ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Clavudale 250 mg Tablet for Dogs
(UK, IE, FR, AT, BE, CZ, GR, HU, IC, LU, NO, PO, PT, SK)
Clavudale 200 mg /50 mg Tablet for Dogs
(DE, NL, DE, ES, FI, SE)

Clavudale 500 mg Tablet for Dogs
(UK, IE, FR, AT, BE, CZ, GR, HU, IC, LU, NO, PO, PT, SK)
Clavudale 400 mg /100 mg Tablet for Dogs
(DE, NL, DE, ES, FI, SE)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0373/002/MR UK/V/0373/003/MR
Name, strength and pharmaceutical form	Clavudale 250 mg Tablet for Dogs Clavudale 500 mg Tablet for Dogs
Applicant	Dechra Limited Dechra House Jamage Industrial Estate Stoke-On-Trent ST7 1XW
Active substance(s)	Amoxicillin (as amoxicillin trihydrate) Clavulanic acid (as potassium clavulanate)
ATC Vetcode	QJ01CR02
Target species	Dogs
Indication for use	For the treatment of bacterial infections susceptible to amoxicillin in combination with clavulanic acid where clinical experience and/or sensitivity testing indicates the product as the drug of choice. Uses include: Skin infections (including deep and superficial pyodermas) associated with Staphylococci and Streptococci; Infections of the oral cavity (mucous membrane) associated with Clostridia, Corynebacteria, Staphylococci, Streptococci, *Bacteroides* spp. and Pasteurellae.; Urinary tract infections associated with Staphylococci, Streptococci, *Escherichia coli* and *Proteus* spp; Respiratory tract infections associated with Staphylococci, Streptococci and Pasteurellae; Gastrointestinal infections associated with *Escherichia coli* and *Proteus* spp.

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.
Date of completion of the original mutual recognition procedure	21st January 2011
Date product first authorised in the Reference Member State (MRP only)	8th January 2010
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Luxembourg, The Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

These were applications for the mutual recognition of two UK authorised products, Clavudale 250 mg Tablet for Dogs and Clavudale 500 mg Tablet for Dogs. Bioequivalence was claimed with the reference products, Synulox Palatable Tablets 250 mg and Synulox Palatable Tablets 500 mg, authorised in the UK since August 1990.

Clavudale tablets contain amoxicillin and clavulanic acid in a ration of 4:1, with the 250 mg tablet containing 200 mg amoxicillin and 50 mg clavulanic acid, and the 500 mg tablet containing 400 mg amoxicillin and 100 mg clavulanic acid.

The products are indicated for the treatment of bacterial infections susceptible to amoxicillin, in combination with clavulanic acid, where clinical experience and/or sensitivity testing indicates the product as the drug of choice. The products may be used for skin infections (including deep and superficial pyodermas), associated with Staphylococci and Streptococci, infections of the oral cavity (mucous membrane) associated with Clostridia, Corynebacteria, Staphylococci, Streptococci, *Bacteroides* spp. and Pasteurellae and urinary tract infections associated with Staphylococci, Streptococci, *Escherichia coli* and *Proteus* spp. The products may also be used for respiratory tract infections associated with Staphylococci, Streptococci and Pasteurellae and gastrointestinal infections associated with *Escherichia coli* and *Proteus* spp.

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. The products are safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the products 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 contains 200 mg amoxicillin per 250 mg tablet and 100 mg amoxicillin per 500 mg tablet, with 50 mg per 250 mg tablet clavulanic acid, and 100 mg clavulanic acid per 500 mg tablet. The excipients are erythrosine (E127), silica colloidal anhydrous, magnesium stearate, sodium starch glycolate (type A), cellulose microcrystalline.

The container system consists of orientated polyamide/aluminium/polyvinyl chloride film, heat sealed with aluminium foil in strips of 6 tablets. Cartons contain 12 or 24 tablets. 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 development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the products have been presented in accordance with the relevant European guidelines.

All ingredients are sieved and blended and the addition of each active substance is adjusted for purity at the expense of microcrystalline cellulose. All components are ground and/or sieved before blending, compacting and tabletting. Tests are performed to examine water content, friability, disintegration, hardness and uniformity of mass. Tablets are marked as appropriate prior to packaging. Validation of the manufacturing process was conducted on three consecutive batches of product. Final specification tests ensure the quality of the products.

