



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 February 2025
EMA/60032/2025
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Omeprazole TriviumVet (EMA/V/C/005345/0000)

INN: Omeprazole

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.



Table of contents

Introduction	4
Scientific advice.....	4
Part 1 - Administrative particulars	5
Summary of the Pharmacovigilance System Master File	5
Manufacturing authorisations and inspection status	5
Overall conclusions on administrative particulars	5
Part 2 - Quality	6
Composition	6
Containers and closure system	6
Product development.....	6
Description of the manufacturing method.....	7
Control of starting materials.....	7
Active substance.....	7
Excipients	8
Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies.....	9
Control tests on the finished product	9
Stability.....	10
Overall conclusions on quality.....	10
Part 3 – Safety documentation (Safety and residues tests).....	11
Safety tests.....	11
Pharmacology.....	11
Toxicology	13
Other requirements.....	18
Excipients	19
User safety	20
Environmental risk assessment.....	21
Overall conclusions on the safety documentation: safety tests.....	22
Part 4 – Efficacy.....	24
Pre-clinical studies	24
Pharmacology.....	24
Dose determination and confirmation	24
Tolerance in the target animal species.....	29
Clinical trial(s)	30
Overall conclusions on efficacy	32
Part 5 – Benefit-risk assessment	35
Introduction	35
Benefit assessment	35
Direct benefit	35
Additional benefits	36
Risk assessment	36

Risk management or mitigation measures.....37

Evaluation of the benefit-risk balance.....37

Conclusion37

**Divergent position on a CVMP opinion on the granting of a marketing
authorisation38**

Introduction

The applicant TriviumVet DAC submitted on 24 April 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Omeprazole TriviumVet, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 10 November 2022 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

At the time of submission, the applicant applied for the following indication:

Treatment of gastric ulcers secondary to therapy with non-steroidal anti-inflammatory drugs (NSAIDs) in dogs. However, based on the data presented and assessment thereof, the proposed indication was not considered acceptable and was subsequently amended to 'As an aid in the treatment of NSAID-induced gastric ulceration in dogs'.

The active substance of Omeprazole TriviumVet is omeprazole. Omeprazole is a proton pump inhibitor (PPI) that inhibits the H^+/K^+ proton pump at the luminal surface of the parietal cell that secretes hydrogen ions into the gastric lumen, thus decreasing gastric acid secretion. Reducing the level of acid formation is widely reported in published scientific literature to promote healing of gastric ulcers and erosions.

The target species is dogs.

Omeprazole TriviumVet gastro-resistant capsule contains 10 mg of omeprazole and is presented in packs containing 30 capsules.

The applicant is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC.

The rapporteur appointed is Paul McNeill and the co-rapporteur is Kim Boerkamp.

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

On 12 February 2025, the CVMP adopted an opinion and CVMP assessment report.

On 2 April 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Omeprazole TriviumVet.

Scientific advice

The applicant received two scientific advices from the CVMP. The scientific advice pertained to the clinical development. Not all of the scientific advice has been followed and discussion on those aspects of the scientific advice that have not been followed is presented under each of the relevant sections of the assessment report below.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF) and has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

Manufacture, micronisation, quality control testing (chemical/physical, microbiological), primary packaging, and secondary packaging of the active substance omeprazole takes place outside the EEA. A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an onsite audit by the manufacturer of the finished product which has taken into consideration the GMP certificate available for the active substance site.

Manufacture of the active substance intermediate takes place outside the EEA. A GMP declaration for the active substance intermediate manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an onsite audit by the manufacturer of the finished product.

Finished product

Manufacture, quality control testing (microbiological, chemical/physical), primary packaging and secondary packaging of the finished product takes place outside the EEA. A GMP certificate has been provided for the manufacturing site of the dosage form.

Quality control testing (microbiological, chemical/physical), of the finished product has GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the activities indicated above, has been provided.

Batch release of the finished product takes place at Acorn Regulatory Consultancy Services Limited, Co. Tipperary, Ireland. The site has a manufacturing authorisation issued on 19th April 2023 by the competent authority of Ireland (HPRA). GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the activities indicated above, issued on 26th April 2023 is available on the EudraGMP database.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file was considered to be in line with legal requirements.

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

The GMP status of the finished product QC testing and batch release sites have been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as pink/white gastro-resistant hard gelatin capsules containing 10 mg/capsule of omeprazole as active substance.

Other ingredients are:

Intra granular ingredients: lactose monohydrate, microcrystalline cellulose and mannitol, sodium laurilsulfate, hydroxypropylcellulose and disodium phosphate dihydrate.

Sub-coating ingredients are hypromellose and talc.

Enteric coating ingredients include methacrylic acid – ethyl acrylate copolymer (1:1) dispersion 30%, triethyl citrate as plasticizer, glycerol monostearate and polysorbate 80, talc and titanium dioxide.

The ingredients in the hard gelatin capsule shells consist of gelatin, titanium dioxide, sodium laurilsulfate and iron oxide red.

Containers and closure system

The primary packaging is a white high-density polyethylene bottle with polypropylene child resistant cap. A 1g silica gel/activated carbon Tyvek sachet is also included as desiccant. Each bottle contains 30 capsules.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Product development

The application for 'Omeprazole TriviumVet 10 mg gastro-resistant capsules for dogs' has been submitted as a full application in accordance with Article 8 of Regulation (EU) 2019/6.

The aim of the development was to produce a solid gastro-resistant dosage form which can be swallowed easily, formulated at a suitable strength for the target population and dosage regimen, meets compendial and other relevant quality standards, and is packaged to ensure dosage form integrity during shipping.

The critical quality attributes (CQAs) considered in detail were assay, content uniformity, dissolution and degradation products.

The formulation and manufacturing development have been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters (CPPs). The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development and process design. The critical process parameters have been adequately identified and form part of the in process control strategy for the finished product.

The dissolution test for the finished product is based on the method specified in the USP monograph for "Omeprazole Delayed Release Capsules". Satisfactory data has been presented to demonstrate that the dissolution test and specification are discriminatory for this product formulation.

The development report discusses physical properties of the active substance. The active substance exhibits polymorphism and this parameter is subject to non-routine control on the dosage form site API specification.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC. The development report includes an excipient compatibility study which demonstrates that the active substance is compatible with the excipients.

The development pharmaceuticals report includes details of trial batches which were manufactured in order to optimise the product formulation and manufacturing process, using results from earlier risk assessment and compatibility studies. It is assumed that some of the initial selection of excipients and concentrations trialled in the various development batches are based on experience with other similar formulations/published information etc. Overall, the formulation development is satisfactorily well described and the applicant's conclusions throughout this process are supported by the data presented.

Description of the manufacturing method

The finished product is a gastro-resistant capsule. The manufacturing process follows a conventional approach for gastro-resistant solid dose manufacturing and involves preparation of granules by an extrusion and spheronisation process. As omeprazole degrades under acidic conditions, an enteric coating is applied in order to provide gastro resistant properties. The enteric coated granules are then encapsulated in hard gelatin capsule shells for delivery to the target species. The process is considered to be a standard manufacturing process.

The dossier includes a stepwise narrative description of the manufacturing process and a manufacturing process flow chart. Factorisation for active substance assay content is applied; no overages are detailed.

In-process controls (IPCs) are detailed on the manufacturing process flow-chart and on a separate in-process test specification. The in-process control strategy for the product consists of the CPPs and the IPCs and is considered acceptable.

Process validation has been conducted on three batches. The applicant has also provided a historic process validation report for three blend batches of 515 kg in size and used this data to justify some of the parameters detailed in the manufacturing process description. This is considered acceptable as the 515 kg blend batches are representative of the proposed commercial product.

Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

A process validation protocol was provided for future full scale production batches and it is accepted that process validation on the largest commercial scale batch size will be performed post authorisation.

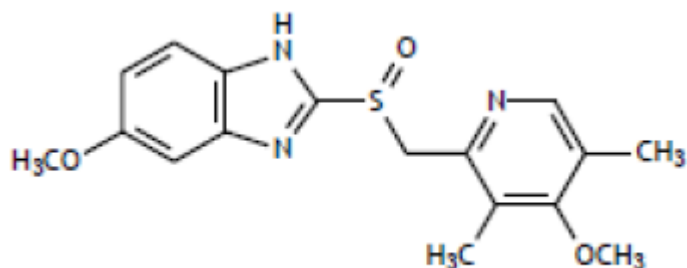
Control of starting materials

Active substance

The active substance is omeprazole Ph. Eur.

The chemical names of omeprazole are 5-Methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1Hbenzimidazole and 5-Methoxy-2-[(RS)[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl]-1Hbenzimidazole.

Omeprazole has the following structure:



Omeprazole is a white to off-white powder with a melting range of 150°C – 160°C and is not hygroscopic in nature. It is soluble in dichloromethane, sparingly soluble in methanol and in alcohol and very slightly soluble in water.

Omeprazole exists as two optical isomers, (R)- and (S)-, due to the asymmetric centre in the sulphur atom. It is a racemic compound consisting of equal parts of the two enantiomers, (R) and (S).

Polymorphism has been observed for the active substance. Active substance polymorphic form is controlled in the dossier. The parameter will be subject to non-routine control, which is acceptable. Data to demonstrate that the active substance supplier consistently produces the same polymorphic form has been presented.

There is a monograph for omeprazole in the Ph. Eur. The manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for omeprazole, a copy of which has been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

The CEP specifies a retest period.

Satisfactory information regarding the active substance primary reference standard and working standard has been presented.

Batch analysis data on 2 batches of the active substance have been provided by the active substance manufacturer. The results are within the specifications and consistent from batch to batch and demonstrate compliance with all tests in the proposed active substance specification.

Excipients

With the exception of the capsule shells, all excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. monographs. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

The dossier indicates that the excipients, microcrystalline cellulose, mannitol, hypromellose, methacrylic acid - ethyl acrylate copolymer and talc are to be controlled in line with Ph. Eur. monographs and for additional parameters. The additional parameters are acceptable. Excipients in line with the proposed specifications were used in the manufacture of the development batches. Additional tests for functionality-related characteristics have been included on the specifications for the

excipients lactose monohydrate, hydroxypropylcellulose, glycerol monostearate, polysorbate 80 and titanium dioxide and are considered acceptable.

The non-pharmacopoeial excipients used in this product are the pink-white hard gelatin capsule shells. The dossier includes the qualitative and quantitative composition of the capsule shells accompanied by a satisfactory control specification.

The colourants in the capsule shell comply with Directive 2009/35/EC and Commission Regulation (EU) No. 231/2012, in line with the requirements of Annex II to Regulation 2019/6.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The product contains materials derived from human or animal origin, specifically gelatin which is a constituent of the capsule shells and lactose monohydrate which is one of the intra granular excipients.

It is confirmed that the lactose used in the manufacture of the finished product is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatin obtained from bovine sources is used in the product. The dossier includes copies of TSE CEPs for the gelatin used by the suppliers of the capsule shells.

Control tests on the finished product

The specifications proposed at release are appropriate to control the quality of the finished product.

The finished product specification includes tests for appearance, active substance identification, assay, degradation products, dissolution, average fill weight, uniformity of dosage units; content uniformity, loss on drying, lock length, microbial quality and identification of colourants.

The dossier states that the product complies with ICH Q3D requirements for elemental impurities. A risk assessment on the control of elemental impurities in the veterinary medicinal product in line with the requirements of the 'Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products' EMA/CVMP/QWP/15364/2018 has been carried out. Based on the risk assessment, no control strategy for elemental impurities is proposed, which is considered acceptable.

