Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Clindaseptin 75 mg Capsules for Dogs
Clindaseptin 150 mg Capsules for Dogs
Clindaseptin 300 mg Capsules for Dogs

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Clindaseptin 75 mg Capsules for Dogs Clindaseptin 150 mg Capsules for Dogs Clindaseptin 300 mg Capsules for Dogs
Applicant	Chanelle Animal Health Ltd. 7 Rodney Street Liverpool L1 9HZ, UK
Active substance	Clindamycin (as clindamycin hydrochloride) 300 mg per capsule.
ATC Vetcode	QJ01FF01
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 applications in accordance with Article 12 (3) of Directive 2001/82/EC as amended. To add a new pharmaceutical form

I. SCIENTIFIC OVERVIEW

These were extension applications for three products, Clindaseptin 75 mg Capsules for Dogs, Clindaseptin 150 mg for Dogs and Clindaseptin 300 mg Capsules for Dogs, produced in order to facilitate the introduction of a new pharmaceutical form. The parent products were Clinacin 75 mg Tablets, Clinacin 150 mg Tablet and Clinacin 300 mg Tablets, authorised in the UK since January 2001. The products are intended to treat 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 products may also be used to provide antimicrobial protection during dental procedures.

The products are administered orally. For wounds, abscesses and oral cavity or dental infections 5.5 mg/kg bodyweight is given every twelve hours for seven to ten days. This equates to one capsule per 54 kg bodyweight twice a day. Treatment may be extended to twenty-eight days if clinical judgment suggests this. If no improvement is seen within four days, there should be a re-evaluation of the pathogens involved.

For superficial pyoderma, 11 mg/kg bodyweight is administered every twenty-four hours. This equates to two capsules per 54 kg bodyweight daily. Treatment should be continued for twenty-one days. For osteomyelitis, 11/mg kg bodyweight is administered every twelve hours, equating to two capsules per 54 kg bodyweight twice daily for at least twenty-eight days. No improvement after fourteen days should instigate a re-evaluation of the pathogens involved. For antimicrobial cover during dental procedures, 5.5 mg/kg bodyweight every twelve hours is recommended five days before and after the procedure. This equates to a ten day course of 1 capsule per 54 kg twice a day.

The products are 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 products can be safely used in the target species, the slight reactions observed are indicated in the SPC[1]. The products are safe for the user, and for the environment, when used as recommended. Suitable warnings and

[1] SPC – Summary of Product Characteristics.

Precautions are indicated in the SPC. The efficacy 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. QUALITY ASPECTS

A. Composition

The products contain clindamycin as clindamycin hydrochloride at 75 mg, 150 mg or 300 mg, and excipients lactose monohydrate, maize starch, magnesium stearate and talc. All capsules are formed from gelatin, and for the 75 mg and 150 mg products, the excipients are azorubine (E122), indigo carmine FD&C blue (E132). The ink for both products is formed from titanium dioxide (E171), iron oxide black (E172), shellac, propylene glycol, sodium hydroxide povidone, ammonium hydroxide 28%, strong ammonia solution and potassium hydroxide. For the 300 mg product, the capsule excipients are patent blue (E131) and titanium dioxide (E171).

The container/closure system consists of the following:-

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 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 products are 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. Process validation data on the product have been presented in accordance with the relevant European guidelines. Manufacturing formulae were provided for all strengths of the product, with target proportions of clindamycin correctly calculated. Raw materials are weighed and sieved, followed by the addition of the active substance and excipients. All ingredients are blended appropriately and filled into capsules before being packaged into blisters and cartons.

C. Control of Starting Materials

The active substance is clindamycin as clindamycin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with certificates of suitability and the principles of good manufacturing practice. Suitable specification tests are performed by the applicant. All excipients are monographed in the Ph. Eur. The capsule components are defined by the manufacturer's specifications. The foil and PVC/PE/PVdc packaging meets the requirements of EC Regulation 1935/2004EC and Commission Directive 2002/72/EC, which includes amendment 2007/19/EC. The laminate also meets the required Ph. Eur standard.

