College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Zitac Vet 100 mg tablets for dogs
NL/V/0119/002/MR

Zitac Vet 200 mg tablets for dogs
NL/V/0119/003/MR

Created: June 2022

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0119/002-003/MR
Name, strength and pharmaceutical form	Zitac Vet 100 mg tablets for dogs Zitac Vet 200 mg tablets for dogs
Applicant	Intervet International BV Wim de Körverstraat 35 5830 AA Boxmeer The Netherlands
Active substance(s)	Cimetidine
ATC Vetcode	QA02BA01
Target species	Dogs
Indication for use	Symptomatic treatment for the reduction of vomiting associated with chronic gastritis in dogs.

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Intervet International B.V.	MRP
	Publicly available assessment report

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	27 September 2006
Date product first authorised in the Reference Member State (MRP only)	31 May 2006
Concerned Member States for original procedure	AT, BE, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, LU, PL, PT, SI, SK, UK Current CMS's: CZ, DK, EL, FI, FR, HU, IE, IT, PT, SI, SK, UK(NI)

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 100 mg Cimetidine and the following excipients:

Lactose monohydrate
Microcrystalline cellulose
Maize starch, pregelatinised
Sodium starch glycolate
Magnesium stearate

The container system consists of push-through blisters (white opaque PVC/Aluminium foil) in a carton box.

The choice of the formulation is justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

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B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

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

C. Control of Starting Materials

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

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on intermediate products

Not applicable.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

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

G. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Toxicological Studies

The applicant has provided bibliographical data which show that the acute and repeat dose toxicity of cimetidine is low and no carcinogenic effects are indicated.

Single Dose Toxicity

LD_{50} in rats is 5000 mg/kg bodyweight. LD_{50} in dogs is 2600 mg/kg bodyweight. In the dog oral repeated dose studies were carried out for 3, 6 or 12 months, using doses from 37 mg/kg up to 504 mg/kg daily. Transient tachycardia was observed in the highest dose group. Reduction in prostate weight was already observed at a dose of 41 mg/kg/day, when given for 6 months. Studies in the rat indicated that this effect was reversible.

Repeated Dose Toxicity

Repeated dose studies in the rat with dosages of 0, 150, 378 or 950 mg/kg/day orally during 12 months did not reveal substantial toxic effects.

In groups of dogs administered 37, 41, 112, 144, 336 or 504 mg cimetidine/kg/day orally, only the highest dosage group showed tachycardia during the first week of the experiment. Two dogs from the 504 mg-group had to be euthanasied. Compared to untreated controls prostate weights were reduced, except for the 37 mg-group.

Reproductive Toxicity, including teratogenicity:

Teratological studies were carried out in the rabbit, rat and mouse, all at oral doses up to 950 mg/kg. From the bibliographic data, it is concluded that cimetidine is not embryotoxic, foetotoxic or teratogenic in rats and mice up to dose rates of 950 mg/kg/day and in rabbits up to 328 mg/kg/day.

Mutagenicity

In vitro studies gave rise to a concern that cimetidine treatment might promote the development of gastric cancer. However, such mutagenic effect could not be demonstrated under *in vivo* studies.

Carcinogenicity:

A long term study in the dog with cimetidine did not indicate the presence of a carcinogenic effect. It is concluded that cimetidine is not likely to lead to gastric cancer.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that after accidental oral ingestion by adults or children, an effect on gastric acid secretion can be expected. However this effect is reversible and mild.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:
The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show that cimetidine is a specific reversible histamine H_2-receptor antagonist and able to inhibit gastric acid secretion. In dogs cimetidine inhibits gastric acid secretion in a dose-dependent manner, both after oral and parenteral administration.

Pharmacokinetic studies show that after oral administration of the recommended treatment dose of 5 mg/kg maximum plasma levels are achieved after 1-1.5 hours. Absorption after oral administration of cimetidine is rapid, with maximum plasma levels reached after about 2 hours. The plasma half-life in the dog after an oral dose of 100 mg was calculated as 1.2 hours. Bioavailability in the dog after oral administration depends on the formulation used and can vary from about 30% to 90%. For Zitac and unfed dogs a bio-availability of 95% was observed. Feeding status has been shown to affect plasma kinetics, resulting in a delay in absorption and a lower bio-availability, compared to unfed dogs. Cimetidine is widely distributed over body compartments. It also crosses the blood-brain barrier. Repeated administration does not result in accumulation. Urine is the major route for elimination of cimetidine, mainly as unchanged compound.