The analytical methods have been adequately described and appropriately validated in accordance with the VICH GL1: *Validation of analytical procedures: definition and terminology* and VICH GL2: *Validation of analytical procedures: methodology*. Satisfactory information regarding the primary reference standard and the working reference standard used for assay and impurities testing has been presented.

The test for microbiological quality is described in the dossier and satisfactorily validated.

Batch analysis results are provided for three commercial scale batches. All results are within specification confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

The specifications proposed at the end of shelf-life are appropriate to control the quality of the finished product.

Stability data for three commercial scale batches of the finished product stored under long term conditions for 36 months at 25 °C/60% RH and for up to 6 months under accelerated conditions at 40 °C/75% RH according to the VICH guideline GL3 *Stability testing of new veterinary drug substances and medicinal products* were provided. The stability batches are identical to those proposed for marketing save for the use of capsule shells of a different colour in the stability batches. The batches were packed in the primary packaging proposed for marketing.

The analytical procedures used are stability indicating.

Results across both VICH stability storage conditions are within the proposed shelf-life specifications and no significant changes have been observed. The data indicates that the product is very stable.

In addition, one batch was exposed to light as defined in the VICH guideline GL5 on photostability testing of new veterinary drug substances and medicinal products which demonstrated that the product is not sensitive to photolytic degradation.

A freeze / thaw study was also carried out on one batch. Results indicate that freezing and thawing does not have an adverse impact on product quality.

The dossier also includes stability data for finished product stored in bulk LDPE bulk bags. Stability results for product packaged in LDPE bulk bags mirror those for product packaged in HDPE bottles.

The stability data supports the proposed shelf-life of 3 years. The applicant has confirmed that post-approval stability data will be generated.

Overall conclusions on quality

The finished product is presented as pink/white hard gelatin gastro-resistant capsules containing 10 mg/capsule of the active substance omeprazole. The capsules contain enteric coated granules.

The product is presented in white high-density polyethylene bottles with polypropylene child resistant caps, fitted with a polypropylene heat seal liner and pulpboard wad, in a carton box. Each bottle contains 30 capsules.

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way.

Part 3 – Safety documentation (Safety and residues tests)

The active substance of Omeprazole TriviumVet is omeprazole. Omeprazole is a substituted benzimidazole and acts as a proton pump inhibitor (PPI).

Omeprazole TriviumVet is intended as a new veterinary medicinal product for use in dogs to reduce gastric acid secretion and thereby be used as an aid in the treatment of gastric ulceration secondary to therapy with non-steroidal anti-inflammatory drugs (NSAIDs) in dogs.

Omeprazole is a new active substance for the target species dogs but is already authorised within the EU as a veterinary medicinal product in a number of pharmaceutical forms (paste and granules) for administration to horses.

A full safety file in accordance with Article 8 of Regulation (EU) 2019/6 has been provided.

The application relies heavily on published scientific literature including the CVMP MRL summary report for omeprazole.

Safety tests

Pharmacology

Pharmacodynamics

Omeprazole is a proton pump inhibitor (PPI) and, like all PPIs, is a substituted benzimidazole which is systemically absorbed in the alkaline environment of the duodenum and carried in the circulation and delivered to the stomach's parietal cell as a prodrug activated by acid. In the acidic environment of the stomach, PPIs accumulate in the secretory canaliculus of the parietal cell and covalently bind to the H⁺/K⁺-ATPase, thereby irreversibly blocking its activity. Through its inhibition, PPIs profoundly and irreversibly inhibit gastric acid secretion. Because the acidic compartment is unique to the gastric parietal cell, PPIs have no effect on other cellular proton pumps. Consequently, no other pharmacodynamic activity is expected or reported for omeprazole outside of the gastric parietal cell. It is recommended that PPIs should be administered before a meal so that the peak serum concentration coincides with the maximal activity of proton pump secretion. Consequently, the product is intended to be administered 30 minutes before feeding.

Although PPIs can produce complete inhibition of gastric acid secretion, there is no evidence that achlorhydria (lack of gastric acid) is harmful. However, long-term use (> 8 weeks) of PPIs is discouraged in humans because such use increases the production of gastrin, which, in turn, stimulates gastric acid secretion and has trophic effects on both the parietal cells and enterochromaffin-like (ECL) cells of the gastric mucosa. Gastric ECL-cell hyperplasia and carcinoids have been observed in life-long studies in rats treated with omeprazole. However, although to date no similar findings have been reported in dogs, it is considered appropriate that in the absence of suitable data, treatment duration should not exceed 8 weeks in dogs.

Secondary pharmacodynamic effects of proton pump inhibitors such as omeprazole include reduced absorption of minerals and vitamins, increase in bacterial infections of the GI tract and hypergastrinaemia resulting in development of gastric carcinoid tumours. However, the majority of these effects are reported after long-term omeprazole administration (the latter only in rats) but none of these effects appear to have been reported in dogs to date. Omeprazole administered orally at a dose rate of 1.1 mg/kg twice daily for 15 days to eight healthy dogs did not significantly alter the

overall phylogenetic composition of the gastric and duodenal microbiota, although quantitative changes in GI tract microbiota were observed.

The information proposed for inclusion in SPC section 4.2 is accepted as being generally reflective of the information provided in the dossier. However, as the proposed indication relates to gastric ulcers, the original proposal to make reference to gastrointestinal (as opposed to gastric) ulceration was omitted. Further, in order to better reflect the findings from the proprietary study data provided and the conditions under which this product will likely be used in practice, the indication was revised to restrict use of the product as an aid in the treatment of NSAID-induced gastric ulceration in dogs.

Pharmacokinetics

In describing the pharmacokinetics of omeprazole in dogs, the applicant has cited published literature and the CVMP MRL summary report for omeprazole, which is considered acceptable. The pharmacokinetic profile of omeprazole is well-described in the published literature and has been studied in the mouse, rat, dog and man. However, of significance is the fact that the literature indicates that pharmacokinetics has limited value in assessing the clinical efficacy of omeprazole. PPI's such as omeprazole have a short half-life (1–1.5 hours in dogs and humans), but their duration of effect is longer (around 28 hours) than would be expected simply on the basis of plasma half-life. Therefore, the pharmacodynamic effect of a PPI is related to the proportion of time during which intragastric pH is maintained above a particular threshold, which is the parameter that correlates with clinical efficacy.

As not all proton pumps are active during the short half-life of omeprazole, it has been reported that only 70% of H⁺/K⁺-ATPases are inhibited after initial dosing. Repeated treatment administration for around 3–4 days is therefore required to reach steady-state inhibition of acid secretion so that a balance is struck between covalent inhibition of active pumps, subsequent stimulation of inactive pumps after the drug has been eliminated from the blood and *de novo* synthesis of new pumps.

Absorption

Omeprazole is rapidly absorbed when administered directly into the duodenum, with a time to maximal plasma concentration (T_{max}) of approximately 5–15 minutes for drug suspended in a buffered polymer suspension. However, T_{max} for a coated pelleted product employing similar technology to the applicant's product was reported to be 1.28 hours in healthy Beagles. Oral bioavailability is low. Coating protects the formulation against the low pH in the gastric environment and permits absorption under more alkaline conditions in the duodenum. Omeprazole has only 15% bioavailability after oral administration in the dog, compared to 70% bioavailability after intraduodenal administration. In the dog, maximum plasma levels are obtained 45 minutes after oral administration. The inhibitory effect of omeprazole (as a PPI) on gastric acid secretion may interfere with the absorption of concomitantly administered active substances that depend on intra-gastric acidity. Consequently, the SPC includes reference to the fact that omeprazole may affect the absorption of medicinal products administered via the oral route that require an acidic environment for bioavailability and which include ketoconazole, itraconazole, iron, ampicillin esters and cyanocobalamin as examples.

Plasma distribution

Omeprazole distributes rapidly to extravascular sites and binds approximately 90% of proteins in canine plasma. PPIs are weak bases which permits the concentration achieved at the site of action (the luminal surface of the proton pump) to be significantly higher than that in the blood.

According to the literature cited by the applicant, dose adjustments in dogs with renal or mild to moderate hepatic disease are not needed but are recommended in patients with severe liver disease. Consequently, a suitable warning has been included in section 3.5 of the SPC – special precautions for safe use in the target species.

Metabolism

Omeprazole undergoes hepatic metabolism by cytochrome P450 enzymes to inactive metabolites, which are excreted as sulphate conjugates via the urine. Metabolism after intravenous and oral administration is extensive in rats, mice and dogs, with only trace amounts of the parent compound found in urine. After oral administration to rats and dogs, 90–100% of the radioactivity from ¹²C-labelled omeprazole is excreted within 72 hours, with 20–30% recovered in urine and the remainder in faeces. The major metabolic pathway in the dog is via aromatic hydroxylation and subsequent oxidation is the most prominent. As omeprazole is metabolised by the hepatic microsomal cytochrome system, inhibitors of isoforms such as CYP1A and as a consequence, inhibition of P450 hepatic enzymes, may result in drug interactions and delayed hepatic clearance of some drugs. Substances known to interact in humans include warfarin, diazepam and phenytoin. The applicant has proposed to include reference to possible delayed clearance of warfarin, diazepam and cyclosporine in section 3.8 of the proposed SPC and this is considered appropriate.

Excretion

According to the CVMP MRL summary report for omeprazole, the half-life of omeprazole is very short, with a $t_{1/2}$ of 1–1.3 hours in dogs. However, a slightly longer half-life of 1.85 hours was reported in other scientific literature cited by the applicant. No accumulation was found after 7 days of treatment in rats and humans, and no change in the pharmacokinetic disposition of omeprazole was observed after 7 years of daily treatment in dogs. In dogs, approximately 80% of total urinary excretion and two-thirds of faecal excretion occurs within the first 24 hours after administration. Mean elimination half-life is approximately 1 hour, ensuring rapid clearance from canine plasma.

Toxicology

Single-dose toxicity

The applicant has made reference to the CVMP MRL summary report for omeprazole, which indicates that acute toxicity was investigated in rats and mice of both sexes after oral dosage. The acute oral LD₅₀ was 1,520 mg/kg bodyweight (bw) for male mice, while, for female mice, it was 1,480 mg/kg bw on day 1 and 1,380 mg/kg bw on day 14, respectively. In rats, the acute oral LD₅₀ was less than 5,010 mg/kg bw for males, while, for females, it was 3,610 mg/kg bw on day 1 and 3320 mg/kg bw on day 14, respectively. All deaths occurred within 1 to 2 days, and most of the surviving animals were free of signs of toxicity such as reduced activity, reduced temperature and respiration, twitching and tremor within 24 hours. No intravenous LD₅₀ could be calculated due to very few deaths since the low solubility of the compound was a limiting factor in the intravenous administration. The applicant's safety expert concludes that the single-dose toxicity data (oral LD₅₀ values) available from the CVMP MRL summary report demonstrate a low single-dose oral toxicity of omeprazole and that additional data are not needed, as results from repeat-dose studies and experience from human use of omeprazole can be used to evaluate user safety. Given that the active substance is a well-established substance widely used in human medicine and was also evaluated during the MRL procedure for

horses, the approach by the applicant can be accepted and the generation/provision of additional toxicity data is considered unnecessary in view of 3Rs principles.

It can be accepted that omeprazole is generally known to have a wide margin of safety. According to the CVMP MRL summary report, omeprazole is poorly absorbed after oral ingestion in humans and there was no need to establish an MRL.

