Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Clindaseptin 25 mg Capsules for Dogs

Date Created: 15th October 2014

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Clindaseptin 25 mg Capsules for Dogs
Applicant	Chanelle Animal Health Ltd. 7 Rodney Street, Liverpool, L1 9HZ
Active substance	Clindamycin (as clindamycin hydrochloride)
ATC Vetcode	QJ0FF01
Target species	Dogs
Indication for use	The product is indicated for the treatment of infected wounds, abscesses, superficial pyoderma and oral cavity/dental infections caused by or associated with clindamycin-sensitive staphylococci, streptococci, bacteroidaceae, *Fusobacterium necrophorum*, *Clostridium perfringens* and osteomyelitis caused by *Staphylococcus aureus*. The product can also be used to help provide antimicrobial cover during dental procedures.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Extension application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

This was an application for an extension to the National Marketing Authorisation for Clinacin 25 mg tablets, in order to authorise a new pharmaceutical form; capsules. The new application was presented under Article 12 (3) of Directive 2001/82/EC, the parent product having been authorised in March 2002. UK national authorisations for Clindaseptin 75 mg, 150 mg and 300 mg Capsules for Dogs were granted in July 2013.

The product contains 25 mg of clindamycin (as hydrochloride), and is used to treat infected wounds, abscesses, and oral cavity/dental infections associated with clindamycin-sensitive *spp* staphylococci, strepotococci bacteroidaceae, *Fusobacterium necrophorum*, *Clostridium perfringens* and osteomyelitis caused by *Staphylococcus aureus*. During dental procedures, the product may also be used to provide antimicrobial cover.

The product can be used for the treatment of infected wounds, abscesses, oral cavity and dental infections. 5.5 mg/kg bodyweight is administered every 12 hours for 7 - 10 days (i.e. 1 capsule per 4.5 kg bodyweight twice daily). Treatment may be extended to a maximum of 28 days, based on clinical judgment. If no improvement is seen within 4 days, the sensitivity of the pathogens involved should be re-determined. The product is also indicated for the treatment of superficial pyoderma. 11 mg/kg is administered every 24 hours (i.e. 2 capsules per 4.5 kg bodyweight once daily). The treatment is continued for at least 21 days. For the treatment of osteomyelitis, 11 mg/kg is administered every 12 hours (i.e. 2 capsules per 4.5 kg bodyweight twice daily) for at least 28 days. If no improvement is seen within 14 days, the sensitivity of the pathogens involved should be re-determined. To help provide antimicrobial cover during dental procedures, a 10 day course of 5.5 mg/kg every 12 hours is recommended (i.e. 1 capsule per 4.5 kg twice a day beginning 5 days before the intended procedure and continuing for 5 days thereafter). The minimum bodyweight to be treated is 4.5 kg.

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.[1] The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions

[1] SPC – Summary of product Characteristics.

are indicated in the SPC. The efficacy[2] of the product was demonstrated according to the claims made in the SPC. A suitable dissolution study confirmed the bioequivalence of the proposed product in comparison to the reference product, Clinacin 25 mg tablets. 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 25 mg clindamycin per capsule and the excipients lactose monohydrate, maize starch, magnesium stearate and talc.

The container/closure system consists of blister strips composed of PVC/PE/PVdC film and sealed with aluminium foil. Capsules are presented as 2, 4, 6, 8 or 10 per strip. Cartons contain blister strips of: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80 , 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 112, 120, 128, 130, 140, 150, 154, 160, 168, 180, 182, 186, 190, 196, 200, 210, 224, 240, 250, 252, 256, 260, 266, 270, 280, 290, 294, 300, 308, 320, 350, 390, 392, 448, 500, 450, 540, 546, 600, 602, 700, 750, 800, 798, 810, 896, 900, 994 and 1000 capsules. Not all pack sizes may be marketed.

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. Process validation data on the product have been presented in accordance with the relevant European guidelines. Materials are weighed and blended before being filled into capsules. The capsules are packed into blisters and sealed with aluminium foil.

II.C. Control of Starting Materials

The active substance is clindamycin, an established active substance described in the European Pharmacopoeia (Ph. Eur). 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

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

specification have been provided. Suitable Ph. Eur. Certificates of Suitability were provided.

Lactose monohydrate, maize starch, talc and magnesium stearate all comply with monographs as cited in the Ph. Eur. The capsule shells are not described in a pharmacopoeia, but comply with a supplier's specification.

II.C.4. Substances of Biological Origin

A declaration was provided stating that the finished product complies with the annex to Directive 81/852/EEC, as amended by 1999/014/EC, relating to transmissible spongiform encephalopathies (TSEs). All gelatin used in the compilation of the capsules is purchased from suppliers who have been granted an European Directorate for the Quality of Medicines & Healthcare (EDQM) certificate of suitability for TSE. A declaration was received stating that lactose monohydrate used in production of the product is sourced from milk approved for human consumption, and that the lactose is prepared without the use of ruminant material other than calf rennet.

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. Tests include those for appearance, packaging, identification of active substance, average contents weight, moisture content, disintegration and dissolution time, related substances, and microbial purity.

