Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Primazym 40000 Ph. Eur. U Capsules for Dogs

Date Created: May 2016

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Primazym 40000 Ph. Eur. U. Capsules for Dogs
Applicant	Eurovet Animal Health BV Handelsweg 25 5531 AE Bladel The Netherlands
Active substance	Lipase 40000 Ph. Eur. Units Amylase not less than 25000 Ph. Eur. Units Protease not less than 1500 Ph. Eur. Units
ATC Vetcode	QA09A A 02
Target species	Dogs
Indication for use	Enzyme supplementation to aid in the treatment of maldigestion in dogs with exocrine pancreatic insufficiency (EPI).

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	Application in accordance with the Veterinary Medicines Regulations. Application accepted under Article 13 (a) (Well-established use), according to Directive 2001/82/EC, as amended.

I. SCIENTIFIC OVERVIEW

This was a full application under Article 13 (a) (Well-established use), according to Directive 2001/82/EC, as amended. Assessment followed EMA guidelines on data requirements related to MUMS[1] applications.
The application consisted of bibliographical references and clinical trials. The product is indicated for use as an enzyme supplementation to aid in the treatment of maldigestion in dogs with exocrine pancreatic insufficiency (EPI).

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, any reactions observed are indicated in the SPC[2]. 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 efficacy[3] 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] MUMS – Minor Use Minor Species.
[2] SPC – Summary of Product Characteristics.
[3] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITIATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains pancreas powder (porcine) 351 - 456 mg, equivalent to lipase 40000 Ph. Eur. Units, amylase not less than 25000 Ph. Eur. Units and protease not less than 25000 Ph. Eur. Units. The excipients in the micro-pellets are methacrylic acid - ethyl acrylate _ copolymer (1:1), triethyl citrate, talc and simethicone emulsion. The gelatin capsules, which contain the micro-pellets, consist of gelatin, red iron oxide (E172), titanium dioxide (E171) and sodium laurylsulphate. The ink consists of titanium dioxide (E171), shellac, anhydrous ethanol, isopropyl alcohol, butyl alcohol, propylene glycol, sodium hydroxide and polyvidone.

The container/closure system consists of amber coloured glass bottle (Ph. Eur. type III) with snap-on LDPE caps. The volume of the bottles are 50 ml, containing 20 capsules, 100 ml containing 50 capsules and 175 ml containing 100 capsules. 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 a variety of sieving, coating and weighing steps, followed by filling and packaging.

II.C. Control of Starting Materials

The active substance is pancreas powder, an established active substance described in the European Pharmacopoeia (Ph. Eur.) 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 and an appropriate Certificate of Suitability was provided.

All excipients and the amber vials used for filling are monographed within the Ph. Eur.

II.C.4. Substances of Biological Origin

For gelatin only, certificates of suitability issued in accordance with the appropriate Directive were provided. No other components of mammalian origin are used in the product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

The tests performed on the sieved film-coated pellets and the filled hard capsules during production are described and conform to the specifications provided.

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 site have been provided demonstrating compliance with the specification. Control tests on the finished product include those for mass, disintegration, identification of active components, loss on drying and microbiological quality.

II.F. Stability

Stability data on the finished product, tested according to VICH[4] conditions were provided. These include data on real-time and accelerated storage. In-use stability tests on the finished product were also conducted. Some moisture uptake was noted and the SPC includes appropriate warnings:

- Do not store above 30 °C. After opening: store in a dry place and keep the bottle tightly closed in order to protect from moisture.

II.G. Other Information

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

Shelf life after first opening the immediate packaging: 6 months.

[4] VICH – The International Cooperation on Harmonisation of Technical Requirements for Veterinary Medicinal Products.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data was provided.

Pharmacodynamics

Pancreatin when administered to rats at up to 5000 mg/kg/day did not result in any secondary pharmacological effects on the respiratory, cardiovascular or nervous system. Anaesthetised rats given 3, 10 and 30 mg/kg of pancreatin showed a small dose-dependent decrease in blood pressure. Respiration rate and amplitude were increased at the highest dose. In humans, oral administration of enteric tablet-coated formulation containing 40000 units of lipase and 2000 units of protease after overnight fasting produced reduction in pancreatic elastase. In isolated guinea pig ileum, contracting effects were observed, which was antagonised by diphenhydramine. In isolated smooth muscle tests no significant anti-acetylcholine, anti-histamine or anti-epinephrine action was observed.