Repeat-dose toxicity

Regarding repeat-dose, the applicant has made reference to the CVMP MRL summary report for omeprazole, which indicates that, in a 3-month repeated dose toxicity study in rats, five groups with 10 males and 10 females per group, were dosed orally with 0, 13.8, 43.1, 138 or 414 mg omeprazole/kg bw/day. There was a tendency for increased hyperkeratosis of the squamous epithelium in the transitional zone between the forestomach and glandular mucosa observed in the high dose group, suggestive of chronic gastric irritation. A toxicological NOEL of 43.1 mg/kg bw/day was retained, based on changes in organ weights, microscopic pathology, clinical chemistry and hormone analyses.

In a 3-month repeated dose toxicity study in dogs, five groups (2 males and 2 females per group) were dosed orally with omeprazole in Methocel solution once daily with 0, 1.035, 5.5, 27.6 or 138 mg/kg bw/day. A slight decrease in packed cell volume, serum proteins and triiodothyronine were observed, mainly in the high dose group. Slight atrophic changes in the gastric mucosa were found in the three highest dose groups. No other treatment-related changes were found. A toxicological NOEL of 1.035 mg/kg bw/day was determined in this study.

In another 3-month repeated dose toxicity study in dogs, two groups of dogs (2 males and 2 females per group) were dosed orally, once daily, with 138 mg omeprazole/kg bw/day. A similar control group received placebo. One treated group and the control group were sacrificed after the treatment period, while the remaining group was sacrificed after 3 additional months without treatment. Post-mortem examination revealed similar atrophic gastric mucosal changes as seen previously immediately after termination of the 3-month treatment. The dogs that were left to recover for three months after the end of treatment showed complete recovery of the chief cell changes, but a discrete focal fibrosis in the lamina propria and the induced hypertrophic foldings of the fundic mucosa persisted.

In a 1-year study in dogs given daily oral doses of 0, 0.7, 5.5 or 28 mg omeprazole/kg bw/day, the only pathological changes that occurred were seen in the acid-secreting areas of the gastric mucosa of the 5.5 and 28 mg/kg bw/day groups. The changes consisted of a reversible atrophy of the chief cells in the dogs receiving 28 mg/kg bw/day and a rugal hypertrophy at doses of 5.5 mg/kg bw/day and above, which was not alleviated after 4 months. Both findings are believed to be linked to the acid-inhibitory effect of omeprazole. No changes were found in the lowest dose group and therefore the toxicological NOEL was set at 0.7 mg/kg bw/day. It is noted that this NOEL was used by the CVMP to establish the ADI for omeprazole.

In a 7-year study in dogs receiving daily doses of 0 or 0.17 mg omeprazole/kg bw/day, it was shown that the disposition of omeprazole expressed by the AUC was not affected by repeated dosing. Neither basal nor meal-stimulated gastrin levels showed any statistically significant difference between the control and omeprazole-treated groups. The mean inhibition of acid secretion in the omeprazole-treated animals was about 50%. There was no trend of change over time during the 7 years of treatment. There were no clinical, paraclinical or pathological changes related to treatment.

It can be accepted that repeated dosing of omeprazole at doses of up to 138 mg/kg bw/day and for durations (lower doses) of up to 7 years have been investigated in dogs. In general, reversible atrophy

of the gastric mucosa and chief cells was observed at doses of 28 mg/kg bw/day, whereas hypertrophic folding of the fundic mucosa was observed at doses of 5.5 mg/kg bw/day, which persisted following cessation of treatment. A NOEL of 0.7 mg/kg bw/day (derived from a 1-year toxicity study in dogs) was used by the CVMP to establish a toxicological ADI of 0.007 mg/kg bw (0.42 mg/person) by applying a safety factor of 100, and which the applicant used in the user safety assessment.

Given that the active substance is a well-established substance widely used in human medicine and which has also been evaluated during the MRL procedure for horses, the generation/provision of additional toxicity data is considered unnecessary in view of 3Rs principles.

Tolerance in the target species

The applicant has conducted a target animal safety (TAS) study investigating tolerance to the final formulation when administered at 1x, 3x, and 5x the maximum proposed dose rate of 1 mg/kg bw twice daily for 77–79 days to young healthy laboratory dogs (refer to part 4 of this assessment report for an assessment of the findings from that study). In addition to the above study, the applicant makes reference to the CVMP MRL summary report for omeprazole, an FDA "Freedom of Information" report and to two published studies.

Reproductive toxicity, including developmental toxicity

In addressing potential for reproductive and developmental toxicity, the applicant makes reference to the information available from the CVMP MRL assessment report for omeprazole. The reference to and use of such data is considered acceptable.

Study of the effect on reproduction

Effects on reproduction were evaluated in a study in rats orally administered 0, 13.8, 43.1, or 138 mg omeprazole/kg bw/day. Treatment was administered from 2 weeks pre-mating to 3 weeks post-partum for females and from 9 weeks pre-mating to 3 weeks post mating for males. Half of the females in each group were sacrificed on day 21 of pregnancy, examined for reproductive performance and subjected to a pathological examination. The remaining dams and litters were sacrificed and examined at day 21 post-partum. The only effects observed were slight, non-statistically significant decreases in litter size, viability and growth in the 138 mg/kg bw group. The NOEL for reproductive toxicity was 43.1 mg/kg bw/day in rats.

No other studies on the effects on reproduction have been provided. Given that the active substance is a well-established substance widely used in human medicine and also evaluated during the MRL procedure for horses, the generation/provision of additional data on reproductive toxicity is considered unnecessary in view of 3Rs principles.

Also, according to Regulation (EU) 2019/6, reproductive toxicity studies are not required for the evaluation of effects on the user and are only required for products intended for use in breeding animals. According to VICH GL43, reproductive safety studies are required for systemically absorbed active pharmaceutical ingredients intended for use in breeding animals. However, if reproductive safety studies have not been conducted in the target species, labelling should reflect this and state that safety has not been determined in breeding, pregnant or lactating animals or their offspring.

The SPC includes reference to the fact that safety of the product has not been established in pregnant, lactating or breeding animals and therefore use in such animals is not recommended.

Study of developmental toxicity

The potential for teratogenicity was evaluated in 3 studies in rats and one study in rabbits after oral administration.

In a study in which pregnant rats were orally dosed with 0, 13.8, 43.1 or 138 mg omeprazole/kg bw/day from days 6–15 of pregnancy and sacrificed on day 21 of pregnancy, no evidence of toxicity in maternal animals and no embryotoxic, foetotoxic or teratogenic effects were found. A NOEL of 138 mg/kg bw/day was established.

In a second study, pregnant rats were orally dosed with 0, 13.8, 43.1 or 138 mg omeprazole/kg bw/day from day 15 of pregnancy to day 21 post-partum. The only adverse effects found were a statistically significant decrease in litter and mean pup weight at day 21 post-partum in the 138 mg/kg bw/day group. Thus, the NOEL was set at 43.1 mg/kg bw/day in this study.

In a third study, groups of pregnant rats were orally dosed with 0 or 138 mg omeprazole/kg bw/day. One group was treated from day 15 of pregnancy to day 10 post-partum, while the second and third groups were treated from day 11 to day 20 post-partum and day 15 of pregnancy to day 20 post-partum, respectively. Bodyweights were monitored up to day 66 post-partum. A statistically significant decrease in litter and mean pup weight at day 21 post-partum in the long-term treatment group was found. After the end of the lactation period, the growth of the pups was similar, and the decreased pup weight was believed to be due to a decrease in milk production. An overall NOEL of 43.1 mg/kg bw/day was overall retained from the three studies.

In rabbits orally dosed with 0, 6.9, 27.6, 69.1 or 138 mg omeprazole/kg bw/day from days 6–18 of pregnancy, maternal toxicity was observed in all but the lowest dose group. The NOEL for maternotoxicity was 6.9 mg/kg bw/day. A dose-related decrease in litter size and an increase in foetal loss was found at doses above 6.9 mg/kg bw/day. Some abnormalities and skeletal variants were observed in the two highest dose groups, which were considered to be secondary to maternal toxicity. However, the frequencies of overall abnormalities in the pups were not statistically significantly different between the groups. Treatment was discontinued after 8 days in the highest dose group and therefore no evaluation of potential teratogenic effects in rabbits could be made.

Given that the active substance is a well-established substance widely used in human medicine and also evaluated during the MRL procedure for horses, the generation/provision of additional data on developmental toxicity is considered unnecessary in view of 3Rs principles.

Also, according to Regulation (EU) 2019/6, developmental toxicity studies are not required for products intended only for use in non-breeding animals unless significant user exposure may be expected. Given that the product is to be presented in gastro-resistant gelatin capsule, significant exposure of the user to omeprazole is not anticipated. Nevertheless, exposure may occur in case of damaged capsules or in case of vomiting after product administration. Therefore, information on developmental toxicity should be taken into account for the characterisation of risk towards pregnant women. Moreover, as highlighted above, the SPC includes reference to the fact that safety of the product has not been established in pregnant, lactating or breeding animals, and therefore use in such animals is not recommended.

Genotoxicity

In addressing the potential for genotoxicity, the applicant makes reference to the information available from the CVMP MRL assessment report for omeprazole. The use of and reference to such data is considered acceptable.

According to that report, the mutagenic potential of omeprazole was tested in:

- 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 cells; and
- an *in-vivo* mouse micronucleus test.

It can be accepted that data has previously been assessed by the CVMP that is reflective of the standard battery of tests generally used to investigate genotoxicity as recommended in VICH GL23. No indication of a mutagenic effect was found, and no indication of bone marrow depression was found.

Also, as omeprazole is an existing active substance used in human medicinal products for over 30 years, it can be accepted that no further data needs to be presented regarding genotoxicity.

Based on the findings of these studies, it can be accepted that there is no indication that omeprazole is genotoxic, mutagenic or suppresses bone marrow.

Carcinogenicity

In addressing the potential for carcinogenic effects, the applicant makes reference to the information available from the CVMP MRL assessment report for omeprazole and additionally to two published studies.

Three 2-year studies were conducted in rats using oral doses of 0, 1.7, 3.4, 13.8, 14.1, 44.0 and 140.8 mg omeprazole/kg bw/day and investigated the clinical and pathological changes observed after treatment with omeprazole. A dose-related increase in stomach weight and mucosal thickness was observed, related to the gastrin concentration and the known trophic effect of the latter hormone on the stomach. A time and dose-related increase in both the incidence and the degree of severity of the ECL cell hyperplasia including ECL-micronodules was observed. Also, dose-related carcinoids in the gastric fundus were found as a continuum of endocrine cell hyperplasia. No evidence of carcinoid metastasis beyond the stomach was found.

A linear correlation between carcinoid incidence and the doses from 1.7 to 140 mg omeprazole/kg bw/day was demonstrated and no long-term toxicological NOEL in rats could be established from these studies. Exogenous gastrin showed the same dose-dependent changes in the stomach as seen with omeprazole and other acid-inhibitors. Therefore, the gastrin level was considered responsible for the changes in ECL-cell density, while omeprazole treatment as such was not likely to affect proliferation of ECL-cells. It was concluded from the carcinogenicity studies in rats that hypergastrinaemia secondary to acid inhibition by omeprazole results in a dose-dependent increase in ECL-cell hyperplasia and micronodule formation, which may lead to dose-dependent formation of end-life ECL-cell carcinoids.