II.F. 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.

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. Stability studies were conducted as define under established VICH conditions of 24 months at 25^{o}C/60%RH and 6 months at 40^{o}C/75%RH. All data were acceptable and the shelf-life was established as cited in the SPC.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

The pharmacological and toxicological aspects of this product are identical to the previously authorised products within this range; Clindaseptin 75 mg Capsules for Dogs, Clindaseptin 150 mg Tablets for Dogs and Clindaseptin 300 mg Tablets for Dogs. No additional data was provided for this application, apart from an overview of the toxicity of the active substance.

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

III.A Safety Documentation

Toxicological Studies/User Safety

The applicant provided summaries of published studies defining the toxicity of the active substance, which concluded that the level of acute oral toxicity is approximately 10 times lower than the intravenous toxicity in mice, (2618 mg/kg versus 245 mg/kg). Via subcutaneous injection, neonatal rats were found to have an acute oral toxicity approximately 10 times that of adult rats. In human studies, instances of reversible hepatotoxicity have been noted. Additionally, it has been stated that clindamycin has no teratogenic, mutagenic or carcinogenic properties.

A user risk assessment was provided in compliance with the relevant guideline Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Adverse reactions noted in an SPC related to a human product containing 150 mg clindamycin per capsule included gastro-intestinal tract complications, transient disorders of the blood, inflammatory effects to the skin, hypersensitivity reactions, jaundice and other abnormalities of the liver, dysgeusia (a modulation to the sense of taste), rare occurrences of hypotension and cardiac arrest. The active substance is widely used to treat acne vulgaris, and mild skin reactions are therefore not uncommon. None of the excipients used in the product are considered to add to the toxicological burden of the product.

An assessment of exposure to the user noted that the target species is the dog, and users comprise of veterinary surgeons and associated staff, and the animal owner. Likely scenarios of exposure were considered and risk assessed. The most significant safety risk is for children, who may ingest the tablets. The SPC carries suitable warnings:

- Those with known hypersensitivity to lincosamides (lincomycin, clindamycin) should not handle the product.

- If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the Doctor this warning. Swelling of the face, lips or eyes, or breathing difficulties are more serious symptoms and require urgent medical attention.

- Accidental ingestion of this product may cause transient gastrointestinal effects, and so should be avoided. If a child accidentally consumes this product, seek medical advice.

Environmental Safety

The Environmental Risk Assessment stopped at Phase I. The product is for use in dogs only, and exposure to the environment will not be extensive. The product is not expected to pose a risk for the environment when used as recommended.

IV CLINICAL DOCUMENTATION

It was deemed acceptable that data presented in the form of a dissolution study were sufficient for bioequivalence with Clinacin 25 mg Tablets to be confirmed for the current application.

IV.I. Pre-Clinical Studies

Pharmacology

The applicant provided bibliographical data previously submitted for parent product dossiers. No further data were required to be submitted.

Pharmacodynamics

Clindamycin exhibits its effect via bacteriostatic action, and is effective against a variety of bacterial species. The 50s subunit of the bacterial ribosome is bound with subsequent inhibition of protein synthesis. Bactericidal properties are also exhibited against some bacterial species, caused by the accumulation of clindamycin within host cells. Inability of the pathogen to adhere to host cells has also been noted, contributing to the ability of the host to mount a successful and appropriate immune response. Anti-parasitic action has also been noted, due to the accumulation of clindamycin in infected cells. The action of the active substance is well-established in the available literature.

Pharmacokinetics

Published data, (previously submitted for parent products), were submitted for this section.

Clindamycin is quickly absorbed from the gastro-intestinal tract in dogs, with peak serum concentration attained after approximately one hour when administered at 10 mg/kg. C_{max}[3] has been observed at 3.3 µg/ml for non-fasted and at 5.0 µg/ml for fasted animals. The active substance is widely distributed, and significantly, there is maintenance of anti-microbial activity within neutrophils. Clindamycin crosses the placenta and is excreted in mammalian milk, but it has not been observed to enter cerebro-spinal fluid in humans. The metabolism of clindamycin is mainly hepatic, and it is excreted in the urine of dogs as unchanged drug, the glucoronide of the active substance, the sulfoxide of the active substance and N-methyl-clindamycin. The active substance has been noted via radio-labelling at a dose of 500 mg/kg in dogs to be eliminated one third via the urine and two thirds via the faeces. Any impairment to renal or liver function may affect elimination.

Tolerance in the Target Species

As bioequivalence between the proposed product and the reference product was confirmed, there was no requirement for further data in this section.

Resistance

Suitable bibliographical references were provided, which outlined instances of resistance to the active substance. Of significance, in Sweden, a rise in resistance to clindamycin was noted, particularly with reference to *S. pseudointermedis.* Suitable warnings and precautions are stated within the SPC.

IV.II. Clinical Documentation

As bioequivalence with a reference product was established, there was no requirement for data 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 product(s) is favourable.

[3] C_{max} – maximum serum concentration of active substance attained.

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)