C. Control of Starting Materials

The active substances are amoxicillin trihydrate and potassium clavulanate, established active substances described in the European Pharmacopoeia (Ph. Eur). The active substances are 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 specification have been provided.

Both active substances are produced in accordance with Certificates of Suitability. Batch analysis data were obtained form a suitable number of batches of each active substance, and these were satisfactory. Excipients described in the Ph. Eur are anhydrous colloidal silica, sodium starch glycolate Type A, magnesium stearate and microcrystalline cellulose. Certificates of analysis were provided in addition to the applicant specification. Erythrosine (E127) is not described in the Ph. Eur, but a satisfactory raw material specification and suitable certificate of analysis were presented.

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

Scientific data and/or certificates of suitability issued by the EDQM[1] have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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. 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 performed on the finished products include those for appearance, weight, uniformity of mass, identity of active substances, impurities, friability, hardness, dissolution and microbiological control.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Batches of amoxicillin trihydrate were stored for 60 months at 25^{o}C, 40^{o}C/75%RH for 6 months, and 25^{o}C/60RH for 48 months. Any degradation in all specimens remained within specified limits. For diluted potassium clavulanate, batches were stored for 24 months at 5^{o}C, and for 6 months at 25^{o}C/65% RH. All specimens remained within specifications.

[1] EDQM – European Directorate for the Quality of Medicines and Healthcare.

For the finished product, three batches of 250 mg and 500 mg tablets were stored under VICH[2] conditions for up to 48 months at 25°C/60%RH, for up to 9 months at 30°C/60%RH and for up to 6 months at 40°C/75% RH. Analysis of data gave rise to the inclusion of the statement 'do not store above 25°C'.

Stability data on the finished products have been provided in accordance with applicable European guidelines, demonstrating the stability of the products throughout shelf life when stored under the approved conditions.

For in-use stability studies, samples of the 250 mg product, as divided tablets, were stored at 40°C/75% RH for up to 16 hours. Test results gave rise to the justification for a 12 hour shelf life once tablets are divided.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life of the products as packaged for sale, 4 years.
Shelf life of the products after first opening the immediate packaging, 12 hours.
Any divided tablet portions remaining after 12 hours should be discarded.

Special precautions for storage:

- Do not store above 25ºC.
- Divided tablets should be stored in the blister pack.

[2] VICH – International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As these are generic applications according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological, and toxocological tests are not required.

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 Testing

User Safety

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the products.

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:-

- Clavudale is an oral antibacterial product consisting of the semi-synthetic antibiotic ampicillin and the β-lactamase inhibitor clavulanate acid.
- The applicant has provided a detailed description of each active substance including structural formulae.
- The applicant has described the indications and pattern of use according to the SPC. [3]
- The applicant states that there is a negligible risk of direct contamination of the environment. Exposure will be via excreta of treated animals.
- With reference to the VICH decision tree the applicant states that: the product is indicated for use in dogs and cats which are non-food producing species (Question 3).
- The assessment therefore stops at Phase I.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the products are used as directed.

[3] SPC – Summary of Product Characteristics.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

The applicant provided a series of bioequivalence studies and dissolution studies.

Pharmacology

A two-way cross-over bioequivalence study of a single dose of Clavudale 250 mg Tablet for Dogs as compared to Synulox Palatable Tablets 250 mg was performed. A suitable number of animals were given half or a whole tablet, based on bodyweight. Blood samples were taken at appropriate time points. Statistical analysis demonstrated that the products were bioequivalent. A comparative dissolution study using the same products, and additionally the 500 mg products demonstrated that dissolution rates between test product and reference product were comparable.

Tolerance in the Target Species of Animals

As bioequivalence was demonstrated between test and reference products, no tolerance studies were required.

Resistance

As bioequivalence was demonstrated between test and reference products, no resistance studies were required.

IV.B Clinical Studies

As bioequivalence was demonstrated between test and reference products, no clinical studies were required.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the producs are 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 Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

This section 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.

•	6th January 2010	Change of Distributor.