In dogs, a 1-year study and a 7-year study employed daily oral omeprazole doses of 0.7, 5.5 or 28 mg/kg bw/day and 0.17 mg/kg bw/day, respectively. The only pathological changes occurred in the acid-secreting areas of the gastric mucosa. The changes consisted of a reversible atrophy of the chief cells in the dogs receiving 28 mg/kg bw/day, and a rugal hypertrophy at doses above 5.5 mg/kg bw/day. Both findings are believed to be linked to the acid-inhibitory effect of omeprazole. No changes were found in the lowest dose group. A NOEL of 0.7 mg/kg bw/day was derived from this study.

The applicant cites a review article from published literature which notes that enterochromaffin-like cell carcinoids have been detected in rats exposed lifelong to omeprazole and which is caused by hypergastrinaemia. However, omeprazole produces modest serum gastrin elevations in humans when monitored over a 24-hour period and gastrin levels are markedly lower and less sustained compared to the situation in rats, suggesting that humans and rats differ markedly both in their gastrin response to a given level of acid inhibition and in their response to the trophic influence of gastrin on enterochromaffin-like cells. The author concludes that the rat model is a false indicator of risk in humans.

In conclusion, based on the available data, prolonged administration of omeprazole (or other PPIs) to rats has been reported to result in ECL cell hyperplasia including ECL-micronodules and subsequently gastric carcinoids. These findings are reported to occur in a dose-dependent manner. It is understood that this is an indirect effect of PPIs resulting from sustained hypergastrinaemia secondary to acid inhibition, albeit similar findings have not been reported in humans or dogs to date.

Based on the information available regarding genotoxicity and that ECL-cell hyperplasia, micronodules and carcinoids appears to be restricted to rats administered life-long omeprazole, it can be accepted that there is currently no concern regarding carcinogenicity either for the user or the target animal arising from the exposure that might be expected when the candidate product is administered in accordance with the proposed SPC.

Other requirements

Special studies

The applicant highlights the fact that it is reported in the CVMP MRL summary report for omeprazole that no indications of immunotoxicity were observed in the toxicity studies conducted, and that this can be presented to provide enough information to support not conducting additional studies addressing this endpoint. Pharmacological studies in healthy human volunteers using doses up to 80 mg/person/day for 5–7 days were conducted and no significant adverse effects on the immune system were reported. The applicant further highlights that a review of the published literature indicates that omeprazole does not possess neurotoxic or endocrine disrupting potential.

Given the nature of the pharmaceutical form (gelatin capsule), significant user exposure is not anticipated and consequently, ocular and dermal irritation studies and skin sensitisation studies have not been conducted. The absence of such studies can be accepted. However, as stated in the product information, exposure may occur in case of damaged capsules. Therefore, the potential for occurrence of hypersensitivity reactions needs to be considered. The applicant has provided information from a safety data sheet provided with the user risk assessment that suggests that omeprazole is a skin and eye irritant and that hypersensitivity reactions to omeprazole have been reported in factory workers manufacturing the compound. Furthermore, for omeprazole-containing human medicinal products, hypersensitivity reactions have been reported (see section on observations in humans).

These possible effects are further discussed in the user safety section.

Observations in humans

The applicant highlights the fact that omeprazole is currently approved in the EU as human medicinal products for a number of indications including the treatment of gastric ulcers. Based on reference to the SmPC of an omeprazole-containing human medicinal products, omeprazole doses generally range from 10–40 mg per day, but doses of up to 120 mg per day are also approved for certain indications.

In the CVMP MRL summary report, a number of study reports in healthy humans have been described. A study in healthy humans showed a low and non-statistically significant decrease in production of gastric acid at a dose of 10 mg per person per day. Eight healthy male subjects were given omeprazole for 5 days in daily doses of 0, 5, 10, 20 and 40 mg. Four subjects were subsequently treated with 80 mg. Treatment periods were separated by at least 1 week. Gastric acid secretion was measured 6 hours and 24 hours after the final fifth dose of omeprazole. Fasting gastrin concentrations were determined immediately before and after the fifth dose, 6 and 24 hours post-dose. Plasma gastrin concentrations measured in the 5 mg per day dosage group were not different compared to the placebo group during both basal and peak acid output measurements, whereas a clear increase was observed in the 20 mg per day dosage regimen. The pharmacological NOEL was 5 mg/person/day, and by applying a safety factor of 10, a pharmacological ADI of 0.00833 mg/kg bw, i.e., 0.5 mg/person/day was established.

Several reports exist in the published literature describing hypersensitivity reactions following omeprazole administration or occupational exposure to omeprazole. Symptoms reported include whole-body rash, skin reactions, diarrhoea, unconsciousness, oliguria suggesting that omeprazole may have the potential to cause contact allergy in humans. However, reports of allergic reactions in the clinical use of omeprazole are rare and direct omeprazole contact with skin would normally be avoided by using coated formulations. Evidence exists that PPI use is associated with an up to fourfold increased incidence in the development of fundic gland polyps in humans, albeit PPI treatment cessation is associated with polyp regression.

Human doses of 20 mg/day are generally reported, equivalent to exposure to two capsules of the candidate formulation. According to the SmPCs of omeprazole-containing human medicines, treatment for gastric ulcers in humans is generally recommended for 4 weeks (20 mg/day), extending to 8 weeks when needed. For those patients with poorly responsive gastric ulcers, 40 mg/day is recommended for up to 8 weeks. It is noted that the duration of treatment of gastric ulcers in humans appears to be up to twice as long as that initially proposed for the candidate formulation in dogs with the same condition. The adequacy of the treatment duration proposed by the applicant will be considered further when assessing the efficacy data provided in part 4.

In light of the information cited from the published literature, it can be concluded that hypersensitivity reactions in humans to omeprazole can occur.

Excipients

The applicant states that all excipients included in the candidate formulation are commonly used in oral pharmaceutical formulations and in many cases are also approved for use in food applications, and thus, concludes that the excipients in the candidate formulation do not raise any toxicological concerns with respect to systemic effects. Acceptable information/data to support this conclusion has been provided. Though, it appears that some excipients are associated with hypersensitivity reactions and this is further discussed in the user risk assessment.

It is noted that the proposed formulation includes titanium dioxide as an excipient and that, in May 2021, EFSA published a scientific opinion on the safety assessment of titanium dioxide as a food additive, concluding that a concern regarding genotoxicity could not be ruled out.

Notwithstanding the above, according to the EMA's Q&A on the replacement/removal of titanium dioxide in medicines, in case an applicant has applied for a marketing authorisation, or an application is close to submission and development work has already started, for the time being, the proposed composition can include titanium dioxide. Nevertheless, applicants are reminded to make all possible efforts to accelerate the research and development of alternatives to replace titanium dioxide.

User safety

A user safety assessment that is generally in accordance with the CVMP "Guideline on user safety for pharmaceutical veterinary medicinal products" (EMA/CVMP/542/03-Rev.1) was provided. The product is presented in a high-density polyethylene container containing 30 capsules. Acceptable certification has been provided to confirm that the HDPE container and closure system meets the requirements set out in ISO 8317:2015 i.e., is child-resistant re-closable packaging. The product was initially proposed to be given orally at a dosage of 0.5 to 1.0 mg/kg bw twice daily for up to 28 days, however, following further consideration of the efficacy data provided, the SPC was amended to indicate that product administration for up to 8 weeks may be needed in some cases. Between 1 and 6 capsules will be handled at each dosing occasion (covering dogs of bodyweight range 10–70 kg bw). As the intact capsules are intended for direct administration to the animal, in most cases, the user will only be exposed to the outer capsule. Only in the case of regurgitation, vomiting or spitting out of a capsule, may contact with the capsule's contents occur. Splitting or opening capsules is in general not anticipated, as only normal conditions of use of the product or foreseeable accidents are addressed. Nevertheless, section 3.9 of the proposed SPC cautions against splitting or opening capsules, as the capsule should remain intact to ensure adequate bioavailability following absorption of the active substance.

Tasks and situations that may lead to exposure were identified as follows: storage of the product, preparation of the required dose (removing from the container) during the pre-application phase, handling the product during administration to the animal during the application phase, storage of the product and disposal of any mis-dosed/waste product or vomitus containing product during the post-application phase. The user will, in most cases, be the animal owner, considered a non-professional, who will administer the product at home after prescription by a veterinarian. Potential routes of exposure include dermal, oral (hand-to-mouth contact or accidental oral exposure by a child ingesting the product) or ocular (hand-to-eye contact).

For dermal and hand-to-mouth exposure, a worst-case scenario is expected to be contact with 10% of the content of 6 damaged capsules on two occasions, 12 hours apart. The ADI of 0.007 mg/kg bw/day (or 0.42 mg/person/day) was used by the applicant as a toxicological reference value (TRV) for the assessment of both acute and chronic exposure (in the absence of an acute TRV). The above-mentioned exposure scenario would result in a total systemic exposure to omeprazole of 12 mg or 0.2 mg/kg bw (assuming 100% dermal absorption), which exceeds the ADI 28.6-fold, indicating a possible risk. The calculated daily exposure also exceeds the pharmacological NOEL of 5 mg/person/day determined from a short-term study in healthy volunteers, and therefore represents a potential risk. It is noted that daily exposure to 12 damaged capsules, which corresponds to presumably all administered tablets on a day, is an overestimate. Moreover, when cleaning damaged capsules or vomit, one may expect to use wipes to do so. Nevertheless, the proposal to wash hands or any exposed skin if the capsule is damaged during administration is considered appropriate. Furthermore, when considering the developmental NOEL of 6.9 or 43.1 mg/kg bw/day in rabbits and rats, respectively, it can be concluded that there is no risk for pregnant women.

For exposure following accidental self-ingestion by a child, a worst-case scenario of accidental ingestion of three capsules was considered. A child weighing 12.5 kg accidentally ingesting three capsules would experience a total systemic exposure of 30 mg omeprazole, which equates to a dose of 2.4 mg/kg bw. The applicant has compared this estimated exposure with the authorised dose rate of omeprazole in children (10–20 mg once daily), although this is not considered appropriate. As exposure is higher than the pharmacological NOEL of 5 mg/person/day in humans and is 71.4 times higher than the toxicological ADI of 0.42 mg/person/day, the applicant concludes that a risk exists and

measures to avoid children accessing the product should be taken. Adequate risk mitigation measures need to be taken, although serious adverse effects are not expected after a single accidental intake.

Based on the user safety assessment, the applicant has proposed a number of risk mitigation measures which include restricting the product to veterinary prescription, supplying the product in a container that has a child-resistant re-closable lid and the inclusion of warnings/advice in the product information.

Based on the information/data provided, it can be accepted that the formulation may cause hypersensitivity reactions. Given the pharmaceutical form (gelatin capsule), exposure to the granules within the capsule is expected to be limited/exceptional. However, the proposal to include a warning relating to the potential for hypersensitivity reactions can be accepted and is considered to be consistent with information available from the published literature. Further, the proposal to advise that adverse gastrointestinal effects and headache may be seen if the product is accidentally ingested is consistent with the information included in the SmPCs of similar human medicinal products containing omeprazole.

Although the applicant suggests that omeprazole is a skin and eye irritant, no ocular or dermal irritation studies have been conducted. Although reference has been made to published information on the active substance and some of the excipients potentially having ocular and/or dermal irritant properties, the relevance for the final formulation has not been demonstrated. Given the pharmaceutical form (gelatin capsule), the proposal to include reference to the risk of ocular and/or skin irritation was considered unnecessary for this product. The risks identified and the risk mitigation measures have been presented using the A, B, C, D format as recommended in the aforementioned CVMP user safety assessment guideline, and this is considered appropriate.

