ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

GastroGard 370 mg/g oral paste

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0185/001/E/001
Name, strength and pharmaceutical form	GastroGard 370 mg/g oral paste
Applicant	Boehringer Ingelheim Animal Health UK Limited Ellesfield Avenue Bracknell Berkshire RG12 8YS United Kingdom
Active substance(s)	Omeprazole
ATC Vetcode	QA02BC01
Target species	Horses
Indication for use	For treatment and prevention of gastric ulcers.

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	Repeat use application in accordance with Article 32 (2) and Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	13 June 2011
Date product first authorised in the Reference Member State (MRP only)	09 January 2003
Concerned Member States for original procedure	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

This application was for a Repeat Use Mutual Recognition Procedure according to Article 32 (2) of Directive 2001/82/EC, and submitted in accordance with Article 12.3 of Directive 2001/82/EC as amended. The product contains 370 mg/g of omeprazole, a proton pump inhibitor, and is indicated for the treatment and prevention of gastric ulcers in horses. For the treatment of gastric ulcers, the product is used at a rate of one administration of 4 mg omeprazole/kg bodyweight per day for 28 consecutive days. Re-treatment is permitted should ulcers recur. Changes in husbandry and training are recommended, see section 4.5 of the SPC[1]. For the prevention of ulcers, the product is given at 1 mg omeprozole/kg bodyweight per day.

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 slight reactions observed are indicated in the SPC. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and 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.

[1] Summary of Product Characteristics.

II. QUALITY ASPECTS

A. Composition

The product contains 37% w/w omeprazole, a well-established active substance cited in the European Pharmacopoeia, and excipients yellow iron oxide (E 172), monoethanolamine, potassium sorbate, cassia oil, sodium stearate, calcium stearate, hydrogenated castor oil, propylene glycol octanoate deconoate and sesame oil. All excipients are monographed in the Eurpoean Pharmacopoeia, British Pharamcopoeia, German pharmacopoeia or the United States National Formulary.

The container system consists of a 10 ml syringe composed of a white polypropylene barrel and white low density polyethylene (LDPE) cap. A rubber rod tip and polypropylene plunger rod with dose calibrations completes the packaging. The syringe contains 6.16 g of paste. 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.

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. The manufacturing process is a simple three-step procedure consisting of pre-blending of some of the exipients, mixing of all ingredients, followed by filling of the syringes.

C. Control of Starting Materials

The active substance is omeprazole, an established substance described in the European Veterinary Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice (GMP).

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

Certificates of Suitability issued by the EDQM 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. Data was in line with appropriate guidance documents.

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 include appearance of the product, uniformity, ejectable content, specific gravity, penetration value, alkalinity and yearly microbiological purity analysis.

G. Stability

Stability data on the active substance were provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A re-test period of 36 months was deemed acceptable. Data were presented on the finished product, stored under VICH[2] conditions of 25°C/60% RH and 30°C/60% RH for 24 months and at 40°C/75% RH for 6 months. Little degradation was seen. No change due to exposure to light was seen. Two batches were subjected to an in-use stability study. Opened syringes with 60% of the contents removed were stored for 39 weeks at 5°C/ambient humidity, 25°C/60%RH, 30°C 60%RH and 40°C/75% RH. No adverse effects were observed except in the 40°C/75% sample, where a small increase in degradation products was noted. No change was seen during submission to a temperature re-cycling programme, apart from a small increase in viscosity. These data contributed to the establishment of a 2 year shelf-life.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years. Shelf life after first opening the immediate packaging: 28 days.

[2] VICH – International Cooperation on Harmonisation of Technical Requirements for Reegistration for Veterinary Products.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacological and Toxicological data were originally submitted to the EMA[3] in support of an MRL[4] application for omeprazole. Summary data was taken from the ensuing CVMP[5] Summary Report. A guinea pig sensitisation test was also provided for the toxicological report.

Pharmacodynamics

Activated H+/K+ -ATPase enzymes are inhibited intracellularly by omeprazole, leading to the transitory inhibition of the gastric acid production of the cell. After inhibition of a sufficient number of parietal cells, acid secretion decreases, raising the pH of the stomach contents. pH increase subsequently raises levels of gastrin.

Pharmacokinetics

The pharmacokinetic parameters of omeprazole were studied in mice, rats, dogs, horses and humans. Bioavailability was demonstrated to be variable depending on route of administration, with extensive metabolism occurring in mice, rats and dogs after intravenous and oral administration. Only trace amounts of the parent compound were found in the urine. Metabolism is also extensive in horses, after intravenous and oral administration. A variety of metabolites are found in the excreta.

