MEB agency / Veterinary Medicinal Products Unit
The Netherlands

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Doxytab vet. Flav. 15 mg tablet for dogs and cats
Doxytab vet. Flav. 50 mg tablet for dogs and cats
Doxytab vet. Flav. 200 mg tablet for dogs
Doxytab vet. Flav. 400 mg tablet for dogs

Created: April 2024

PRODUCT SUMMARY

EU procedure number	NL/V/0331/001-004/DC
Name, strength and pharmaceutical form	Doxytab vet. Flav. 15 mg tablet for dogs and cats Doxytab vet. Flav. 50 mg tablet for dogs and cats Doxytab vet. Flav. 200 mg tablet for dogs Doxytab vet. Flav. 400 mg tablet for dogs
Applicant	CP-Pharma Handelsgesellschaft mbH Ostlandring 13 31303 Burgdorf Germany
Active substance(s)	doxycycline hyclate
ATC vetcode	QJ01AA02
Target species	Dogs and cats
Indication for use	Treatment of the following conditions caused by bacteria sensitive to doxycycline: <u>Dogs:</u> Rhinitis caused by *Bordetella bronchiseptica* and *Pasteurella* spp.; Bronchopneumonia caused by *Bordetella* spp. and *Pasteurella* spp.; Interstitial nephritis caused by *Leptospira* spp.; <u>Cats:</u> Respiratory infections caused by Bordetella bronchiseptica, Chlamydophila felis, Pasteurella spp.

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Reference product (RP)	Doxoral 15 mg tabletten met smaakstof voor honden en katten
Marketing authorisation holder	Ast Farma B.V.
Marketing authorisation number EU procedure number	REG NL 4304 (national registration in the Netherlands)
Date of authorisation	25 July 1991
Date of completion of the original decentralised procedure	6 May 2020
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	AT, BE, DE, DK, ES, FI, FR, HU, IE, IT, PT, PL, SE, UK.
Concerned Member States for subsequent recognition procedure	Not applicable

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the reactions observed are indicated in the SPC.

The VMP is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the VMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The VMP contains doxycycline, dependant on the strength, 15 mg doxycycline (as 17.3 mg doxycycline hyclate), 50 mg doxycycline (as 57.7 mg doxycycline hyclate), 200 mg doxycycline (as 230.8 mg doxycycline hyclate) or 400 mg doxycycline (as 461.7 mg doxycycline hyclate).

All four strengths contain the following excipients: sodium starch glycolate (type A), colloidal hydrated silica, microcrystalline cellulose, lactose monohydrate, chicken flavour and magnesium stearate. The choice of excipients is justified.

The tablet is cross scored and meant to be broken into equal halves or quarters.
The tablets are packaged in an aluminium-PVC/PE/PVDC blister.

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

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data on the VMP have been presented in accordance with the relevant European guidelines and the tests performed during production are adequately described.

The product is manufactured using conventional manufacturing techniques. Suitable pre-approval validation results on two pilot batches of all tablet strengths have been provided.

C. Production and 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 from the supplier. Batch analytical data demonstrating compliance with this specification have been provided. All excipients are in conformity with the Ph.Eur. requirements with the exception of chicken flavour, which has been adequately specified.

The magnesium stearate is of vegetable origin. In regard to chicken flavour, a TSE declaration and Viral Safety Evaluation are provided. Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

The packaging is conformity with the Ph. Eur. and EU Food Directive.

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 VMP.

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.

F. Stability tests

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A re-test period of 4 years was approved.

Stability data on the finished product have been provided in accordance with applicable European guidelines. Given the stability results provided, a shelf life of 30 months was granted.

3. SAFETY DOCUMENTATION (safety and residues tests)

As this is a generic application according to Article 13(1) of Directive 2001/82/EC, the MAH has performed bioequivalence studies to demonstrate essential similarity to a reference VMP. Therefore, additional toxicological, pharmacological and clinical tests are not required.

Warnings and precautions as listed on the product literature are the similar to those of the reference VMP and are adequate to ensure safety of the product to users and the environment.