Whilst the calculated exposures greatly exceed the ADI, it can be accepted that the product is presented in a gelatin capsule and therefore the risk for dermal (including hand-to-mouth and hand-to-eye) exposure is expected to be limited. That said, the warning to avoid contact with the contents of the capsule (particularly in individuals with known hypersensitivity to omeprazole or any of the excipients) and to wash hands or any exposed skin if the capsule was damaged during administration is considered appropriate. Further, the product information includes a recommendation to seek medical advice if symptoms persist in case of accidental ingestion of the product (particularly by a child) or in case of hypersensitivity reactions and this is considered appropriate.

It can be concluded that the candidate formulation will not present an unacceptable risk to the user provided the product is stored, handled, administered and disposed of in accordance with the recommendations proposed for inclusion in the SPC.

Environmental risk assessment

A phase I environmental risk assessment (ERA) was provided according to relevant CVMP/VICH guidelines. According to question 3 in the phase I decision tree ("Will the VMP be used only in non-food animals?"), the ERA can stop in phase I and no phase II assessment is required because the VMP will only be used in non-food-producing species.

It can be accepted that the proposed product will not present an unacceptable risk for the environment when stored, handled, administered and disposed of in accordance with the recommendations included in the proposed SPC.

Overall conclusions on the safety documentation: safety tests

Pharmacology:

Information on the pharmacodynamics of omeprazole has been primarily sourced from the published literature. It can be accepted that the published literature cited confirms the well-established use of omeprazole as a proton pump inhibitor (in both humans and animals) used to treat ulcerative disorders of the gastrointestinal tract by decreasing intraluminal acidity.

In describing the pharmacokinetics of omeprazole in dogs, the applicant has cited published literature and the CVMP MRL summary report for omeprazole, which is considered acceptable. The pharmacokinetic profile of omeprazole has been studied in the mouse, rat, dog and man and, according to the literature cited, pharmacokinetics have limited value in assessing the clinical efficacy of omeprazole. PPI's such as omeprazole have a short half-life ($t_{1/2}$ of 1–1.85 hours), but their duration of effect is longer (around 28 hours). Therefore, the pharmacodynamic effect of omeprazole is related to the proportion of time during which intragastric pH is maintained above a particular threshold and which correlates with clinical efficacy. It has been reported that repeated treatment administration for approximately 3–4 days is required to reach steady state inhibition of acid secretion.

In dogs, omeprazole is highly protein-bound (approximately 90%) in plasma and is completely metabolised prior to elimination (with 20–30% of metabolites being detected in urine and the remainder in faeces). No change in the pharmacokinetic disposition of omeprazole has been observed after 7 years of daily treatment in dogs. Approximately 80% of total urinary excretion and two-thirds of faecal excretion of omeprazole occurs within the first 24 hours after administration.

No pharmacokinetic data specific to the candidate formulation have been presented. Given that, in this instance, the pharmacokinetic profile of the active substance has limited relevance for assessing its pharmacological effect and as the adequacy of the PK profile has been directly assessed within the context of a study investigating the effect of the candidate formulation on gastric pH in dogs and within the context of the dose confirmation studies, the omission of formulation-specific PK data can be accepted. However, information on the period of time for which gastric pH was maintained at or above pH 3 has been included in section 4 of the SPC in order to provide product-specific information that is related to the duration of pharmacological effect of omeprazole in the candidate product.

Toxicology:

Reference has been made to the CVMP MRL summary report for omeprazole in addressing single-dose and repeat-dose toxicity. Given that the active substance is a well-established substance widely used in human medicine, the approach by the applicant can be accepted and the generation/provision of additional toxicity data is considered unnecessary in view of 3Rs principles.

It can be accepted that repeated dosing of omeprazole at doses of up to 138 mg/kg bw/day and for durations (lower doses) of up to 7 years have been investigated in dogs. In general, reversible atrophy of the gastric mucosa and chief cells was observed at doses of 28 mg/kg bw/day, whereas persistent hypertrophic folding of the fundic mucosa was observed at doses of 5.5 mg/kg/day. The lowest NOEL of 0.7 mg/kg bw/day was observed in a 1-year study in dogs.

Reproductive toxicity was only studied in laboratory animals and not in the target species. The NOEL for reproductive toxicity was 43.1 mg/kg bw/day in rats. In the absence of studies on the effects on reproduction, the use of the product is not recommended for breeding animals, and the SPC includes reference to the fact that safety of the product has not been established in pregnant, lactating or breeding animals. The NOEL for developmental toxicity was 43.1 mg/kg bw/day in rats and 6.9 mg/kg bw/day in rabbits. Data in rats and rabbits indicate that omeprazole is not a developmental or reproductive toxicant.

According to the CVMP MRL summary report, results of genotoxicity studies indicate that omeprazole is not genotoxic. Carcinogenicity studies have been conducted in rats and dogs. Results from the studies in rats indicate that hypergastrinemia secondary to acid inhibition by omeprazole results in a dose-dependent increase in ECL-cell hyperplasia and micronodule formation, which may lead to dose-dependent formation of end-life ECL-cell carcinoids. Similar findings were not observed in dogs.

Safety data sheets provided as part of the user safety assessment suggest that omeprazole and some of the excipients may be a skin and ocular irritant. However, in the absence of information/data identifying a specific risk for ocular or dermal exposure that is relevant for the candidate formulation and noting that dermal and/or ocular exposure is not expected given the pharmaceutical form (capsule), reference to the product being an ocular and skin irritant was considered unnecessary. Omeprazole has been reported to cause hypersensitivity reactions.

The applicant has provided acceptable data and information on all excipients and it can be accepted that there are no concerns for systemic effects.

User safety:

A user safety assessment in line with the relevant guidance document has been presented. Based on that assessment, a potential health risk of the product to all users (adults and children) is considered low when it is used in accordance with the SPC. Given the pharmaceutical form (gelatin capsule), exposure to capsule contents is not expected under normal conditions of use. However, should exposure to the capsule contents occur, (e.g. in the case of a capsule being damaged during administration), a risk to the user may arise.

The worst-case scenario for user safety is considered to be accidental ingestion of 3 tablets by a child, with an estimated exposure equating to 28.6 times the ADI. Appropriate safety advice/warning statements are included in the SPC to mitigate the risks. The closure system has been demonstrated to be child-resistant in accordance with the requirements set out in ISO 8317:2015. Based on the information provided, the user safety warnings were updated to indicate that contact with the contents of the capsule should be avoided, particularly by individuals known to be hypersensitive to omeprazole or any of the excipients, and to wash hands or any exposed skin should contact occur. It can be concluded that the candidate formulation will not present an unacceptable risk to the user provided the product is stored, handled, administered and disposed of in accordance with the recommendations in the proposed SPC.

Environmental risk assessment:

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when stored, handled, administered and disposed of in accordance with the recommendations in the proposed SPC.

Part 4 – Efficacy

Pre-clinical studies

Omeprazole TriviumVet gastro-resistant capsules contain 10 mg of omeprazole as active substance.

Pharmacology

Pharmacodynamics

See Part 3.

Pharmacokinetics

See Part 3.

Dose determination and confirmation

Dose justification and dose determination studies

The applicant justifies the proposed posology of 0.5-1 mg/kg bw administered twice daily for a minimum of 14 days by way of reference to a large number of published literature and proprietary data. However, the published literature does not relate specifically to aiding the treatment of canine gastric ulcer disease secondary to NSAID use (proposed indication) but instead relates to a number of different clinical presentations/aetiologies in dogs.

The majority of the peer-reviewed literature supports the selection of an oral dose rate of 0.5-1.0 mg/kg bw either once or twice daily, but several publications indicate that twice daily administration is preferable. Reference is also made to the 2018 consensus statement by the American College of Veterinary Internal Medicine (ACVIM) expert review panel, which concluded that twice-daily administration of omeprazole is superior to alternative gastro-protectants for treating acid-related gastroduodenal ulceration and erosion; however, no guidance on the dose rate or the duration of treatment is provided.

The proposal to make use of published literature in support of the proposed dose rate, frequency and duration of administration is considered to be in accordance with the scientific advice previously provided to the applicant by the CVMP. However, the applicant was advised that the frequency of treatment and the duration of treatment should be further substantiated. The literature cited indicates that omeprazole has been used in dogs for more than 30 years and that the dose rate of omeprazole administration is generally reflective of that proposed by the applicant. In line with the scientific advice, the references cited also support the proposed frequency, i.e. twice daily administration of omeprazole to dogs. However, information from the scientific literature on the duration of treatment is limited, with some references suggesting that a treatment duration longer than that initially proposed by the applicant (28 days) may be needed (up to 8 weeks).

One of the studies conducted by the applicant was a randomised, blinded two-way cross-over trial conducted to determine the effect of the applicant's omeprazole product on gastric pH in six healthy dogs following 5 days of twice daily administration of 0.53-1.0 mg omeprazole/kg bw. Intragastric pH was continuously monitored via implantation of a pH monitoring capsule. Results indicate that over the

course of the pH monitoring period, the mean percentage time that the intragastric pH was ≥ 3 was 95% and the mean percentage time that the intragastric pH was ≥ 4 was 92%. These results indicate that twice daily administration of the candidate formulation in the dose range 0.53-1.0 mg/kg bw (median dose administered was 0.86 mg/kg bw) results in the intragastric pH of healthy dogs meeting the target pH and time duration above that pH recommended when treating human patients with ulcerative gastric disease (i.e. pH ≥ 3 for at least 75% of the day). These findings are also consistent with the 2018 consensus statement by the American College of Veterinary Internal Medicine expert review panel which recommends that omeprazole should be administered twice daily to approach pH goals that were established for the treatment of acid-related disorders in people (intra-gastric pH of ≥ 3 or 4 for approximately 75% of the day).

Dose confirmation studies

Three laboratory dose confirmation studies (two pilot and one pivotal) were presented; these studies were designed based on a model of canine NSAID-induced gastric ulcer reported by Elfadadny *et al.*, 2018. The studies were conducted to GCP standards. The two pilot dose confirmation studies were conducted to assess the suitability of a NSAID-induced gastric ulcer disease model in laboratory dogs and treatment was with a human medicinal product containing omeprazole.

In the first GCP-compliant pilot study, eight healthy Beagle dogs aged >9 months were randomised into two cohorts of four animals each (2 male and 2 female). In each cohort, two dogs were treated whilst the other two dogs remained untreated (control). Cohort 1 animals were in the bodyweight range 13.2–16.7 kg and cohort 2 animals were in the bodyweight range 14.0–16.15 kg. In cohort 1, induction of gastric ulceration was attempted using subcutaneously administered meloxicam (0.2 mg/kg bw) and orally administered diclofenac (4 mg/kg bw). NSAID administration was stopped on study day 6 based on the clinical assessments, clinical pathology and video camera endoscopy (VCE) observations which suggested significant ulceration had developed. As dogs in cohort 1 were reported to have signs consistent with severe ulceration in the small intestines, the model was refined by halving the diclofenac dose for cohort 2 (reduced to 2 mg/kg bw), in an attempt to elicit gastric lesions only. However, faecal blood was also observed in three out of four animals in cohort 2, suggesting that intestinal injury also occurred with the modified dosing schedule.

The two treated animals in cohort 1 were administered omeprazole gastro-resistant capsules (human medicinal product) for 21 days, whereas the two animals in cohort 2 were treated for 28 days. Omeprazole was administered in the dose range 0.6 to 0.8 mg/kg bw twice daily and was given 30 minutes before feeding in the morning and without feeding in the evening.

