ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Zodon 88 mg Chewable Tablets for Dogs
Zodon 150 mg Chewable Tablets for Dogs
Zodon 264 mg Chewable Tablets for Dogs

Zodon vet 88 mg Chewable Tablets for Dogs
Zodon 150 mg Chewable Tablets for Dogs
Zodon 264 mg Chewable Tablets for Dogs
(Finland, Denmark, Norway, Belgium)

Givix vet
Givix vet
Givix vet
(Sweden)

PuAR correct as of 06/07/2018 when RMS was transferred to FR.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0511/001/DC UK/V/0511/002/DC UK/V/0511/003/DC
Name, strength and pharmaceutical form	Zodon 88 mg Chewable Tablets for Dogs Zodon 150 mg Chewable Tablets for Dogs Zodon 264 mg Chewable Tablets for Dogs
Applicant	Ceva Animal Health Ltd Unit 3, Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB
Active substance(s)	Clindamycin
ATC Vetcode	QJ01FF01
Target species	Dogs
Indication for use	For the treatment of infected wounds and abscesses, and oral cavity/dental infections, caused by or associated with *Staphylococcus* spp.*, Streptococcus* spp. *(*except *Streptococcus faecalis), Bacteroides* spp.*, Fusobacterium necrophorum,* and *Clostridium perfringens.* For the treatment of superficial pyoderma associated with *Staphylococcus pseudintermedius.* For the treatment of osteomyelitis, caused by *Staphylococcus aureus.*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended (Zodon 150 mg Chewable Tablets for Dogs) Generic hybrid application in accordance with 13(3) of Directive 2001/82/EC as amended (Zodon 88 mg Chewable Tablets for Dogs and Zodon 264 mg Chewable Tablet for Dogs).
Date of completion of the original decentralised procedure	22 May 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

Zodon chewable tablets for dogs are presented as three strengths containing 88 mg, 150 mg and 264 mg clindamycin (as clindamycin hydrochloride). Zodon 150 mg chewable tablet is a generic product submitted in accordance with Article 13(1) of Directive 2001/82/EC as amended by 2004/28/EC. Zodon 88 mg and Zodon 264 mg chewable tablet are generic hybrid products, submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended by 2004/28/EC. The reference product is Antirobe capsules 150 mg, marketed by Zoetis, which has been authorised in the UK since 9 June 1898. A bioequivalence study between Zodon 150 mg chewable tablets and the reference study was conducted.

The product is indicated for the treatment of infected wounds and abscesses, and oral cavity/dental infections, caused by or associated with *Staphylococcus* spp.*, Streptococcus* spp. *(*except *Streptococcus faecalis), Bacteroides* spp.*, Fusobacterium necrophorum,* and *Clostridium perfringens;* the treatment of superficial pyoderma associated with *Staphylococcus pseudintermedius.*and for the treatment of osteomyelitis, caused by *Staphylococcus aureus.* The products should not be used in cases of hypersensitivity to the active substance or to any

of the excipients and is contraindicated for use in rabbits, hamsters, guinea pigs, chinchillas, horses or ruminants as ingestion can cause severe gastro-intestinal disturbances.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be used safely in the target species; the slight reactions observed are indicated in the SPC[1]

The product is safe for the end user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The products contains 88 mg, 150 mg and 264 mg clindamycin (as hydrochloride) and the excipients microcrystalline cellulose, lactose monohydrate, silica colloidal anhydrous, copovidone, sodium croscamellose, magnesium stearate, yeast extract and chicken flavour.

The container system consists of blister strips containing 6, 8 or 10 Zodon tablets of 88 mg, 150 mg or 264 mg respectively in cartons. The blister packs are comprised of laminate of polyvinylchloride / Thero-elast / polyvinylidene chloride sealed with aluminium foil. The particulars of the containers and controls performed are provided and conform to the regulation. The absence of preservative is justified.

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

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured passing the starting materials through a screen, and then mixing. Magnesium stearate and colloidal anhydrous silica is then passed through a screen and added to the mixture. The compression mix is then tableted into the appropriate strength. Process validation data on the product have been presented in accordance with the relevant European guidelines.

[1] SPC – Summary of Product Characteristics

C. Control of Starting Materials

The active substance is clindamycin, as established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is manufactured in accordance with certificates of suitability and the principals 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.

The excipients yeast extract and chicken flavour are not described in the pharmacopoeia and the specifications has been provided. All other excipients comply with the relevant Ph. Eur. monographs. Certificates of analysis have been provided.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Not applicable.

F. 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. The tests include appearance, identification and assay of clindamycin, average weight, uniformity of dosage units, dissolution, moisture, related substances and microbial purity. Satisfactory validation data for the analytical methods have been provided.

G. Stability

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. The retest periods for the active substance are described in the certificates of suitability as 4 years for one of the active substance manufacturers and 3 years for the other active substance manufacturers.

