I. INTRODUCTION

This application for a Marketing Authorisation for Clinacin 300 mg Tablets for Dogs was submitted as an extension application, in order to add the 300 mg tablet to the already existing repertoire of 25 mg, 50 mg and 150 mg tablets. Clinical trials were carried out on the originator product of the range, the 75 mg tablet. Dissolution studies supported the comparable bioavailability of the 75 mg and 300 mg tablets. The proposed dosages are the same as for those of the 75 mg tablet. Clinacin 300 mg Tablets for Dogs are indicated for the treatment of infected wounds, superficial pyoderma, abscesses, osteomyelitis and oral cavity/dental infections caused by or associated with clindamycin-sensitive bacteria. These include *Staphylococcus* spp., (including *Staphylococcus aureus*), *Streptococcus* spp., *Bacteroidaceae* spp., *Fusobacterium necrophorum* and *Clostridium perfringens*. The tablets may also be used to provide anti-microbial support during dental procedures. Prior to the use of Clinacin 300 mg Tablets for Dogs, the identification of causative micro-organisms and sensitivity to clindamycin should be established. Periodic liver and kidney function tests should be carried out where the product is used for more than one month.

The product is for oral administration. For the treatment of infected wounds, oral cavity/dental infections and abscesses the dose rate is 5.5 mg/kg bodyweight every twelve hours for seven to ten days. Treatment may be extended to twenty-eight days, dependent on clinical judgement. If no improvement in condition is noted within four days, the sensitivity of the pathogens involved should be redetermined. In treating superficial pyoderma, the dose rate is 11 mg/kg bodyweight every twenty-four hours. Treatment should continue for at least twenty-one days.

For the treatment of osteomyelitis, the product should be administered at a dose rate of 11 mg/kg every twelve hours for at least twenty-eight days. If no improvement is seen within fourteen days, the sensitivity of the pathogens involved should be redetermined. To provide anti-microbial cover during dental procedures, a ten day course of Clinacin 300 mg Tablets for Dogs at a dose rate of 5.5 mg/kg every twelve hours is recommended.

II. QUALITY ASPECTS

Product Development and Composition

The 300 mg tablet has been designed to enable easier dosing of larger dogs. All formulations are blended identically and vary only in weight.

Dissolution profiles were provided for 75 mg and 300 mg Clinacin tablets. These tests were performed in suitable buffers. For both tablets, dissolution data was comparable, with 85% dissolution being achieved in fifteen minutes. Hardness in excess of other tablets was predictably seen in the 300 mg form, but data were provided that showed halving of the 300 mg tablets facilitated acceptable dissolution, in comparison with the 75 mg form.

Active Substance

All sources of clindamycin used in the product are supported by a Certificate of Suitability (CEP), from the EDQM (European Directorate for the Quality of Medicines). The specification of the dosage form for the active substance is compliant with the monograph in the European Pharmacopoeia (Ph. Eur), and also includes limits for residual solvents and particle size. Once the supply of clindamycin is qualified, tests on receipt of batches are appearance, identification and certificate of analysis compliance. If potency adjustment of the active substance is

required, assay and moisture checks are also performed. Batch data provided were in compliance with the CEPs. Ludipress is a proprietary mixture composed of Lactose Monohydrate, Povidone 30 and Crospovidone.

Other Substances

Excipients in Clinacin 300 mg Tablets for dogs are as follows: Ludipress, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Colloidal Silicon Dioxide and Magnesium Stearate. With the exception of Ludipress, all excipients comply with the requirements of current Ph. Eur monographs, and are proven to be of well-established use.

Packaging Materials

Clinacin 300 mg Tablets for Dogs are presented in white, high density polyethylene bottles with child-resistant, tamper evident polypropylene closures. These contain 6, 10, 14,16, 20, 28, 30, 42, 50, 56, 60, 70, 80, 84, 98, 100 and 200 tablets. The product is also available in a blister pack composed of 45 µm soft temper aluminium and 30 µm hard temper aluminium, consisting of pack sizes of 6,10, 14, 20, 28, 30, 42, 50, 56, 60, 70, 84, 98, 100, 140, 180, 200, 250, 280, 300, 500 and 1000 tablets.

Manufacture of the Finished Product

With regard to the prevention of the transmission of transimissible spongiform encephalopathies, lactose present in the excipient Ludipress was declared as being sourced from healthy animals and from milk fit for human consumption.

Two batch sizes are manufactured and the amount of clindamycin hydrocholoride is factored for potency, with the target amount being achieved by changing the amounts of microcrystalline cellulose added. The excipients are blended, followed by the addition of the active substance, then direct compression of the product is performed. In-process controls are satisfactory, and acceptable process validation data were presented for three production-scale batches of the tablets.