General health observations were performed once daily and included but were not limited to bodyweight, general behaviour, faeces (colour, consistency, blood, mucous), locomotion and other symptoms (i.e. presence of abnormal urine, salivation, vomit, blood or respiratory disorders). A video capsule was administered to animals at three timepoints during the study - once during the ulcer induction phase, one week before end of the treatment phase and at the end of the treatment phase. Blood samples were collected at regular intervals for general clinical chemistry and haematology analysis and urine was collected at regular intervals for urinalysis.

All animals in both cohorts showed significant weight loss during the ulcer inducement phase. Red blood cells, haemoglobin and haematocrit decreased compared with baseline values in all animals following NSAID administration, indicating presence of gastrointestinal haemorrhage. Further, all animals presented leucograms with inflammatory changes (i.e. increased neutrophils), hypoalbuminaemia, and increases in creatinine and blood urea nitrogen after the NSAID induction phase.

Following cessation of NSAID administration, all animals showed a rapid improvement in clinical signs (faecal quality, presence of faecal blood, presence of vomitus) and in one of the four untreated dogs, healing appears to have been complete by Day 28. Although 3 out of the 4 omeprazole-treated animals were reported to have complete healing by day 28, one did not, with two suspected small ulcers and one area of haemorrhage remaining following 21 days of treatment, suggesting that 21 days treatment may not be adequate.

Treatment with omeprazole appears to have resulted in a positive effect on body weight and red blood cell parameters; however, due to the small sample size (only 4 animals administered omeprazole), only descriptive statistics were presented. As assessment of healing by way of clinical symptoms and video capsule endoscopy stopped when omeprazole administration stopped, it is not considered possible to determine whether relapse occurred in any of the study animals. Consequently, it is not considered possible to conclude from this study that a treatment duration of 28 days (as initially proposed by the applicant) is adequate.

Following completion of the above study, a second pilot study was conducted. Given the observation of frank faecal blood in three of four animals in cohort 2 of the first study, suggesting significant intestinal injury even with the modified dosing schedule, the method of gastric ulcer induction was modified to allow initiation of NSAID dosing with a single substance (meloxicam) in the second pilot dose confirmation study. In this GCP-compliant pilot dose confirmation study, a single group of 4 dogs (2 male and 2 female) aged >9 months and in the bodyweight range 12.7-15.0 kg was administered meloxicam by subcutaneous injection once daily for 19 days.

Two animals in the group were administered omeprazole gastro-resistant capsules (a human medicinal product) for 28 days in the dose range 0.56 – 0.81 mg/kg bw twice daily, given 30 minutes before feeding in the morning and without feeding in the evening. The criteria for determining whether study animals developed moderate gastric ulceration was the same as in the first pilot study, as was the administration and use of video capsule endoscopy, general health observations, veterinary examinations, blood sample collection for general clinical chemistry and haematology analysis and urine sample collection for urinalysis.

After 18 days of meloxicam treatment, none of the animals were deemed to have met the clinical criteria considered necessary to conclude that moderate gastric ulceration had been achieved and, according to the applicant, the method was deemed inadequate in terms of achieving moderate to severe gastric ulceration. That said, VCE showed that all four animals in the study developed gastric ulceration and/or erosion, with variable degrees of haemorrhage, by study Day 18 and, during the ulcer induction phase, the quality of faeces was reduced in all animals and frank blood and/or melaena were present in the faeces of three of the four animals. Plasma creatinine kinase increased during the ulcer inducement phase (with very significant increases at various timepoints) before reducing again at the end of the study. Results indicate that gastric ulceration resolved in one dog in each group (treatment/no treatment) by Day 46 of the study (following 28 days of treatment). The fact that gastric ulceration in one of the treated dogs was not considered to have resolved after 28 days of treatment calls into question the efficacy of the initially proposed treatment duration (up to 28 days). However, as only two animals were administered omeprazole in this study, the sample size is considered inadequate to draw any meaningful conclusions other than that the ulcer induction method used in this pilot study appears to have been inferior to that used in cohort 2 of the first pilot study.

The above pilot studies were too small (4 treated dogs in the first pilot study and 2 treated dogs in the second pilot study) to conclude on efficacy and the gastric ulceration induced in the second pilot study was considered inadequate. As a result, it was decided to use in the pivotal GCP laboratory study the NSAID-induced gastric ulcer model used on cohort 2 of the first pilot study, namely, injectable meloxicam and oral diclofenac.

The pivotal GCP-compliant dose confirmation study was planned as a placebo-controlled, randomised and blinded parallel arm design conducted in two stages: following the development of NSAID-induced gastrointestinal ulceration in all dogs (GUI phase, up to 8 days), dogs would then be either treated twice daily with omeprazole or remain untreated as control group (treatment phase).

Thirty-two dogs (17 Beagles and 15 Foxhounds) in the age range 1.5-9 years and in the bodyweight range 12-35 kg were administered meloxicam subcutaneously at a dose rate of 0.2 mg/kg bodyweight once daily for up to 8 days and diclofenac orally once daily for up to 8 days. As both male and female animals were included in the study and there was a variety of ages and bodyweights, it can be accepted that the gender, age and bodyweight of the study animals are sufficiently representative of the intended target population. Although only two breeds of dogs were included, it can be accepted that there are no reports in the scientific literature, and there is no physiologic rationale, to assume that breed influences treatment outcome in dogs with NSAID-induced gastric or gastroduodenal ulceration, and consequently it is accepted that the data generated can be extrapolated to the intended target population.

Due to an error in following the study protocol, diclofenac was unintentionally administered at a higher than intended daily dose of 2.52 – 3.42 mg/kg bw (the intended dose was 1.25 – 1.5 mg/kg bw daily). Two study animals were reported to have died as a result of perforated ulcers (one gastric and one duodenal) during the gastric ulcer induction (GUI) phase. Due to concerns about the condition of more animals deteriorating, it was therefore decided that all animals in the study would be administered omeprazole, i.e. to change the design of the study to an uncontrolled single-arm study. The result of not including a (negative) control group is that the before-after design is now very weak, meaning that it cannot be concluded that clinical improvement is the actual result of the treatment, or that improvement would have also occurred if no treatment, or (as was the case in current study) only supportive treatment was provided. Since the change in design calls into question the internal validity of the study, the outcome of this study is not sufficient on its own to conclude on effectiveness of the product.

The final formulation of Omeprazole TriviumVet gastro-resistant capsules was administered twice daily to study animals within 30 minutes after feeding. Although not in line with the SPC recommendation to administer 30 minutes before feeding, the timing of treatment administration in this study can be accepted as representing a 'worst case' scenario given that pre-clinical data suggest maximum benefit arises when omeprazole is administered before feeding. Study animals were administered doses in the range 0.52 – 0.99 mg/kg bw, which can be accepted as being in line with the dose range (0.5 – 1.0 mg/kg bw) proposed for inclusion in the SPC.

Owing to the frequency and severity of the expected clinical signs of gastroduodenal ulceration associated with NSAID administration, all dogs were given broad-spectrum antibiotic cover (metronidazole and/or amoxycillin-clavulanate) and antinausea/anti-emetic (maropitant and/or ondansetron) for 3-4 days. In addition, where indicated, dogs were given opioid analgesia (buprenorphine), crystalloid fluid (0.9% sodium chloride) and additional antibiotics (amoxycillin-clavulanic acid) as supportive systemic medications for the management of the NSAID-induced clinical signs. Whilst the administration of these medications may be considered as representing standard care, the absence of a control group results in such treatments potentially confounding any effect of omeprazole treatment.

Each animal was individually assessed for development of and recovery from gastric ulceration on the basis of clinical assessments, clinical pathology and gastroduodenoscopy. Clinical observations included bodyweight, measurement of PCV and total protein, food consumption and a scoring system was used for lethargy, restlessness, abdominal pain, faecal consistency, presence of faecal blood and vomitus. Gastroduodenoscopy was performed under general anaesthesia and the stomach and duodenum were

divided into five anatomical regions for the purpose of gastroduodenoscopy scoring. Each region was scored and assessed separately on a scale of 1-12, with greater weight assigned to findings of ulceration (9-12) than erosion (6-8) or submucosal haemorrhage (2-5). The scores for all 5 regions were used to calculate a total score which was assigned to each dog at each endoscopy. Dogs with a total gastric ulceration score of ≥ 30 or a single region with a score >6 were considered eligible for enrolment to the treatment phase of the study (n=26).

Blood samples were collected for general clinical chemistry and haematology analysis and urine samples were collected for urinalysis. The primary efficacy outcome parameter was the proportion of dogs with resolution of NSAID-induced gastroduodenal ulceration (i.e. no single anatomical region score >6 or any region scoring 6 at endpoint assessment with no change from baseline) after 2 weeks of treatment with omeprazole. The secondary efficacy outcome parameters included the same assessment but after 4 weeks of omeprazole treatment and mean ulcerations scores at 2 and 4 weeks post-treatment commencement. All study animals had at least one region with a score of >6 , with the majority of animals having more than one region with a score of >6 (only five study animals had only a single region with a score >6). The weighting of lesion scoring (higher score afforded to more severe lesions) and the fact that efficacy was based on regional scoring as opposed to total scoring can be accepted as representing a more stringent approach to demonstrating efficacy.

Although the proposed indication relates to gastric ulcers, one of the five regions of the gastrointestinal tract assessed for efficacy was the proximal duodenum. However, it was clarified that only 3 of the 26 animals would have been excluded from the study if proximal duodenal scores were not considered. Furthermore, only one animal was demonstrated to be a treatment success with sole reliance on the score for the proximal duodenum. Consequently, it was accepted that the inclusion of scores for the proximal duodenum will not have biased the total scores.

Results indicated that diarrhoea, frank faecal blood and vomiting began to reduce immediately after the end of the GUI phase and had mostly resolved by Day 4/5 of omeprazole administration. After 2 weeks of treatment, resolution of gastric ulceration was observed in 34.6% of dogs (9/26 dogs). The lower bound of the 95% confidence interval for the estimate of effect was 17.21%. After 4 weeks of treatment, resolution of gastric ulceration was observed in 100% of the remaining dogs (17/17 dogs). The lower bound of the 95% confidence interval for the estimate of effect was 80.49%.

Although diclofenac is not authorised for use in dogs in the EU, it can be accepted that gastric ulcers were successfully induced in this study as evidenced by the mean ulceration score of 5.8 (range 5-14) at pre-enrolment and which increased to 22.9 (range 15-42) at the end of the gastric ulceration induction phase. During the treatment phase, the mean ulceration score reduced to 11.9 (range 5-23) after two weeks of treatment and 5.6 (range 5-9) after four weeks of treatment. Nine dogs were removed from the study after 2 weeks of treatment as their gastric ulcers were considered to have healed completely. Although no further gastroendoscopy was conducted, these animals were returned to the colony and monitored and no signs of ill-health were observed.

The changes in design of the study (absence of a control group, randomisation and blinding) present difficulties in reaching reliable conclusions and in particular, reliably attributing any effects to omeprazole in the absence of a comparator group. For example, it cannot be excluded that the cessation of NSAID administration and the administration of anti-emetics etc. were responsible for the rapid improvement in clinical signs as opposed to the effect being as a result of omeprazole administration. As no further clinical observations or gastroscopy results are available following the final dose of omeprazole treatment, it is not considered possible to determine whether any of the treated animals may have subsequently relapsed and therefore whether the initially proposed 28 days treatment duration is adequate. In order to address the concerns raised in respect of the adequacy of the proposed treatment duration, it was agreed that the SPC recommends that the product be

administered for a minimum treatment duration of 14 days and that the treatment duration should be extended until resolution of clinical signs and according to a benefit-risk evaluation by the responsible veterinarian; however, treatment duration should not exceed 8 weeks.