Stability data on the finished product have been provided in accordance with European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Data were provided for pilot batches stored at 25ºC/60%RH for 36 months, 30ºC/65%RH for 12 months and 40ºC/75%RH for 6 months.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
- Shelf life after first opening the immediate packaging: 72 hours
- Do not store above 30ºC.
- Tablet portions should be stored in the blister pack.
- Any tablet portions remaining after 72 hours should be discarded.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Zodon 150 mg chewable tablet is a generic product submitted in accordance with Article 13(1) of Directive 2001/82/EC as amended by 2004/28/EC. Zodon 88 mg and Zodon 264 mg chewable tablet are generic hybrid products, submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended by 2004/28/EC. The generic product is formulated as a chewable tablet containing 150 mg clindamycin as clindamycin hydrochloride and the generic hybrid products are similar preparations of the 150 mg tablet containing either 88 mg or 264 mg of clindamycin as clindamycin hydrochloride. The 150 mg formulation is bioequivalent to the reference product

III.A Safety Testing

Pharmacological Studies

A summary of the pharmacodynamics, pharmacokinetic and antimicrobial activity data for the active substance along with supporting references has been provided. Due to the legal basis of the applications and the demonstrated bioequivalence between the test products and the reference product, results of pharmacological studies are not required.

Toxicological Studies

Due to the legal basis of the applications and the demonstrated bioequivalence between the test products and the reference product, results of toxicological studies are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which identified the most relevant routes of exposure and probability of exposure. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- People with known hypersensitivity to lincosamides (lincomycin and clindamycin) should avoid contact with the veterinary medicinal product.
- Wash hands after handling tablets.
- Accidental ingestion may result in gastro-intestinal effects such as abdominal pain and diarrhoea. Care should be taken to avoid accidental ingestion.
- In case of accidental ingestion, particularly by children, seek medical advice immediately and show the package leaflet or label to the physician.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that as the product is for use in non-food animals only it will pose minimal risk to the environment. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The application for Zodon 150 mg tablets is submitted in accordance with Article 13 (1) of Directive 2001/82/EC (as amended by 2004/28/EC), therefore results of safety and residue tests or pre-clinical and clinical trials are not required if it can be demonstrated that the medicinal products is a generic of the reference product. The application for Zodon 88 mg and Zodon 264 mg tablets are submitted in accordance with Article 13 (3) of Directive 2001/82/EC (as amended by 2004/28/EC). In line with CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products, both products are homothetic to and have similar dissolution profiles to Zodon 150 mg tablets the results of safety test or pre-clinical and clinical trials are not required. Based on the literature review provided, the pharmacodynamics of clindamycin have already been adequately characterised.

Pharmacokinetics

An *in vivo* bioequivalence study and *in vitro* dissolution studies were presented.

For the bioequivalence study, a two treatment period, two sequenced randomised GLP[2] study with a 7 day wash-out period was performed in the target species. A suitable number of animals were divided into two groups, and

[2] GLP – Good Laboratory Practice

given either the test product, 150 mg Zodon Chewable Tablets for Dogs, or Antirobe capsules 150 mg. Dose of the product delivered ranges from 11.5 to 14.6 mg/kg. Blood samples were taken before and after administration from Day -1, at various time points. In the bioequivalence study the pharmacokinetic profiles for the active substance (clindamycin) were not considered to have been adequately characterised and therefore bioequivalence was not accepted on this basis alone. However clindamycin is eligible for a biowaver in humans, which reduces the requirement for *in vivo* bioequivalence studies. Solubility studies were performed to determine if this biowaver could be applied to clindamycin in dogs. Clindamycin is known to have high bioavailability in dogs and there are no excipients present in the formulation that are likely to affect the bioavailability of the active. As a result further *in vivo* studies were not required and since *in vitro* studies had demonstrated that the dissolution profile for Zodon and Antirobe were similar, bioequivalence was therefore accepted.

Tolerance in the Target Species of Animals

Target animal studies were not submitted. Summaries to support the safety of each excipient were provided. The omission of safety studies based on the nature of the applications is acceptable.

Resistance

Literature review on the development and occurrence of resistance to clindamycin was provided. Resistance to clindamycin has been reported from several European countries. Adequate warnings and precautions appear on the product literature:

- Official and local 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 clindamycin and may decrease the effectiveness of treatment with lincomycin or macrolide antimicrobials due to the potential for cross-resistance.
- Clindamycin and erythromycin show parallel resistance. Partial cross-resistance has been demonstrated between clindamycin, erythromycin and other macrolides antibiotics.
- Clindamycin belongs to the lincosamide group of antibiotics. Resistance can develop to the lincosamides alone, but more commonly cross-resistance occurs among macrolides, lincosamides and streptogramin B antibiotics (MLS_B group). Resistance is the result of methylation of adenine residues in the 23S RNA of the 50S ribosomal subunit, which prevents drug binding to the target site. Different bacterial species are able to synthesize an enzyme, encoded by a series of structurally related erythromycin ribosomal methylase (*erm*) genes. In pathogenic bacteria, these determinants are mostly borne by plasmids and transposons that are self-transferable. The erm genes occur predominantly as variants erm(A) and erm(C) in *Staphylococcus aureus* and as variant erm(B) in *Staphylococcus pseudintermedius*, streptococci and enterococci . Bacteria resistant to macrolides but initially susceptible to clindamycin,

rapidly develop resistance to clindamycin when exposed to macrolides. These bacteria present a risk of *in vivo* selection of constitutive mutants.

- MLS_B inducible resistance is not detected by standard in vitro susceptibility testing methods. The CLSI recommends the D-zone test to be routinely performed in veterinary diagnostic laboratories in order to detect clinical isolates with inducible resistance phenotype. Clindamycin use should be discouraged in these patients.
- The incidence of resistance to lincosamides in *Staphylococcus* spp. appears to be wide-ranging in Europe. Recent studies (2010) report an incidence between 25 to 40%.

IV.B Clinical Studies

The omission of clinical trial results based on the natures of the products is justified.

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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.

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

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.

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