Finished Product Quality Control

The finished product is tested for: appearance, identification of clindamycin, dissolution, friability, hardness, weight, uniformity of mass, uniformity of dosage units, assay, related substances and microbial quality. Details of the HPLC methods for assay of the 300 mg tablet were comparable to those used for the 75 mg tablets, and were considered acceptable with suitable modification. Satisfactory validation data were provided for the HPLC methods for assay and dissolution, and also for microbial quality.

Stability of the Product

Active substance

Retest periods of two and three years were acceptable from two manufacturers of the active substance.

Finished Product

The shelf-life of the product as packaged for sale in HPDE (high density polyethylene) containers is four years.

Shelf life of the product as packaged for sale in blisters is two years.

CONCLUSIONS ON QUALITY

The application was fully supported with regard to quality.

III. SAFETY ASPECTS

Introduction

Data were provided on pharmocolological, toxicological and user safety aspects.

Pharmacology

Pharmacodynamic and pharmacokinetic data similar to that provided for the 25 mg and 150 mg strengths of Clinacin tablets were provided. These data were acceptable with regard to the safety assessment for the 300 mg form.

Toxicology

Toxicological data were submitted that were similar to that presented for the 25 mg and 150 mg forms of the Clinacin tablet. These data supported the use of the 300 mg form.

Residues

Clinacin 300 mg Tablets for Dogs are for use in a non-food producing species, therefore residues documentation is not required for this application.
Not applicable.

Environmental Safety

This product is for use in dogs, and therefore environmental risk assessment ends at Phase I.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

A user risk assessment provided by the applicant identified people most likely to be exposed to this product are; veterinarians, pet owners and children. Parameters investigated included accidental ingestion, dermal exposure and risk management. The risk of toxicity after accidental ingestion or dermal exposure was considered to be low, and there is no evidence of reproductive toxicity, mutagenic toxicity, or teratogenic effects. As the product is supplied in blister packs or child-resistant containers, the product does not present a significant risk to children. No specific user warnings were required. The SPC for the product is identical to currently marketed products, and there are no new parameters to evaluate.

Conclusions on Consumer Safety

Not applicable.

Conclusions on Environmental Safety

This product is for use in dogs, and therefore environmental risk assessment ends at Phase I.

IV. CLINICAL ASPECTS

Introduction

Clinical Pharmacology

Pharmacodynamics

Several references were submitted supporting the bacteriostatic action of clindamycin, which binds the bacterial 50s ribosomal subunit, inhibiting the early stages of protein synthesis. Elongation of the early peptide chain is achieved. Clindamycin is also associated with accumulation within granulocytes, known to congregate at infection sites due to chemotaxis. This also contributes to bacteriostatic action.

Clindamycin has been shown to be most effective against Gram-positive bacterial strains, including *Staphyloccal, Streptococcal* and *Pnemococca*l species. Effective action has also been seen against Gram-positive and Gram-negative bacterial species. However, clindamycin is not effective against Gram-negative anaerobic bacteria. The applicant submitted a series of data on antimicrobial resistance to clindamycin.

Pharmacokinetics

Published data were submitted in support of absorption, distribution and elimination of clindamycin. Clindamycin is almost completely absorbed at a rapid rate after oral administration to dogs, before being distributed widely in body tissues and fluids. Clindamycin is then excreted in the urine and faeces as unchanged drug, along with various residues. Details of a titrium-labelled study on the pharmacokinetics of clindamycin administered to dogs and rats were provided. Dogs received a 500 mg/kg dose, and peak plasma radioactivity was recorded within two hours, while elimination was two thirds via the faeces and one third via the urine. 85.35% of the total dose was recovered after two weeks. Reports were also presented on dose linearity

and steady state. Dose linearity between a dose of clindamycin varying from 2.75 – 11.02 mg/kg and subsequent plasma levels, when the drug was given to dogs, was observed. No significant accumulation of drug was observed after the administration of several doses. A further study reviewed the use of clindamycin at 5.5 mg/kg, given orally to dogs. 90% absorption was seen, with peak plasma levels being reached within two hours of administration. An additional study was reported in which animals received multiple doses of clindamycin at 5.5 mg/kg, given every twelve hours. A steady state serum level of the drug was maintained in excess of the MICs, for most susceptible organisms.