Tolerance in the Target Species of Animals

Tolerance was studied using Zitac tablets at 3 and 5 times the recommended treatment dose over a 13-week treatment period. Animals were treated with cimetidine at doses of 0, 1, 3 or 5 times the recommended treatment dose for a 90 day period. 24 dogs were included in the study, each of the four treatment groups contained 3 male and 3 female dogs. The control group was treated with placebo tablets. All doses were administered by oral administration 3 times daily for 90 consecutive days. Treatment with cimetidine as Zitac tablets up to 5 times the recommended treatment dose did not affect weight, feed intake, biochemical and haematological parameters, compared to placebo treated controls. Clinical examinations did not indicate the presence of treatment related adverse effects. Two bitches showed mammary gland swelling, corresponding to signs of naturally occurring pseudopregnancy. A relation with treatment cannot be ruled out

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

Field Trials

The applicant has conducted three field trials which show that cimetidine as Zitac tablets is effective in controlling vomiting. Zitac is not effective against gastritis itself. The recommended dose of 5 mg/kg BW, 3 times daily, appears to be effective in practice. Although bioavailability of cimetidine is lower when given with food, clinical data indicate that administration with food is effective in reducing the vomiting frequency.

The first the field studies was a double-blinded, placebo controlled field study among dogs presented to a practitioner, which were divided in two groups (cimetidine and placebo). Data from 14 dogs (7 in both groups) were analysed. Vomiting scores were significantly different between the cimetidine-treated and the placebo-treated groups, with less vomiting in the treated group.

The second study was a double-blinded, multicentre, placebo controlled and randomised field trial. Dogs were randomly assigned to one of the study groups (cimetidine or placebo). Data from 16 dogs treated with Zitac and 13 dogs treated with a placebo were analysed. It was observed that a 4-weeks treatment with Zitac was able to reduce vomiting and that this effect was retained during the following 2 weeks, without treatment. It is also apparent that dietary measures are of significance.

The third study was a double-blinded, multicentre, placebo controlled and randomised field trial. Data from 5 dogs treated with Zitac and 7 dogs in the placebo group were analysed Results indicate that vomiting can be controlled by cimetidine treatment, at a dose rate of 5 mg/kg 3 times daily, in combination with dietary measures. A minimal treatment period of 4 weeks is recommended. Cimetidine treatment only controls the symptom vomiting. No obvious effect on gastritis could be demonstrated.

In practice, dogs offered with a history of persistent vomiting can be put on cimetidine medication. Tablets should be administered for at least 2 weeks after signs have resolved, meaning that treatment has to be continued for about 4 weeks. If successful, medication can be ended. A 2-weeks medication-free period is necessary to see if vomiting occurs again. Dietary measures should always be maintained. If a dog starts vomiting again, treatment can be re-initiated, without any risk for intolerance. It is recommended that dogs, showing persistent vomiting, should preferably be referred to a specialist for gastroscopy. These items are addressed properly in the SPC of the products.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Summary of change (Type; application number)	**Section updated**	**Approval date**
Update of CEP of an already approved manufacturer NL/V/0119/002-003/IA/009	N/A	6 January 2021
Update of CEP of an already approved manufacturer NL/V/0119/002-003/IB/008	N/A	3 May 2019
Changes to the DDPS ES/V/xxxx/IA/031/G	N/A	26 October 2018
Changes to the DDPS NL/V/xxxx/IA/017/G	N/A	21 November 2016
Changes to the DDPS NL/V/xxxx/IA/011/G	N/A	28 November 2014
Deletion of manufacturer of the active substance NL/V/0119/002-003/IA/004	N/A	15 January 2014
Withdrawal of Zitac Vet 50 mg tablets for dogs (NL/V/0119/001) in RMS and all CMS's	Tables in Module 1	October 2013
Changes to the DDPS NL/V/0119/001-003/IA/003	N/A	24 October 2012
Renewal NL/V/0119/001-003/R/001	N/A	29 April 2011
Change in the name and/or address of the marketing authorisation holder NL/V/0119/001-003/IA/002	Module 1	11 December 2009
Addition of new in-process tests or limits applied during the manufacture of the product NL/V/0119/001-003/IB/001	N/A	11 March 2009