Because of the deficiencies in the design of the study, it is not considered possible to reliably attribute the improvement in clinical condition of study animals solely to the administration of omeprazole, as opposed to a general improvement of clinical condition as a result of the concomitantly administered treatments and/or time to permit resolution and healing of the gastric ulcers and erosions.

Tolerance in the target animal species

One pivotal GLP-compliant target animal safety study was conducted in accordance with VICH GL43 to evaluate the safety of omeprazole when administered orally to laboratory Beagle dogs twice daily for 77 (cohort 1) or 79 (cohort 2) days at 0, 1x, 3x, and 5x the maximum proposed recommended treatment dose (RTD). Thirty-two Beagle dogs (16 male and 16 female) were enrolled in the study. Animals were approximately 6-7 months old and randomly allocated to four groups (sham-dosed, 1x, 3x or 5x RTD), with the treated groups administered mean dose rates of 1.56, 3.82 or 5.79 mg omeprazole/kg bw twice daily.

As the product was initially intended for administration for up to 28 days, it would have normally been expected that the treatment would be administered for 84 days (as opposed to the 77/79 days the product was actually administered for). Although no justification for the slightly shorter treatment duration has been provided, given that the mean overdoses administered were slightly higher than generally required, it can be accepted that an adequate safety margin has been assessed in this target animal safety study.

Animals were administered the test product in the fed state (as opposed to a fasted state). Given that the information provided in Part 3 suggests that omeprazole has a greater inhibitory effect on gastric acid secretion when administered in the fasted state and that it is generally recommended that PPIs should be administered before a meal so that the peak serum concentration coincides with the maximal activity of proton pump secretion, it is unclear as to how the timing of product administration in this study may be considered to represent a 'worst case' approach. Clinical observations were conducted twice daily throughout the study and once on euthanasia days. Blood was collected for haematology, clinical chemistry and coagulation and urine was collected for urinalysis once during acclimation, twice during the testing phase and once prior to euthanasia.

Due to a high percentage of dogs experiencing loose faeces during acclimatisation, faecal parasitological analyses were performed on all dogs. *Giardia* spp. cysts were present in 28 of 36 dogs and all dogs in the study were treated with a 5-day course of fenbendazole. On study Day 5, a dog in the 3x RTD group experienced a significant amount of diarrhoea and vomiting. A faecal sample from this dog revealed infections with *Campylobacter jejuni* and canine enteric coronavirus. Subsequent to this finding, a faecal sample was collected from each study dog and 26 of 32 dogs tested positive for *Campylobacter jejuni* and treatment with erythromycin for 5 days was initiated on study Day 29 for all dogs. This results in further difficulties when attempting to assess what signs are potentially caused by the treatment with omeprazole, and what signs may be the result of the infections that were present in the animals prior to treatment with the product.

Statistically significant ($p < 0.10$) reductions in bodyweight and food consumption were observed in all three groups of treated animals compared to controls, with the effect being most noticeable during the first week of treatment. These findings suggest that the test article may reduce appetite and food consumption particularly when first initiating treatment. Mild hypercholesterolaemia and thrombocytosis were observed among all dogs that received the test article and were considered as

possibly related to test article administration by the study investigators. Test article-related microscopic gastric mucosal changes were evident in all dogs administered omeprazole, consisting of degeneration and loss of chief cells with glandular dilatation. Mucosal changes were highest in incidence and severity in the fundus of animals in the 3x and 5x RTD groups and more frequently extended into the cardia. These findings have been included in the product information, and this is considered appropriate.

Given the high frequency with which vomiting and loose faeces were reported in study animals (including in the control group and before initiation of omeprazole administration), the subsequent diagnosis of *Giardia*, *Campylobacter jejuni* and canine enteric coronavirus infections and the requirement to treat study animals with fenbendazole and erythromycin, it is not considered possible to determine to what extent omeprazole administration may have resulted in gastrointestinal symptoms.

The results from the pivotal target animal safety study were also reflected in the pre-clinical studies, where the main adverse reactions reported were vomitus, diarrhoea, inappetence, chief cell degeneration and glandular dilatation. The product information includes the main adverse events reported as being at least possibly treatment-related and this is considered appropriate.

In addition to the target animal safety study, the applicant commissioned a report using the Small Animal Veterinary Surveillance Network (SAVSNET) through the University of Liverpool in the UK in order to obtain electronic health records relating to the prescribing practices and use of omeprazole in clinical practice. A total of 1,356 dogs were identified that had received an initial dispensing event for omeprazole within 30 days of a NSAID dispensing event. The main reasons for prescribing omeprazole within 30 days of NSAID administration related to vomiting and/or diarrhoea (n=749; 55.24%), non-specific gastrointestinal symptoms (n=104; 7.67%), prophylactic gastro-protectant (n=82; 6.05%), gastritis (n=72; 5.31%) and suspected ulceration (n=41; 3.02%). Out of these 1,356 dogs, approximately 3% developed a suspected ulceration (location not specified), although it is possible that gastric ulceration may have been present for some of the other indications mentioned in the case narratives.

In conclusion, reductions in bodyweight and food consumption, mild hypercholesterolaemia, diarrhoea, vomiting and microscopic gastric mucosal changes consisting of degeneration and loss of chief cells with glandular dilatation were considered to be omeprazole related and occurred at the recommended treatment dose. The possibility for such effects to occur is reflected in the product information. As microscopic changes were most prominent at overdose and were not associated with macroscopic changes or clinical signs, such changes are mentioned in the 'overdose' section of the product information

Clinical trial(s)

No clinical trial data has been provided. In justifying the absence of clinical trial data, the applicant highlighted the following:

- Omeprazole is already 'standard of care' for canine gastric ulceration and published literature confirms its well-established use for the reduction of gastric acid secretion.
- The conduct of a placebo-controlled field study is not considered a feasible option on moral, ethical, and practical grounds.
- Only indirect evidence of efficacy can be gathered from a field trial due to the likely reluctance of animal owners to consent to gastroscopy under general anaesthesia when their dogs are improving.

- No new information/data to that which is already known is expected to be derived should a field trial be conducted and therefore from a 3Rs perspective, there appears to be no need to conduct a field trial.
- An appropriate increase in gastric acid pH and for an appropriate duration comparable with the goals of PPI therapy in human patients was demonstrated in healthy Beagle dogs.

In general, it is expected that dose confirmation studies conducted under laboratory conditions are supported by clinical trial data generated under field conditions. However, no clinical trial data is available. Although two pilot dose confirmation studies have been conducted, they were considered by the applicant's Clinical Expert to be too small to conclude on efficacy and the gastric ulceration induced in the second pilot study was considered inadequate. The pivotal dose confirmation study lacked a control group, randomisation and blinding and therefore presents difficulties in reaching reliable conclusions. In the absence of a comparator group, it is not considered possible to reliably attribute the improvement in clinical condition of study animals solely to the administration of omeprazole, as opposed to a general improvement of clinical condition as a result of the concomitantly administered treatments and/or time to permit resolution and healing of the gastric ulcers and erosions.

Whilst it is acknowledged that the efficacy data package submitted with this application is not consistent with that proposed and reviewed in the scientific advice previously provided to the applicant, the CVMP accepts the following:

- Extensive evidence of the well-established use of omeprazole for the treatment of gastric ulceration in dogs has been provided, as evidenced by the extensive literature cited in this application.
- The pivotal dose confirmation study was designed to be consistent with the previous scientific advice, but the change in design arose due to circumstances that were not foreseen and in order to protect the welfare of study animals.
- The proposed dose of 0.5–1.0 mg omeprazole/kg bw and frequency of administration (twice daily) is consistent with the body of evidence in the scientific literature and including the 2018 consensus statement by the American College of Veterinary Internal Medicine expert review panel, suggesting this to be the most appropriate posology in dogs.
- The final formulation administered at the proposed treatment dose range has been demonstrated to increase intragastric pH to levels in excess of those established for the treatment of acid-related disorders in people (intra-gastric pH of ≥ 3 or 4 for approximately 75% of the day). That is, the candidate formulation has been demonstrated to effect the physiological change in intragastric pH considered necessary to facilitate healing of gastric ulcers.
- The proposal to restrict the indication to use of the product as an aid in the treatment of NSAID-induced gastric ulceration in dogs is considered to substantively address the concerns raised in respect of the deficiencies identified with the pivotal dose confirmation study, and, in particular, the potential confounding effect of the concomitant treatments administered in that study.

However, a number of the references cited by the applicant indicate that hypergastrinaemia may result from prolonged inhibition of gastric acid secretion by PPIs, with evidence for an increased risk of gastric tumours in laboratory animals. Therefore, it is generally not recommended to administer PPIs for longer than 8 weeks. Consequently, in the absence of clinical data to indicate a requirement to administer omeprazole to dogs for a duration in excess of 8 weeks, the product information indicates a maximum treatment duration of up to 8 weeks. In the absence of robust data/evidence to the contrary, the applicant's proposal to recommend dose tapering is not considered compatible with the

efficacy data provided nor the proposed pharmaceutical form, and reference to the proposed dose tapering has been omitted from the product information.

Overall conclusions on efficacy

Pharmacology

Omeprazole acts as a proton pump inhibitor (in both humans and animals) and is used to decrease gastric acidity by inhibiting gastric acid secretion.

Pharmacodynamics

See Part 3.

Pharmacokinetics

See Part 3.

Dose determination and confirmation

The applicant justifies the initially proposed posology of 0.5-1 mg/kg bw administered twice daily for up to 28 days by way of reference to published literature and proprietary data. This approach is in line with CVMP scientific advice. However, whilst the literature cited can be accepted as being generally supportive of the proposed dose rate and frequency of administration, the information from published literature on the duration of treatment is limited. Results from a blinded two-way cross-over trial conducted to determine the effect of the applicant's omeprazole product on gastric pH in six healthy dogs indicated that twice daily administration of the candidate formulation in the dose range 0.53-1.0 mg/kg bw results in the intragastric pH of healthy dogs meeting the target pH and time duration above that pH recommended when treating human patients with ulcerative gastric disease (i.e. pH ≥ 3 for at least 75% of the day).

Three laboratory dose confirmation studies (two pilot and one pivotal) were conducted. The pilot studies were too small to conclude on efficacy and the gastric ulceration induced in the second pilot study was considered inadequate. In the pivotal GCP-compliant dose confirmation study, the study design was changed from a negatively controlled, randomised and blinded study to a non-controlled single-arm study. Because of the deficiencies in the design of the study, it is not considered possible to reliably attribute the improvement in clinical condition of study animals solely to the administration of omeprazole. In order to address this concern, the indication was revised to restrict use of the product as an aid in the treatment of NSAID-induced gastric ulceration in dogs. In order to address the concerns raised in respect of the adequacy of the proposed treatment duration, it was agreed that the SPC recommends that the product be administered for a minimum treatment duration of 14 days and that the treatment duration should be extended until resolution of clinical signs and according to a benefit-risk evaluation by the responsible veterinarian; however, treatment duration should not exceed 8 weeks.