A. Safety tests

Pharmacological studies

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Doxytab Vet. Flav. 15 mg tablet for dogs and cats (CP-Pharma Handelsgesellschaft mbH, Germany) was compared with the pharmacokinetic profile of the reference product Doxoral 15 mg tabletten met smaakstof voor honden en katten (Ast Farma B.V., Netherlands).

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution study results and composition.

Study 1 – single dose, 10 mg, fed conditions in dogs

A single dose, two period, two-sequence, crossover bio-equivalence study was carried out in dogs to demonstrate bioequivalence between the reference product and the investigated product. Administration under fed conditions is accepted, since it is in accordance with the SPC proposed (and SPC of recently authorised doxycycline containing tablets) to prevent adverse gastro-intestinal tract events. The study design was considered appropriate and the study was performed according to the principles of GLP. Certificates of quality assurance and certificates of analysis have also been submitted and are satisfactory.

Suitable statistical analyses were performed on the samples obtained, and bioequivalence was determined based on log-transformed C_{max} and AUC_{last}. The results of this study indicate that the 90% confidence interval for the primary variables fell within pre-defined limits. As such, this study successfully demonstrated bioequivalence between the reference product and the investigated product in dogs.

Study 2 – single dose, 10 mg, fed conditions in cats

A single dose, two period, two-sequence, crossover bio-equivalence study was carried out in cats to demonstrate bioequivalence between the reference product and the investigated product. The applicant selected a single dose of 5 mg/kg bw twice daily instead of a 10 mg/kg bw dose once daily, since dosing of multiple tablet in the cats was known to be very difficult.

The dose administered is considered appropriate, and it is considered appropriate that animal welfare was taken into account. Administration under fed conditions is accepted, since it is in accordance with the SPC proposed (and SPC of recently authorised doxycycline containing tablets) to prevent adverse gastro-intestinal tract events. The study design was considered appropriate and the study was performed according to the principles of GLP. Certificates of quality assurance and certificates of analysis have also been submitted and are satisfactory.

Suitable statistical analyses were performed on the samples obtained, and bioequivalence was determined based on log-transformed C_{max} and AUC_{last}. The results of this study indicate that the 90% confidence interval for the primary variables fell within pre-defined limits. As such, this study successfully demonstrated bioequivalence between the reference product and the investigated product in cats.

Conclusion on bioequivalence studies

Based on the submitted bioequivalence studies, the test product Doxytab Vet. Flav. 15 mg tablet for dogs and cats (CP-Pharma Handelsgesellschaft mbH, Germany) is considered bioequivalent with the reference product Doxoral 15 mg tabletten met smaakstof voor honden en katten (Ast Farma B.V., Netherlands) in dogs and cats.

The results of Study 1 and Study 2 with the 15 mg formulation can be extrapolated to other strengths (50 mg, 200 mg, 400 mg) based on *in-vitro* dissolution data. The dissolution test data were appropriate to confirm the waiving of additional *in-vivo* bioequivalence testing for the additional strengths. Therefore, bioequivalence for all four strengths of Doxytab Vet. Flav. is sufficiently proven.

Toxicological studies

As this is a generic application according to Article 13(1) of Directive 2001/82/EC, the MAH has performed bioequivalence studies to demonstrate essential similarity to a reference VMP. Therefore, additional toxicological, pharmacological and clinical tests are not required.

Development of resistance and related risk in humans

This is a generic application submitted according to Article 13(1) and (3) of Directive 2001/82/EC. In case bioequivalence with the reference product has been established, the applicant is not required to submit additional results of toxicological, pharmacological and clinical tests. In accordance with the 'Revised guideline on the SPC for antimicrobial products' (EMEA/CVMP/SAGAM/383441/2005), appropriate resistance information has been included in the product literature.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that the product may cause hypersensitivity reactions and it may cause serious gastrointestinal effects if ingested, especially by children.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the VMP.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the VMP will only be used in non-food animals.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a generic application according to Article 13(1) of Directive 2001/82/EC and bioequivalence with the reference VMP has been demonstrated by means of bioequivalence studies both in dogs and cats, efficacy studies are not required. The results of the bioequivalence studies on the 15 mg formulation could be extrapolated to the other strengths using dissolution studies.

The efficacy claims for this VMP are equivalent to those of the reference VMP.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

Sequence of significant variations

None.