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.

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

A suitable TSE declaration in accordance with EMA guidance was provided, in addition to a declaration from the capsule supplier stating that gelatine from bovine origin is from supplier granted an EDQM certificate of suitability. Declarations were provided stating that lactose is obtained from cattle from which milk is collected for human consumption.

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 their 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 clindamycin, average weight, uniformity of dosage units, moisture, dissolution, related substances and microbial purity.

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. Stability studies on the

finished product were conducted on product packed in blister packs and stored under VICH[2] conditions of 25°C/60% RH and 40°C/75% RH for up to 12 months.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The shelf-life of the veterinary medicinal products as packaged for sale is 5 years. The products do not require any special storage conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As these were line extension applications, there was no requirement for toxicological data under Annex II of Regulations 1085/2003.

III.A Safety Testing

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline which showed that as the products are dispensed by a veterinarian and administered by the user at home, there should be no reason for contact with contents of the capsules unless the products are accidentally swallowed. Any risk to, in particular, a child ingesting the tablet is the same risk as that posed by the tablet products. The low oral toxicity of clindamycin provides reassurance with respect to accidental ingestion. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that as the products will be administered orally in small numbers of animals, there is little risk to the outside 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.

[2] VICH - International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

IV CLINICAL ASSESSMENT (EFFICACY)

As the test products differ in formulation to the parent products, full pre-clinical and clinical documentation are required unless the different presentations can be demonstrated to be pharmacologically equivalent. Bibliographic data submitted for the parent products, and dissolution studies supporting equivalence between tablet and capsule formulations were provided. Some new bibliographic data were also included.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Clindamycin is a member of the lincoside antibiotic group, exerting primarily a bacteriostatic action on many Gram-positive organisms. Binding occurs between clindamycin and the 50S ribosomal subunit of the target parasite, imposing a bacteriostatic action on the organism. Accumulation of clindamycin in cells can also confer a bactericidal action, and may additionally to confer antiparasitic activity.

Pharmacokinetics

Clindamycin is rapidly and almost completely absorbed in dogs after oral administration. In one study, C_{max}[3] was been shown to be obtained when given at 11mg/kg bodyweight at approximately 1 hour, at T_{max}[4] 0.75 – 1.5 hours. Bioavailability was 72.55 ± 9.86%. The active substance is widely distributed throughout the body, crossing the placental barrier and excreted in milk. It is metabolised mainly in the liver and excreted in urine as unchanged drug, the glucuronide, the sulfoxide and N-methyl-clindamycin. The drug is also eliminated via the faeces. In one study, the elimination half-life was shown to be 4.37 ± 0.73 hours. Further data were provided describing steady state attainment in excess of the minimum inhibitory concentration, and dose linearity was seen in one study in which dogs were given 2.75 to 11.02 mg/kg clindamycin phosphate when injected subcutaneously. In the same study, no significant accumulation of drug was observed.

Dissolution Studies

The applicant carried out comparative dissolution studies in order to claim bioequivalence with the parent products.

[3] C_{max} – Maximum plasma concentration of the active substance.

[4] T_{max} – Time at which maximum plasma concentration is reached.

Clinacin 75 mg tablets were compared with Clinacin 75 mg capsules, Clinacin 150 mg capsules, Clinacin 300 mg capsules in water. In addition, Clinacin 75 mg Tablets were compared with Clinacin 300 mg capsules in different pH-buffered solutions. Bioequivalence between relevant products was suitably established.

Tolerance in the Target Species of Animals

As bioequivalence with a parent product was demonstrated by suitable dissolution studies, no tolerance data were required.

Resistance

Resistance to clindamycin has been noted in some jurisdictions, particularly with relation to *S. pseudointermedius.* Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

As bioequivalence with a parent product was demonstrated by suitable dissolution studies, no tolerance data were required.

Field Trials

As bioequivalence with a parent product was demonstrated by suitable dissolution studies, no tolerance data were required.

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.

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