Tolerance in the target animal species

One pivotal GLP-compliant target animal safety study was conducted in accordance with VICH GL43. The study investigated tolerance to doses of 1x, 3x and 5x the maximum recommended treatment dose (RTD) of 1.0 mg/kg bw administered twice daily for up to 79 consecutive days. Due to the high frequency of vomiting and loose faeces reported in study animals and the subsequent diagnosis of *Giardia* infection and infection with *Campylobacter jejuni* and canine enteric coronavirus infections in the majority of study animals which necessitated treatment of all study animals, it is not considered possible to determine to what extent omeprazole administration may have resulted in gastrointestinal

symptoms. Therefore, the product information indicates that diarrhoea and vomiting may be commonly observed following administration of the product. Reductions in bodyweight and food consumption, mild hypercholesterolaemia, mild thrombocytosis (with or without associated signs) and microscopic gastric mucosal changes consisting of degeneration and loss of chief cells with glandular dilatation were considered to be omeprazole related. The potential for such effects to occur, either as adverse events or in case of an overdose, is reflected in the product information.

Clinical trials

No clinical trial was provided, but the applicant cross-referred to the dose confirmation studies and published literature. However, in general, and as also considered by the scientific advice given by the CVMP, it is expected that dose confirmation studies conducted under laboratory conditions are supported by clinical trial data generated under field conditions.

As the pivotal dose confirmation study lacked a control group, randomisation and blinding, it therefore presents difficulties in reaching reliable conclusions. Whilst it is acknowledged that the efficacy data package submitted with this application is not consistent with that proposed and reviewed in the scientific advice previously provided to the applicant, the CVMP accepts the following:

- Extensive evidence of the well-established use of omeprazole for the treatment of gastric ulceration in dogs has been provided, as evidenced by the extensive literature cited in this application.
- The pivotal dose confirmation study was designed to be consistent with the previous scientific advice, but the change in design arose due to circumstances that were not foreseen and in order to protect the welfare of study animals.
- The proposed dose of 0.5–1.0 mg omeprazole/kg bw and frequency of administration (twice daily) is consistent with the body of evidence in the scientific literature and including the 2018 consensus statement by the American College of Veterinary Internal Medicine expert review panel.
- The 2018 consensus statement by the American College of Veterinary Internal Medicine expert review panel recommends that omeprazole should be administered twice daily to approach pH goals in dogs and cats that were established for the treatment of acid-related disorders in people.
- The final formulation administered at the proposed treatment dose range has been demonstrated to increase intragastric pH to levels in excess of those established for the treatment of acid-related disorders in people (intra-gastric pH of ≥ 3 or 4 for approximately 75% of the day). That is, the candidate formulation has been demonstrated to effect the physiological change in intragastric pH considered necessary to facilitate healing of gastric ulcers.
- The proposal to restrict the indication to use of the product as an aid in the treatment of NSAID-induced gastric ulceration in dogs is considered to substantively address the concerns raised in respect of the deficiencies identified with the pivotal dose confirmation study, and, in particular, the potential confounding effect of the concomitant treatments administered in that study.

A number of the references cited by the applicant indicate that hypergastrinaemia may result from prolonged inhibition of gastric acid secretion by PPIs, with evidence for an increased risk of gastric tumours in laboratory animals. Therefore, it is generally not recommended to administer PPIs for longer than 8 weeks. In the absence of clinical data to indicate a requirement to administer omeprazole to dogs for a duration in excess of 8 weeks, the product information indicates a maximum treatment duration of up to 8 weeks.

In the absence of more robust data/evidence to the contrary, the applicant's proposal to recommend dose tapering is not considered compatible with the efficacy data provided nor the proposed pharmaceutical form, and reference to dose tapering has been omitted from the product information.

In conclusion, based upon the totality of the data package presented with this application and noting in particular that:

- the product has been demonstrated to be safe when administered at doses of up to 5.79 mg/kg bw twice daily for up to 79 days,
- evidence has been provided demonstrating that omeprazole is in well-established use for the proposed indication,
- the proposed posology has been suitably supported by a combination of proprietary data and reliance on scientific literature,

it can be concluded that the efficacy of the candidate formulation has been adequately supported and therefore a marketing authorisation may be granted.

Part 5 – Benefit-risk assessment

Introduction

Omeprazole TriviumVet is a gastro-resistant capsule containing 10 mg of omeprazole which is a well-known active substance having been authorised for use in humans and horses.

Omeprazole is a proton pump inhibitor (PPI), it inhibits the H⁺/K⁺ proton pump at the luminal surface of the parietal cell that secretes hydrogen ions into the gastric lumen, thus decreasing gastric acid secretion. Reducing the level of acid formation promotes healing of gastric ulcers. The therapeutic effect of omeprazole in the treatment of gastric ulcer disease is supported by the well-documented effect gastric acid suppression has on gastric ulcer healing.

The product is intended for use as an aid in the treatment of NSAID-induced gastric ulceration in dogs.

The application has been submitted in accordance with Article 8 of Regulation (EU) 2019/6 - full application.

Benefit assessment

Direct benefit

The proposed benefit of Omeprazole TriviumVet is in the treatment of gastric ulcers secondary to therapy with non-steroidal anti-inflammatory drugs (NSAIDs) in dogs. The benefit of PPIs such as omeprazole in reducing gastric acid secretion and raising gastric pH has been well-documented in the cited published literature. The effect of omeprazole when administered using the final formulation at the proposed dose rate of 0.5-1.0 mg/kg bw twice daily was investigated in a laboratory study in six healthy dogs. Results indicate that the candidate formulation is able to raise and maintain gastric pH to the target threshold recommended in human patients (≥ 3 for approximately 75% of the day) and which is recommended in the consensus statement by the American College of Veterinary Internal Medicine (ACVIM).

Two pilot dose confirmation studies were conducted with the principal objective of developing a suitable gastric ulcer induction method. Although omeprazole was administered to a total of 6 dogs in these studies, the pilot studies were too small to conclude on efficacy and the gastric ulceration induced in the second pilot study was considered inadequate.

Although a pivotal GCP-compliant dose confirmation study was conducted, the study design was changed from a negatively controlled, randomised and blinded study to a non-controlled single-arm study. Because of the deficiencies in the design of the study, it is not considered possible to reliably attribute the improvement in clinical condition of study animals solely to the administration of omeprazole, as opposed to a general improvement of clinical condition as a result of the concomitantly administered treatments and/or time to permit resolution and healing of the gastric ulcers and erosions following cessation of NSAID administration. In order to address this concern, the indication has been amended so that the product is to be indicated as an aid in the treatment of NSAID-induced gastric ulceration.

As there was no follow-up period following cessation of omeprazole treatment in any of the three dose confirmation studies, and findings suggest that the initially proposed 28 days treatment duration may not be adequate in all cases, the product information was revised to recommend that the product is

administered for a minimum period of 14 days and which may be extended until resolution of clinical signs; however, treatment duration should not exceed 8 weeks.

Additional benefits

In the absence of any veterinary medicinal products currently being available that include omeprazole as active substance and which are authorised for use in dogs, Omeprazole TriviumVet is considered to introduce a new veterinary medicinal product as an aid in the treatment of NSAID-induced gastric ulceration in dogs.

Omeprazole TriviumVet is presented in capsule form to be administered twice daily and therefore is expected to be relatively easy for the dog owner to administer.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has generally been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal

Administration of Omeprazole TriviumVet in accordance with SPC recommendations is expected to be generally well tolerated. Reductions in bodyweight and food consumption, diarrhoea, vomiting, mild hypercholesterolaemia, mild thrombocytosis and microscopic gastric mucosal changes consisting of degeneration and loss of chief cells with glandular dilatation were considered to be omeprazole-related in the target animal safety study and other pre-clinical studies. These findings are reflected in the product information, and this is considered appropriate.

As risks for use in pregnant, lactating or breeding animals have not been investigated, suitable warnings have been included in the product information.

Risk for the user

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Omeprazole TriviumVet can pose a risk to the user (both adult and child) should the contents of the capsule be accidentally ingested or contact is made with the granules contained within the capsule. The most severe risk is accidental ingestion by a child. Appropriate warnings are proposed for inclusion in the product information and the product is intended to be marketed in packaging with a child-resistant re-closeable lid.

Risk for the environment

Omeprazole TriviumVet is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

Information has been included in the product information to advise on the potential risks of this product relevant to the target animal and user and to provide advice on how to prevent or reduce these risks, and the risk management and mitigation measures are considered appropriate.

User safety

User safety risks have been identified, particularly in respect of accidental ingestion by children. These risks are mitigated by the inclusion of warnings to keep the product out of the sight and reach of children and by the presentation of the product in packaging with a child-resistant closure system. The proposed risk mitigation measures are considered adequate to ensure safety for the user.

Environmental safety

No specific risk mitigation measures in respect of the environment are considered necessary.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

The veterinary medicinal product is subject to a veterinary prescription.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: Treatment of gastric ulcers secondary to therapy with non-steroidal anti-inflammatory drugs (NSAIDs) in dogs.

In response to concerns raised during the assessment of the application, the indication was subsequently amended to: As an aid in the treatment of NSAID-induced gastric ulceration in dogs.

Based on the data presented to date, the overall benefit-risk balance is considered positive. The product information has been reviewed and is considered to be satisfactory and in line with the assessment.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Omeprazole TriviumVet is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) No 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.

Divergent position on a CVMP opinion on the granting of a marketing authorisation

For Omeprazole TriviumVet (EMA/V/C/005345/0000)

The undersigned have a divergent position to the CVMP opinion on 12 February 2025, for the reasons outlined below:

The undersigned are of the opinion that the data package in support of the benefit-risk balance of Omeprazole TriviumVet is insufficient for a positive opinion.

The dossier has been submitted as a full application according article 8 of Regulation 2019/6. The indication was considered to constitute a limited market according to Regulation article 4(29), however, the product was not granted reduction of data requirements according to article 23.

The undersigned are of the opinion that the data package is too limited to draw conclusions on the efficacy of the product

- No dose determination studies were presented for the proposed indication. Although a cross-over study in six healthy Beagle dogs demonstrated a substantial effect of omeprazole on gastric pH at the proposed dose, alternative doses were not investigated.
- Duration of treatment has not been substantiated.
- Two pilot dose confirmation studies were conducted with NSAID induced gastric ulcerations. The first study included four omeprazole treated dogs and this number of experimental animals was too low to draw statistical conclusions. The second pilot study failed to induce gastric ulcerations.
- A dose confirmation study was performed where gastric ulcers initially were induced by diclofenac. This study was planned as a two-armed study with an omeprazole treatment group and a placebo group. However, due to a mistake in the experimental model, where diclofenac was overdosed resulting in severe disease, the experiment was finalized without a control group and with use of concomitant medication. The study is therefore inconclusive.
- No clinical studies were presented although requested in the scientific advice (EMA/V/SA/301/19/I & EMA/V/SA/334/20/II).
- The substance is used commonly off-label in practice, but no studies are available to confirm the effect on the claimed indication.

The undersigned are therefore of the opinion that a positive opinion on the benefit-risk balance cannot currently be granted as the data package has not been able to provide sufficient documentation of the benefit of the product for the proposed indication. The pathophysiology of the gastric healing process is not directly influenced by the suppression of gastric acid. Proton-pump inhibitors (PPIs) work by reducing the amount of acid the stomach produces, preventing further damage to the ulcer as it heals naturally. Thus, dose and duration of treatment with proton-pump inhibitors must be proven in clinical trials.

Amsterdam, 12 February 2025

Niels Christian Kyvsgaard

Keith Baptiste

Minna Leppänen

Hanne Bergendahl