Pharmacokinetics

The pharmaceutical formulation of the product has been designed to maximise the appropriate absorption of pancreatin. Radiolabelled pancreatin has been observed in rats, guinea pigs and rats to be rapidly eliminated. Undigested pancreatin is excreted in the faeces.

Toxicological Studies

The applicant provided bibliographical data in order to discuss the following aspects of toxicity:

- Single Dose Toxicity

In studies in rats and mice, showing high LD_{50} values (>10 g/kg following oral administration, 2.1 - 2.5 g/kg following intraperitoneal administration and 3.8 - 5 g/kg following subcutaneous administration), pancreatin was shown to be essentially non-toxic. Some local tissue irritation was observed following injection.

- Repeated Dose Toxicity

Sub-acute toxicity studies in rats given 200, 1000 and 5000 mg/kg/day, and a 4-week oral study in rats given 1000 mg/kg demonstrated no toxic effects.

- Reproductive Toxicity, including Teratogenicity:

In studies in rats and rabbits given daily doses less than 4000 mg/kg for 12 - 15 days, no changes were noted in fertility, or in the number of uterine implantations. Some delayed ossification was noted.

- Mutagenicity

No mutagenic effects have been reported for the Ames test, DNA repair system, Saccharomyces-D7-cells and EUE cells.

- Carcinogenicity

Pancreatin is not considered to be carcinogenic.

Studies of Other Effects

The effects of exocrine pancreatic insufficiency on the numbers and types of bacteria in duodenal juice followed by dietary supplementation with bovine pancreatic extract were studied in 6 dogs. Insufficiency was induced by ligation of the pancreatic ducts which resulted in large increases of total numbers of bacteria. It was noted that the observed effects were likely due to the increase in gastric secretion in addition to the ligation. Microbial contamination decreased after dietary supplementation with bovine pancreatic extract to values that were not significantly different from those determined before duct ligation. In dogs, it was also noted that iron absorption may be reduced by the administration of pancreatin.

Observations in Humans

Pancreatin has been demonstrated to have an effect on the absorption of folate. Irritant contact dermatitis has also been observed. Fibrosing colonopathy or thickening of the colon wall has also been noted.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Data were provided on hazard identification and characterisation, exposure scenarios, and qualitative risk characterisation. Estimated levels of human exposure to the product after accidental ingestion are unlikely to cause anything more than a gastrointestinal disturbance. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product, and should be followed

Individuals with hypersensitivity to pork protein should take special precautions to avoid contact with the product. Normal hygienic measures may be applied to the product, and as a matter of principle the product should be kept out of sight and reach of children:

- This product may cause contact dermatitis in susceptible people. It is recommended that those people who know that they have protein contact dermatitis wear protective gloves when handling the product, or food to which the product has been added. Wash hands after use. Ingestion of the product may cause gastrointestinal disturbance and/or mild allergy-type reactions. In case of accidental ingestion and when symptoms do not resolve soon afterwards, seek medical advice and show the package leaflet or label to the physician.

Environmental Safety

A Phase I Environmental Assessment Report was submitted and accepted. The product will be used in a small number of companion animals, and is not expected to pose undue threat to the environment, when used as directed.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The enzyme-containing micro-pellet which characterises the product dissolves at approximately pH 5.6, thus ensuring that the active substances are not disintegrated in the stomach. When administered whole, the gelatin capsule dissolves in the stomach, and the enzymes are released in the intestine, supporting digestion.

The applicant provided a series of published references to support the application, in general describing the pharmacodynamic properties of the active substance in humans. Further references were provided to justify extrapolation of the data to dogs.

Pharmacokinetics

The applicant provided a number of references to demonstrate the pharmacokinetics of pancreatic enzymes. Although these data were in general from species other than dogs, it was accepted that the enzymes within the proposed product would be processed similarly to those of other species. Based on these data, it appears that there is minimal absorption of the pancreatic enzymes from the intestine into the systemic circulation. Any enzymes not absorbed are digested or eliminated via the faeces.

Tolerance in the Target Species

Tolerance in the target species was investigated in eight beagle dogs administered with the proposed product during three phases with the normal dose (14 days, first phase) followed by a two- and threefold overdose (28 days

each phase, second and third phase). A wash-out period of 14 days was conducted between treatments.