Bioequivalence studies were originally conducted in dogs, using Clinacin 75 mg Tablets for Dogs, with the reference product being Cleorobe 75 mg Capsules. Clinacin 75 mg Tablets for Dogs and Cleorobe 75 mg Capsules were found to be bioequivalent in terms of AUC, C_{max} and T_{max}. Clinacin 300 mg Tablets for dogs have the same ratio of active ingredient, the same excipients, are for the same target species and are administered via the same route as the 75 mg form. Data for the 75 mg tablet is therefore relevant to the 300 mg tablet, when supported by relevant dissolution studies.

Data were submitted demonstrating that Clinacin 300 mg Tablets for Dogs had a comparable dissolution profile to the 75 mg form. Studies were performed at pH 4.5 and pH 6.8 in 0.1M hydrochloric acid. Linearity was demonstrated over a range of 60% to 140% of the test concentration, with results showing that both tablet strengths attained >86% dissolution within fifteen minutes. Dissolution curves were similar.

Tolerance in the Target Species

A GLP-compliant study was performed to investigate the tolerance of clindamycin hydrochloride capsules in dogs. A suitable number of animals received clindamycin at a dose rate of 300 mg/kg/day for twenty-eight days, a further group of animals received clindamycin at 600 mg/kg/day for twenty-eight days, and a final group received no clindamycin. The dogs were observed for reactions to the clindamycin, and these included analysis of feed and water consumed, amount and appearance of faeces and urine, and bodyweight. Blood samples were taken at regular intervals in order to study biochemical and haematological parameters, and liver biopsies were performed on days twelve, twenty-four and forty-two. Few adverse reactions were noted in the 300 mg clindamycin group as compared with the 600 mg clindamycin group.

Published data were also submitted in support of this application. No evidence was found of hepatotoxicity or nephrotoxicity after a year-long study analysing the tolerance of dogs to clindamycin. However, the applicant has included a warning to monitor hepatic and renal function during prolonged use of the product, with caution being advised where the patient has liver or kidney problems.

No data were provided with regard to use of the drug in pregnant and lactating bitches. However, the product is not recommended for use in these animals.

Resistance

The applicant provided details of published data on clindamycin resistance, highlighting that acquired resistance may occur in normally sensitive strains of Gram-negative aerobes which are intrinsically resistant to clindamycin. Resistance is though to be caused by methylation of the ribosomal binding site, chromosomal mutation of the ensuing ribosomal protein, and occasionally, enzymatic inactivation by a plasmid-mediated adenyltransferase. Complete cross-resistance has been demonstrated between clindamycin and lincomycin, this type of resistance

being usually inducible. It was concluded that issues relating to resistance do not impact on the use of Clinamycin 300 mg Tablets for Dogs.

Clinical Efficacy

Infected wounds and abscesses

Published data were provided which gave details on a blinded, placebo-controlled study, in which a number of dogs were infected with anaerobic bacterial infections, after which the efficacy of subsequently used clindamycin and a product containing lincomycin were assessed. The clinacin product used was Antirobe Capsules (clindamycin). One group of animals were exposed to *Bacteroides fragilis*, *Bacteroides melaninogenicus* and *Fusobacterium necrophorum*, another group of animals were exposed to *Bacteroides fragilis* and *Clostridium perfringens*. Treatment groups received clindamycin at a dose of 5.5 mg/kg or 11 mg/kg twice a day, or lincomycin at 22 mg/kg twice a day. Therapy commenced eighteen to twenty-four hours after inoculation and was continued for seven days. Minimum inhibitory concentrations (MICs) for clindamycin for isolates used in the study were:-

B. fragilis – 0.5 ug/ml
B. melaninogenicus – 0.02 ug/ml
F. necrophorum – 0.06 ug/ml
C. perfringens – 2 ug/ml

Dogs treated with clindamycin had significantly less lesion development than placebo treated dogs, and clindamycin was seen to give superior results than those gained using lincomycin.

Additional published data were submitted on Antirobe Capsules. This report outlined a negatively controlled dose-determination study conducted in dogs infected with *Staphylococcus* and *Streptococcus* infected wounds. The optimum dose for treating the animals was 5.5 mg/kg. A field trial followed, in which a large number of dogs with infected wounds and abscesses were treated with 5.5 mg/kg clindamycin every twelve hours for seven days. Treatment with clindamycin was successful. Results of a further, uncontrolled field trial were also submitted in which a variety of bacterial infections were treated at a dose rate of 5.5 mg/kg every twelve hours for seven days. An 88% positive response rate was seen.

