I. INTRODUCTION

Clavucill 400 mg/100 mg, Tablets for Dogs are oral tablets containing amoxicillin trihydrate and potassium clavulanate equivalent to 400 mg amoxicillin and 100 mg clavulanic acid, for use as a broad spectrum treatment for bacterial infections in dogs. A dosage rate of 12.5 mg/kg bw for up to 7 days is indicated, although the dose could be doubled and the duration of administration could be longer (up to 28 days) with chronic infections. The tablets are presented in blister packs and come in boxes of up to 500 tablets. Amoxicillin has been shown to be effective in treating a wide range of diseases of dogs including: skin disease (including deep and superficial pyoderma), urinary tract infection, respiratory disease involving upper and lower respiratory tract, enteritis, dental infections (e.g. gingivitis), and soft tissue infections (e.g. abscesses and anal sacculitis). The product is not indicated for cases involving *Pseudomonas* spp.

The application for a Marketing Authorisation for this product was granted as a generic product under Article 13(1) of Directive 2001/82/EC as amended b Directive 2004/28/EC to an established product. For this type of application, applicants are exempted from the usual requirement to produce evidence of safety and efficacy, if they show that the composition of the proposed product is essentially similar to, i.e. closely resembles that of an established product.

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

II. QUALITY ASPECTS

Product Development and Composition

The product contains the active substances amoxicillin trihydrate (equivalent to amoxicillin) and potassium clavulanate diluted (equivalent to clavulanic acid). The sensitivity of clavulanic acid to degradation in the presence of moisture was recognised in devising the product. Excipients were selected for their suitability in a dry granulation process. Excipients include colloidal anhydrous silica, sodium starch glycolate, microcrystalline cellulose, erythrosine and magnesium stearate . The choice of formulation is justified.

The tablets are presented in blister packs formed from polyethylene-coated aluminium foil in strips of 10 tablets. This packaging was selected for its impermeability to moisture and oxygen. Single or multiple strips are packed in cartons with a package insert. The particulars of the containers and controls performed are provided and conform to the regulation.

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

Active Substances

Active substance 1

Amoxicillin Trihydrate: is 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. Certificates of analysis demonstrating compliance with this specification have been provided.

Active substance 2
Potassium clavulanate diluted is also 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. Certificates of analysis demonstrating compliance with this specification have been provided.

Other Substances
Excipients described in a pharmacopoeia:
Satisfactory raw material specifications have been presented in respect of colloidal anhydrous silica, sodium starch glycolate, microcrystalline cellulose and magnesium stearate, and comply with the relevant monograph of the European Pharmacopoeia. Acceptable certificates of analysis have been presented.

Excipients not described in a pharmacopoeia:
A satisfactory specification and certificate of analysis have been presented for erythrosine, which complies with European requirements for food colour E127.

Packaging Materials
Specifications and certificates of compliance with European Pharmacopoeia and food contact regulations have been presented for the polyester/aluminium/polyethylene laminate used to form the strip pack. The product comes in pack sizes of 10, 20, 30, 50, 80, 100, 250 and 500 tablets.

Manufacture of the Finished Product
The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The applicant has provided details of the stages of manufacture which includes blending, granulation, sieving, compression, dedusting and packaging. In process controls have also been described. Process validation data on the product have been presented in accordance with the relevant European guidelines.

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

Finished Product Quality Control
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

Stability of the Product
Active substance
No stability data are presented for either active ingredient in the dossier. The applicant has placed reliance upon the certificates of suitability for the raw materials.

Finished Product
Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A 24 month shelf life has been justified.

In-Use
Any half used tablets must be returned to the opened strip-pack and used within 24 hours.

CONCLUSIONS ON QUALITY
The product is satisfactorily formulated and manufactured and controlled. Stability data justify the shelf-life of 24 months. Product literature bears the appropriate warnings “Do not store above 25°C” and “Return any halved tablet to the opened strip-pack and use within 24 hours. The shelf-life of the product after immediate opening is 24 hours.

III. SAFETY ASPECTS

Pharmacology
As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

The pharmacological aspects of this product are identical to the reference product.

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 .

Toxicology
As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

The toxicological aspects of this product are identical to the reference product.

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, the environment and consumers.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline that considered likely routes of exposure. Risks from dermal contact were considered to be low; a warning that persons with a known hypersensitivity should not handle the product was recommended. The most significant exposure is considered to be accidental ingestion by children. However, this was considered to be mitigated by the product only being available on prescription.

Environmental Safety
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was not required.

CONCLUSIONS ON SAFETY

Conclusions on User Safety
The user safety risk assessment provided by the applicant is comprehensive and backed up by references. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:-

- Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact.
- Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reaction to these substances may occasional be serious.
- Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.
- Handle this product with great care to avoid exposure, taking all recommended precautions.
- 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 difficulty with breathing are more serious symptoms and may require urgent medical attention.
- In the event of accidental ingestion seek medical advice. Wash hands after handling the tablets.

Conclusions on Environmental Safety

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 ASPECTS

Clinical Pharmacology

Pharmacodynamics

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, pharmacodynamic studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Pharmacokinetics

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, pharmacokinetic studies are not required. The efficacy claims for this product are equivalent to those of the reference product. The applicant has however provided a number of references detailing the absorption, distribution, metabolism and excretion of the actives amoxicillin and clavulanate in man. The Applicant has also provided references detailing the PK profiles of amoxicillin and clavulanate in dogs. These data were extracted from literature references, using different formulae of amoxicillin and clavulanate than that concerned with this product. The applicant demonstrated that the active substances are highly bioavailable, and readily absorbed (high solubility and permeability) in the target species.

Tolerance in the Target Species

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, target species tolerance studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Resistance

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, resistance studies are not required. The efficacy claims for this product are equivalent to those of the reference product. However the Applicant has presented several literature references on the subject demonstrating that resistance to the active substances does not appear to be emerging.

Clinical Efficacy

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, clinical studies are not required. The efficacy claims for this product are equivalent to those of the reference product

CONCLUSIONS ON CLINICAL ASPECTS

The overall risk benefit assessment for the product was acceptable for efficacy

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.

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