Appropriate clinical examinations took place before medication, daily during treatment phases, and after the last medication. Laboratory tests including blood tests also supported the safety of the product. Each dog served as its own control.

No serious adverse, study-related effects were seen. The applicant additionally provided several bibliographical references. It was concluded that Primazym 40 000 capsules given at x2 and x3 the recommended dose did not induce significant clinical or laboratory abnormalities.

IV.II. Clinical Documentation

In vitro study – TNO dynamic model (Supportive data)

This study, which used a simulated, computer controlled model of conditions within the stomach of the dog, sought to assess the efficacy of the proposed product as compared to a reference product by comparing the digestibility of fats when each of the products was used. The digestibility of fats was measured within the model for the fed state, using wet canned dog food. The digestibility of fats was increased in the presence of the pancreatin-containing products, and was equivalent between the two products. The data were considered to be supportive rather than pivotal.

Field Trials

Study performed by applicant:

Study title	Study on the clinical efficacy of an enzyme supplement following oral administration to dogs with exocrine pancreatic insufficiency y
Objectives	To assess the improvement of clinical signs associated with EPI using a proposed product
Test site(s)	multi-centre, (veterinary practices), Germany
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Pankreatin enzyme supplement as capsules containing micro pellets, (the final formulation of Primazym), containing the active substance pancreas powder (40 000 Ph. Eur. Units lipase). Dose: 1 capsule per meal for all but one animal. Adjustment made if no reversal of clinical signs of disease and dog did not gain weight.
Control product/placebo	Dogs served as own control.
Animals	15 client-owned dogs, of mixed sex and age and breed. Diagnosed with EPI. Previous treatment ceased at least 14 days prior to study. Dogs excluded that had diseases that would interfere with the study.
Outcomes/endpoints	Statistical assessment of reduction of clinical signs associated with EPI – gastro-intestinal complications, weight loss, loss of appetite.
Randomisation	Not randomised.
Blinding	Not blinded.
Method	Clinical examinations were performed at the start of the study, dogs were fed normally by clients and the appropriate dose of pancreatin given. Clinical signs were monitored by the client.
Statistical method	For each parameter tested, mean score per week was calculated and with these values a one-way ANOVA with repeated measures was performed and 95% confidence intervals for mean weekly scores of the various parameters were calculated by Friedman-Test analysis.
RESULTS	
Outcomes for endpoints	Some efficacious effects were noted. Statistically significant improvement in bodyweight and improvement in clinical scores for several other parameters, (although not statistically significant).
Adverse events	No significant adverse reactions attributable to the proposed product were seen.

DISCUSSION	In conjunction with another clinical study performed by the applicant, and submission of a key bibliographic reference, this study was considered as being suitably supportive of the application, and a Marketing Authorisation was granted.

Key reference study submitted in support of the efficacy of the proposed product

Study title	Mas *et al* (2012): A blinded randomised controlled trial to determine the effect of enteric coating on enzyme treatment for canine exocrine pancreatic efficiency. *BMC Veterinary Research* 8:127.
Objectives	The study compared the efficacy of an established (non-authorised) enteric-coated pancreatic enzyme supplement, with a non-enteric coated product.
Test site(s)	Single site, UK
Compliance with Regulatory guidelines	Not stated
Test Product	Lypex, 30 000 Ph. Eur. U lipase, 18 750 Ph. Eur. U amylase, 1200 Ph. Eur. U protease per capsule.
Control product/placebo	Positive control treatment: non-enteric-coated pancreatic enzyme supplement, otherwise identical to Lypex.
Animals	Client-owned dogs diagnosed with EPI were sourced from vets, with client consent. 35 of 40 dogs starting the study completed the trial. Dogs were of various breeds, age and gender. Exclusions included any concurrent disease that might affect diagnosis, response to treatment or prognosis. Any previous treatment with pancreatic enzyme supplementation.
Outcomes/endpoints	The primary outcome was change in body weight. Secondary outcomes included change in severity of clinical signs, the dose of treatment used for each dog, and the requirement for additional medications. For clinical signs, a composite score was created, by adding together the results of all clinical signs recorded in a questionnaire.
Randomisation	Randomised
Blinding	Blinded
Method	Suitable clinical examination took place prior to the study. A two-group parallel design was used. 20 dogs were assigned to the test group, 20 to the control group.
Statistical method	The effect of treatment on body weight (the primary outcome measure) was investigated using a mixed-effects linear regression model in STATA. The effect of treatment was assessed using a multivariable model, which included treatment group, the visit number and their interaction. Serum cobalamin concentrations were

