mechanisms of acquired resistance to tetracycline class antibiotics include active efflux and ribosomal protection. A third mechanism is enzymatic degradation.

Cross-resistance to other tetracyclines is common but depends on the mechanism conferring resistance. Due to the greater liposolubility and greater ability to pass through cell membranes (in comparison to tetracycline), doxycycline retains a certain degree of efficacy against microorganisms with acquired resistance to tetracyclines via efflux pumps. However, resistance mediated by ribosomal protection proteins confer cross-resistance to doxycycline.

(See also 'Resistance' below).

Pharmacokinetics

Absorption
After oral administration, the bioavailability of doxycycline is approximately 45% in dogs and cats. Peak concentrations of 1.4 µg/ml (dogs) and 4.3 µg/ml (cats) are reached within 3 hours after oral administration, supporting that doxycycline is rapidly absorbed from the gastro-intestinal tract.

Distribution
Doxycycline is broadly distributed throughout the organism due to its physicochemical characteristics, as it is highly liposoluble. Protein binding in dogs is reported as 91.75 % ± 0.63 and 91.4% in the literature. In cats a publication reports a protein binding of 98.35% (+/-0.24).
The tissue concentrations, with the exception of the skin, are generally higher than the plasma levels, including the excretion organs (liver, kidney and intestines) and for the lungs.

Elimination
After a single administration, the half-life elimination (T1/2) is 8.37 hours in cats. Excretion occurs in an unchanged active form (90%) via the faeces (approximately 75%), via the urine (approximately 25%) and less than 5% via the bile ducts.

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}[2], T_{max}[3] and AUC_{last}[4], (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.

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

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.

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.

MODULE 4

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 Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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