Toxicological Studies

The applicant provided bibliographical data, which cited several reports.

Single Dose Toxicity

Acute oral toxicity data in rats and mice for omeprazole were submitted. Signs of toxicity were reduced activity, twitching and tremor, and reduced temperature and respiration.

Repeated Dose Toxicity

Several reports were submitted investigating repeat dose toxicity in relation to

[3] EMA – European Medicines Agency.
[4] MRL – Maximum Residues Limit.
[5] CVMP – The Committee for Medicinal Products for Veterinary Use.

omeprazole. In one report, dose toxicity was studied in rats divided into five groups dosed orally with 0, 13.8, 43.1, 138 or 414 mg/kg bodyweight/day. In the highest dosed group, a tendency to increased hyperkeratosis of the squamous epithelium between the fore-stomach and glandular mucosa was seen, possibly indicating a low degree of chronic gastric irritation. Increased kidney and liver weights appeared to be a physiological adjustment to drug elimination. A toxicological NOEL[6] of 43.1 mg/kg bodyweight/day was established. A further study observed repeat dose toxicity in dogs, the NOEL for the study was established as 1.035 mg/kg bodyweight/day.

In a third long-term study in dogs, given 0, 0.7, 5.5 or 28 mg/kg bodyweight/day, the only change noted was a reversible atrophy of the chief cells in the gastric mucosa of dogs give either 5.5 or 28 mg/kg bodyweight/day. The NOEL was established as being 0.7 mg/kg bodyweight/day. In another study, no clinical changes were noted in dogs given 0 or 0.17 mg/kg bodyweight/day over a period of 7 years.

Reproductive Toxicity

The only effects seen in rats, where a NOEL of 43.1 mg/kg bodyweight/day was established for reproductive toxicity, were a slight non-significant decrease in litter size, viability and growth where animals had been given 138 mg/kg bodyweight/day.

Embryotoxicity, fetotoxicity (Including teratogencity)

Minor abnormalities were found during studies in rats and rabbits, with statistically significant effects being a slight decrease in litter size and pup weight at doses of 138 mg/kg bodyweight/day.

Mutagenicity

No indication of mutagenicity was seen in any tests performed, which consisted of an Ames *Salmonella* test, an *in vitro* mouse lymphoma assay, *in vitro* assays for chromosome aberrations and polyploidy in human lymphocyte cultures, an *in vivo* assay for chromosomal aberrations in mouse bone marrow and an *in vivo* mouse micronucleus test.

Carcinogenicity

Extensive studies were performed with regard to carcinogenicity, as omeprazole is authorised for human use.

In rats three 2-year studies were performed. Oral doses of 0, 1.7, 3.4, 13.8, 14.1, 44.0, and 140.8 mg/kg bodyweight/day were given. Effects noted were a dose-related increase in stomach weight and mucosa thickness, and a time and dose-related increase in cell hyperplasia. No long-term toxicological NOEL in rats could be defined. At the end of the study, a direct correlation between plasma gastrin level and Entero-Chromatofin-Like (ECL) cell density, also

[6] NOEL – No Observable Effect Limit.

between histidine-decarboxylase (HDC) activity and histamine levels. It was concluded that hypergastrinemia secondary to acid inhibition by omeprazole resulted in a dose-dependent increase in ECL-cell hyperplasia, possibly leading to dose-dependent formation of end-life ECL-cell carcinoids.

In a 1 year study in dogs which were given 0.7, 5.5 or 28 mg/kg bodyweight/day, and in a 7 year study in dogs given 0.17 mg/kg bodyweight/day, the only reversible pathological changes (seen at the highest dose), occurred in the acid-secreting areas of the gastric mucosa. In addition, a rugal hypertrophy was seen at doses higher than 5.5 mg/kg bodyweight/day. The NOEL was 0.7 mg/kg bodyweight/day.

Other Studies

Irritancy and Hypersensitisation

Delayed contact hypersensitivity reactions were seen in 18/20 animals in a guinea pig sensitisation test, when the animals were treated with both a 0.2% and 5% topical solution of omeprazole.

Observations in Humans

Omeprazole has been widely used in humans for many years, with a recommended dose rate of 20 mg/day for the treatment of gastric ulcers and 10 mg/day for the prevention of relapse. The NOEL is 5 mg/kg /person/day. In studies, statistically significant reactions were noted only at ≥ 20 mg.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

The SPC advises that the product may cause hypersensitivity, and that direct contact with skin and eyes must be avoided. Impervious gloves are to be used while handling the product, and hands or any exposed skin should be washed after use. In case of contact with the eyes, the user is recommended to wash the eyes immediately with running water and seek medical advice. Do not eat or drink when handling and administering the product. Any reaction developed after handling the product should preclude the user handling the product in the future.