	included in the form hypocobalaminaemic and normocobalaminaemic when results were less than and greater than the lower limit of the reference range, respectively. Enzyme dose and body condition score (BCS) data were analysed with the signed ranks test (for time differences) and the Mann-Whitney test (for differences between groups at each time-point).
RESULTS	
Outcomes for endpoints	**Primary outcome measurements** Median body weight increased progressively in both groups during the trial ($p<0.001$), but the magnitude of increase was greater for the test treatment than for the control treatment ($p<0.001$): by day 56, this was 17% (95% confidence interval 11% - 23%) in the test treatment group and 9% (95% confidence interval 4% - 15%) in the control treatment group. **Secondary outcome measures:** BCS increased in both groups over time ($p<0.001$ at 56 days). However, the BCS of the dogs in the test treatment group increased more than those in the control treatment group ($p=0.032$ at 56 days). The dose of enzyme used increased with time ($p<0.001$ at 56 days), but there was no significant group difference at any time point. Clinical disease severity score decreased significantly over the trial ($p=0.011$ at 56 days), but no difference was noted between treatment groups.
Adverse events	Some adverse events unrelated to the study were noted.
DISCUSSION	In conjunction with two clinical studies performed by the applicant, this study was considered as being suitably supportive of the application and a Marketing Authorisation was granted. The applicant provided appropriate justification to extrapolate the results obtained from Lypexto their own product.

Study title	Clinical efficacy of a new formulation of pancreatic enzyme supplement, Primazym, in dogs with exocrine pancreatic insufficiency
Objectives	To establish the clinical efficacy of Primazym in dogs with naturally occurring exocrine pancreatic insufficiency (EPI)
Test site(s)	Single centre
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Primazym capsule (containing porcine pancreas powder): (Final formulation of Primazym). Lipase not less than 40 000 Ph. Eur. Units Amylase not less than 25 000 Ph. Eur. Units

	Protease not less than 1 500 Ph. Eur. Units.
Control product/placebo	Positive control, Tryplase capsule Intervet UK Ltd (containing porcine pancreas powder): Lipase not more than 14 000 Ph. Eur. Units Amylase more than 10 000 Ph. Eur. Units Protease more than 500 Ph. Eur. Units
Animals	41 dogs of which 11 client-owned dogs of different breeds, age and gender completed the study.
Outcomes/endpoints	Comparison of efficacy between the proposed and control product using statistical analysis. Primary efficacy variable: percentage faecal fat. Secondary variable: assessment of clinical signs associated with EPI.
Randomisation	Computer-generated, four block randomisation, further stratified by weight and gender.
Blinding	Owners and veterinarians blinded to treatment assigned to patients.
Method	The trial consisted of two treatment periods for the animal, each lasting three weeks. Capsules were given at meals according to bodyweight. In the first period, the animal received either the test product or the comparator product; and in the second period, the animal received the opposite product to the one in the first period. No wash-out period to avoid complications from lack of treatment. Upon completion of the trial, the owner could select which treatment they wished to continue with (i.e. that received in the first or second three week period).
Statistical method	Percent faecal fat:.Friedman Test used to compare percent faecal fat between the two treatments. Secondary parameters were subject to analysis using appropriate tests. Statistical significance was set at $p<0.05$ for two-tailed tests
RESULTS	
Outcomes for endpoints	The 90% confidence interval (CI) for the mean difference in % fat (Primazym-Tryplase) was -7.79, -1.14 and for median was -8.96, 0.69. Primazym was accepted as being non-inferior to the control product.
Adverse events	Some adverse events unrelated to the study were noted.
DISCUSSION	In conjunction with another clinical study performed by the applicant, and submission of a key bibliographic reference, this study was considered as being suitably supportive of the application, and a Marketing Authorisation was granted.

In conclusion, it was accepted that combined data demonstrated acceptable evidence of efficacy in order that the product could be accepted under a Limited Marketing Authorisation.

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(s) 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.

(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)