Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Equizol 400 mg Gastro-resistant Granules for Horses

Date Created: August 2018

PuAR correct as of 17/10/2018 when RMS was transferred to DE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0628/001/DC
Name, strength and pharmaceutical form	Equizol 400 mg Gastro-resistant Granules for Horses
Applicant	CP Pharma Handelsgesellschaft mbH Ostlandring 13 31303 Burgdorf Germany
Active substance(s)	Omeprazole
ATC Vetcode	QA02BC01
Target species	Horses
Indication for use	For the treatment of gastric ulcers in horses

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	9th August 2018
Concerned Member States for original procedure	Italy

I. SCIENTIFIC OVERVIEW

This was an application for a marketing authorisation for a generic 'hybrid' product; Equizol 80 mg/g Gastro-resistant Granules for Horses, submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended. The reference product is GastroGard 37% w/w Oral Paste for Horses, marketed by Merial Animal Health Limited, which was authorised nationally in the UK on 9th January 2003. This was determined a generic 'hybrid' application because changes to the pharmaceutical form with regards to the reference medicinal product have been made and bioequivalence cannot be demonstrated.

The product is indicated for the treatment of gastric ulcers in horses. The proposed dosing regimens are a dose rate of 2mg omeprazole per kg bodyweight for 28 consecutive days for the treatment of gastric ulcers. The SPC cites mixing the appropriate number of sachets into a small amount of the horse's feed.

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, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Not authorised for use in animals producing milk for human consumption. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] 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.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains Omeprazole and the excipients sugar spheres, hypromellose, anhydrous lactose, sodium laurilsulfate, sodium starch glycolate (type A), disodium phosphate dodecahydrate, tiatnium dioxide, methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30% (Eudragit® L. 30 D-55),triethyl citrate, talc, apple flavour and purified water.

The container/closure system consists of a heat sealed laminated foil sachet, comprising: paper (50 g/m2) / aluminium (9 µm) / polyethylene (9 µm). 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. The manufacturing method consists of multiple-step film coating of active gastro-resistant granules and apple-flavoured granules.

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

II.C. Control of Starting Materials

The active substance is omeprazole, 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. Batch analytical data demonstrating compliance with this specification have been provided.
The active may be sourced from either of two suppliers, each in accordance with a certificate of suitability.

All excipients, other than the apple flavour feature in the European Pharmacopoeia and it is stated that they comply with their respective monograph.

Apple flavour 052681 T consist of a mixture of flavouring components, each of which is stated to comply with the provisions of EC regulation 1334/2008 (flavourings and certain food ingredients with flavouring properties for use in and on foods).The flavour does not contain any animal-derived ingredients and does not contain or consist of genetically modified organisms.

The finished product is packed in heat-sealed sachets (5 g granules per sachet, equivalent to 400 mg omeprazole) of standard compound foil comprising:

Polyethylene 50 µm (product contact layer)
Aluminium 9 µm
Paper 50 g/m^2

II.C.4. Substances of Biological Origin

The only material of animal origin is lactose. The applicant has provided a declaration stating compliance with the Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products (EMEA/410/01 rev. 3).

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 sites have been provided demonstrating compliance with the specification. Control tests on the finished product are those for appearance, odour, average mass of sachet filling, uniformity of dosage units, water content, identification by HPLC and UV spectroscopy, impurities, dissolution and microbial limits.

II.F. Stability

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.

G. Other Information

This veterinary medicinal product does not require any special conditions.

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

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this in an application for a generic (hybrid) product, the applicant is not required to provide toxicological and pharmacological data.

Toxicological Studies

As this in an application for a generic (hybrid) product, the applicant is not required to provide toxicological and pharmacological data.

User Safety

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- This product may cause adverse gastrointestinal effects or hypersensitivity (allergic) reactions if accidentally ingested, particularly by children.
- Do not eat or drink whilst handling or administering the product.
- Wash hands or any exposed skin after use.
- Any part-used sachets should be returned to the original carton and suitably stored to prevent access by children.
- In case of accidental ingestion, especially by a child, seek medical advice if symptoms persist.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH[3] and CVMP[4] guidelines.

Phase I
The applicant provided a very brief ERA which stops at question 5 of the VICH Decision Tree.

[3] VICH – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.
[4] CVMP – Committee for Medicinal Products for Veterinary Use.

The product will be used to treat a small number of animals in a flock or herd and as such environmental exposure will be low. A Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

Due to the nature of the application, no residue depletion studies were conducted.

MRLs

Not applicable.

Withdrawal Periods

Based on the data provided, a withdrawal period of 2 days for meat in horses is justified. The product is contraindicated for use in animals producing milk for human consumption.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

As this in an application for a generic (hybrid) product, the applicant is not required to provide pharmacodynamic data. However, published literature submitted states that omeprazole is a substituted benzimidazole proton pump inhibitor. Following oral administration, omeprazole is absorbed from the intestine and transported to the parietal cells of the stomach. Omeprazole is there converted to a sulphonamide derivative that binds the cells to H+/K+ ATPase, thereby inhibiting the transport of hydrogen ions to the stomach.

Pharmacokinetics

A pilot bioequivalence study demonstrated that the proposed product is suprabioavailable compared to the reference product. A further pharmacokinetic study attempted to refine the dose of the proposed product as compared to that of the reference product.

It was seen that suprabiovailability of the proposed products was demonstrated at 2 mg/kg, in comparison to the reference product at 4mg/kg.

Target animal safety studies using multiples of 1x, 3x and 5x the recommended treatment dose given for 90 days in young animals did not produce any treatment-related adverse effects. No adverse reactions were noted at either 2mg/kg mg or 4 mg /kg bodyweight.

Four studies were referenced which demonstrated no negative impact of a higher dose of omeprazole > 4mg/kg on assessed pathological parameters.

Although bioequivalence was not demonstrated in trials, no adverse reactions associated with the product were noted in any study, and any concerns on suprabioavailability of the proposed product as opposed to the reference product were resolved.

Published literature showed that although bioequivalence between proposed and reference products could not always be demonstrated, similar acid secretion inhibition profiles were obtained. All assessed data, when taken in entirety, assured proof of efficacy.

Tolerance in the Target Species

As this in an application for a generic (hybrid) product, the applicant is not required to provide tolerance data.

IV.II. Clinical Documentation

Field Trials

The applicant conducted a field efficacy study to compare the test formulation with placebo for the treatment of gastric ulcers. However, this study was considered not pivotal to the conclusions on efficacy due to several flaws and shortcomings in the design and conduct.

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 is favourable.

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.

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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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