Ecotoxicity

Omeprazole will not directly enter the environment; however residues of the active substance will reach the environment in the excreta of treated animals. Data suggest that the occurrence of gastric ulcers occurs almost exclusively in performance horses, as non-performance and leisure horses are not subjected to relevant predisposing factors. Treatment of non-performance horses is therefore negligible. In racing yards, the wood shavings from stables is taken to

landfill sites, and in other yards (where horses perform at a lower level, i.e. show horses), amounts reaching the environment when manure is spread or when animals defecate onto pasture are within acceptable limits. The environmental risk assessment stopped at Phase I.

III.B Residues documentation

Residue Studies

Residues data were originally submitted by the applicant to the CVMP in support of an application for the inclusion of omeprazole in a specific Council Regulation. Summary data was taken from the ensuing CVMP Summary Report, from which it was noted that omeprazole undergoes extensive and rapid metabolism.

A residue depletion study in horses was conducted, using radiolabelled omeprazole in a sodium carbonate, sodium bicarbonate buffer. 1 mg omeprazole/kg bodyweights was administered for 7 days. Post-mortems took place at various time points after the final dose and tissues were analysed. The majority of the active substance was found in the urine and the remainder in the faces and cage wash. No evidence of accumulated radioactivity was found. Maximum plasma concentrations were similar following 1 day and 7 daily doses. No significant differences in absorption and elimination between intravenous or oral administration were seen.

Withdrawal Periods

The withdrawal period for meat and offal from treated animals is 1 day. The product is not permitted for use in mares producing milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

(Data provided from the original National Procedure; includes any updates to the SPC)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The active substance, omeprazole is an antacid, belonging to the substituted benzimadizole class of compounds. Gastric acid secretion is suppressed by the inhibition of the H+/K+-ATPase enzyme system, (the proton pump within the gastric mucosa), at the surface of the parietal cell. The active substance irreversibly binds to the enzyme, blocking acid secretion. It was found that after 8,16 and 24 hours post-administration with omeprazole at 4 mg/kg bodyweight/day, acid secretion was inhibited by 99%, 95% and 90% and basel secretion inhibited by 99%, 90% and 83%. Optimum inhibition is obtained 5 days after first administration.

Pharmacokinetics

The median bioavailability of omeprazole after oral administration as a paste is 10.5% (range 4.1 to 12.7%). Maximal plasma concentration is reached approximately one hour after dosing. Omeprazole is rapidly metabolised principally into specific derivatives. After oral administration at 4 mg/kg, omeprazole is detectable in the plasma for 9 hours after treatment, and is detectable in urine as hydroxyomeprazole and O-desmethylomeprazole at 24 hours but not at 48 hours. Omeprazole is eliminated quickly, mainly by urinary route and to a smaller extent by faecal route. After repeated oral administration, there is no evidence of accumulation.

Tolerance in the Target Species of Animals

Four trials evaluated the safety of omeprazole paste in horses. All trials were conducted to GLP standards.[7] The active substance was delivered at up to five times the recommended dose over a period of three months. The animals varied with regard to age and sex, and sham-dosed horses were included in each trial. Further trials investigated the use of ten times the recommended dose, and effects of the active substance in breeding stallions. Post-mortem and during the trials, no undue adverse effect were seen in relation to the use of omeprazole.

IV.B Clinical Studies

Laboratory Trials

The applicant conducted dose determination and confirmation studies which demonstrated the acceptability and efficacy of omeprazole in healing gastric ulcers in horses maintained in race training.

Field Trials

A series of trials, (all conducted to GCP[8]) were conducted, involving a range of horse breeds under different management systems. In the first trial, the product was administered at the optimum dose of 4 mg/kg bodyweight/day for 28 days, after the animals were divided according to ulcer score, availability, sex and age. Horses were paired as replicates as much as possible, from which groups one animal was sham-treated. The entire treated group had healed ulcers at the end of the study.

A second trial using five replicates of four horses, paired as replicates where possible. From each group of pre-examined animals, horses were either sham treated or given omeprazole paste at 4 mg/kg bodyweight/day for 0 - 27 days, followed by 2 mg/kg bodyweight for 28 – 57 days. At the end of specific trial

[7] GLP – Good Laboratory Practise.
[8] GCP – Good Clinical Practice.

periods, the animals were in normal training. All treated horses had improved gastric lesion score.

Further, similar studies provided data in which improvement was seen in gastric ulcer lesion score

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.

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