Superficial pyoderma

Staphylococcus intermidius is the most common bacterium associated with superficial pyoderma. Several published reports were submitted demonstrating the use of clindamycin as being an effective treatment for this disease. The first study was a randomised, positively controlled field study in which a number of dogs suffering from superficial pyoderma were treated either with clindamycin or lincomycin. Clindamycin hydrochloride was given once daily as Antirobe Capsules, at a dose rate of 11 mg/kg/day with a positive response rate of 81% over three weeks, and lincomycin hydrochloride (as Lincocin Tablets) was given twice daily at a dose rate of 22 mg/kg over three weeks. After a further three week period of treatment for dogs which did not respond initially, the overall positive response rate for all dogs was established as being 94% for clindamycin and 93% for lincomycin.

Dental infections

Periodontal disease is common in the dog, with disease-causing bacteria commonly being *Bacteroides* and *Fusobacterium* spp. Several literature reviews were submitted relating to the use of clindamycin in dental disease.

One study was conducted amongst veterinary practitioners specialising in dentistry, and the efficacy of clindamycin for a range of dental diseases was evaluated. The dose rate was 5.5 mg/kg twice a day for ten days, with therapy extended if required. In 91% of cases, a good or excellent response to treatment was received.

A second study investigated the use of clindamycin alone, buccodental procedure alone, or a combination of buccodental procedure and anti-bacterial treatment for use in dental disease in the dog. The trial was carried out by experienced veterinarians, and consisted of dogs being divided into the three groups described. Clindamycin (Cleorobe Capsules) was given at a dose rate of 5.5 mg/kg, twice daily for ten days. If necessary, treatment was extended to thirty-eight days in total. Where clindamycin was used alone, 84% positive responses were seen. If clindamycin was not used, the positive response rate fell to 51%. Where clindamycin was used in collaboration with dental procedures a 100% positive response rate was received. Only mild adverse effects were seen in a minority of cases. A third study analysed tolerance and efficacy of clindamycin used in association with scaling in gingivitis and periodontitis of the dog. A number of animals received clindamycin (Clerobe Capsules) twice a day for ten days, after ultrasound teeth scaling. A second group of animals received no antibiotics after scaling. Swabs were taken from the mucosae of dogs with either healthy or inflamed oral mucosae prior to treatment, and blood samples were taken at various time points from treated and control dogs. Animals that received clindamycin in addition to dental scaling displayed significantly better results when compared to dogs that had received scaling alone.

Osteomyelitis

Details of a placebo-controlled, blinded study to investigate the efficacy of a variety of dosing regimens of clindamycin in relation to experimentally induced oteomyelitis attributable to *Staphylococcus aureus* were submitted. A number of dogs were involved in the trial. Two weeks after infection with *S. aureus*, animals were divided into the following groups:-

Group 1 – 5.5 mg/kg clindamycin every twelve hours for fourteen days
Group 2 – 5.5 mg/kg clindamycin every twelve hours for twenty-eight days
Group 3 – 11 mg/kg clindamycin every twelve hours for fourteen days
Group 4 – 11 mg/kg clindamycin every twelve hours for twenty-eight days
Group 5 – No treatment

Bone lesions were analysed at a variety of time points, and by the last day of treatment S. aureus was not isolated from any animal. Two weeks after treatment, the majority of animals were still negative for *S. aureus*, while the negative control group were all positive for *S. aureus*.

Details of a second, placebo-controlled, blinded study were also submitted. This study analysed the efficacy of clindamycin (Antirobe capsules, Antirobe Aquadrops), at a dose rate of 11 mg/kg every twelve hours for twenty-eight days for the treatment of induced posttraumatic osteomyelitis caused by *S. aureus*. A number of dogs were experimentally infected with *S. aureus*, and two weeks after infection were placed into one of two groups:-

Group 1 - Dogs treated with clindamycin at 11 mg/kg every twelve hours for twenty-eight days

Group 2 – Untreated dogs as negative controls

Two weeks after the end of clindamycin treatment, *S. aureus* was undetected in 93.7% of treated dogs as compared to 46.1% of control dogs. No dogs treated with clindamycin exhibited osteomyelitis histopathologically, whereas a large proportion of the control dogs presented with osteomyelitis.

CONCLUSIONS ON CLINICAL ASPECTS

The legal basis of this application was well-established use, and was an extension of the authorisation for Clinacin 75 mg Tablets for Dogs. Much of the data submitted for the 75 mg form of the tablet was relevant for this application, and the spectrum of antibiotic activity and mode of action for clindamycin have been satisfactorily justified, supported by recent MIC data. The general pharmacokinetics of oral clindamycin is supported by published data, and bioequivalence was established between the 75 mg tablets and the original reference product, Cleorobe 75 mg Capsules. Comparative dissolution data for Clinacin 75 mg Tablets for Dogs and Clinacin 300 mg Tablets for Dogs was acceptable.

PART V. OVERALL CONCLUSION ON THE PRODUCT

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.

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)