9 April 2025
EMA/163823/2025
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Emevet (EMEA/V/C/006439/0000)

INN: Maropitant

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

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Introduction

The applicant CP-Pharma Handelsgesellschaft mbH submitted on 6 February 2024 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Emevet, 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 5 October 2023 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:

- Prevention of nausea induced by chemotherapy in dogs.
- Prevention of vomiting induced by motion sickness in dogs.
- Prevention and treatment of vomiting, in conjunction with maropitant solution for injection and in combination with other supportive measures in dogs.

The active substance of Emevet is maropitant, an anti-emetic, which is a neurokinin-1 (NK1) receptor antagonist, which acts in the central nervous system by inhibiting Substance P, the key neurotransmitter involved in vomiting. The target species is dog.

Emevet chewable tablets contains 16mg, 24mg, 60mg and 160mg of maropitant and are presented in packs containing 10, 30, 50 and 100 tablets.

The rapporteur appointed is Minna Leppänen and the co-rapporteur is Ricardo Carapeto García.

The dossier has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 – a generic application. The reference product is Cerenia (EMEA/V/C/000106), 24, 60 and 160 mg tablets for dogs.

On 9 April 2025, the CVMP adopted an opinion and CVMP assessment report.

On 2 June 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Emevet.

Scientific advice

Not applicable.

Limited market status

Not applicable.

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) with reference number LOC-1 000 1 0485, 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

The active substance is manufactured at two sites. The first site is located in the EEA and the activities performed are manufacture of active substance, quality control testing (chemical/physical), primary packaging, secondary packaging and storage and/or distribution of active substance. A declaration has been provided for the active substance manufacturer from the QP at the batch release site stating that the active substance is manufactured in compliance with EU GMP.

The second site is located outside the EEA. A GMP certificate is not available in EudraGMDP for this site. A declaration has been provided for the active substance manufacturer from the QP at the proposed batch release site stating that the active substance is manufactured in compliance with EU GMP.

Finished product

Site of batch release:

CP-Pharma Handelsgesellschaft mbH, Ostlandring 13, 31303 Burgdorf, Germany.

A GMP certificate issued by Germany, covering batch release and secondary packaging, is available in EudraGMDP. The certificate was issued on 26 October 2023, based on an inspection carried out on 23 August 2023.

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 are in line with legal requirements.

Part 2 - Quality

Composition

Emevet is a generic veterinary medicinal product of a refence medicinal product previously authorised in the community, Cerenia 24mg tablets, for which the marketing authorisation holder (MAH) is Zoetis Belgium SA.

Emevet chewable tablets contain 16, 24, 60 and 160 mg maropitant citrate monohydrate (In-house grade) as the active substance. The round, convex chewable tablets are off-white to light brown with brown spots and have a cross-shaped break line on one side and all tablets can be divided into 4 equal doses. The tablets have different diameters; 16mg: 6mm diameter, 24mg: 7mm diameter, 60mg; 10mm diameter and 160mg; 15mm diameter and they have a chicken aroma. The composition of the different strengths is qualitatively identical and quantitatively proportional. The compositions are adequately described and the functions of the excipients are indicated. The excipients are cellulose, microcrystalline, lactose monohydrate, croscarmellose sodium, silica, colloidal hydrated, magnesium stearate and chicken flavour.

Containers and closure system

It is confirmed that intermediate storage of drug product complies with the requirements as stated in the current Commission Regulation (EU) 10/2011. The technical documentation (incl. IR-spectrum and declarations), release specification and a sample certificate of analysis were presented and are acceptable.

The product is presented in aluminium [PVC/Alu/oPA]- blisters packed into cardboard boxes. The blister is composed of a top-foil (45 µm) and a blister bottom foil (20 µm) and the material used complies with the requirements as stated in the current version of the EU-food directive 2002/72/EC. The technical documentation (incl. IR-spectrum) and declaration of compliance with Commission Regulation (EU) No 10/2011, release specification and a sample certificate of analysis are presented.

Product development

The applicant’s goal during the development of Emevet was to make a chewable tablet which is bioequivalent to Cerenia 24 mg tablets. A commercially available maropitant as citrate monohydrate, the same salt as the reference product, is also used as the API for the generic product. Emevet contains the excipients lactose monohydrate, cellulose microcrystalline, croscarmellose sodium and magnesium stearate which are also present in the reference product (as per the reference SPC). In addition, Emevet also contains silica colloidal hydrated and chicken flavour. The tablets have a cross-shaped breakline intended to break into four equal doses. The functionality of the tablet break line is confirmed by the Ph. Eur. test Subdivision of tablets as described in the monograph 0478 “Tablets”.

The applicant stated that the qualitative and quantitative compositions of the proposed chewable tablets are based on publicly available information, development studies and the contract manufacturer's experience. The applicant’s goal was to make flavoured chewable tablets using the chicken flavour to increase palatability. It is the use of the chicken flavour that gives the finished product its appearance of off white to light brown with brown spots.

The applicant developed a common blend containing 16% maropitant (as base) and proposed to use this common blend to manufacture varying tablet sizes and therefore different strengths. The proposed

tablet weights of 100, 150, 375, and 1000 mg correspond to chewable tablets containing 16, 24, 60 and 160 mg of maropitant, respectively. The varying sizes and the shape of the tablets are to ensure adequate dosing range for a range of target weights in dogs.

There are no differences in color or shape of the tablets which have no embossing or markings on the tablets. However, the applicant demonstrated how the dimensions and weight of the tablets (16mg/100mg/6 mm, 24mg/150mg/7 mm, 60mg/375mg/10 mm, 160mg/1000mg/15 mm) are considered sufficient to distinguish between the strengths in line with the Quality of Medicines Q&A on the EMA website.

The applicant aimed to develop a chewable tablet and as such the formulation was developed to ensure that the resulting tablets are in line with the Ph. Eur. requirements for chewable tablets. The maropitant tablets have been designed with a higher amount of disintegrant than non-chewable tablets and the addition of chicken flavour is to enhance palatability. Friability and hardness were also considered, and friability is controlled in the finished product.

The fast disintegration, and corresponding dissolution, time was demonstrated in studies conducted by the applicant.

The applicant investigated two different methods of manufacture, using different quantities of excipients, before concluding on a method of direct compression due to better powder flowability. Comparative dissolution with the reference product was carried out.

Validation of the method used to control particle size has been provided and validation is acceptable.

Description of the manufacturing method

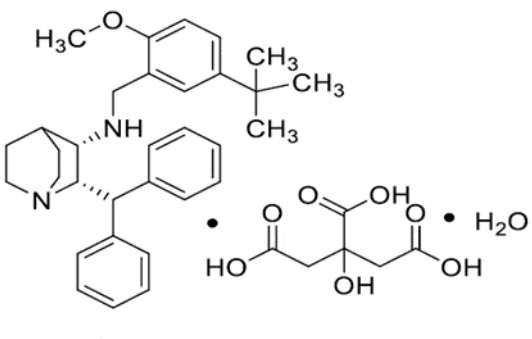
A standard manufacturing process consisting of blending and mixing, followed by direct compression of the final tablet was described. A single blend is proposed for all four tablet strengths with tablets of different sizes being compressed (proportional tablets). Process validation has been done with two pilot size batches. The process validation scheme for production scale batches to be followed is included in the dossier. It is acceptable and in line with "Guideline on process validation for finished products — information and data to be provided in regulatory submissions" (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1).

The manufacturing steps and in process controls are described.

Control of starting materials.

Active substance

The chemical name of maropitant citrate monohydrate is: (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl) quinuclidin-3-amine citrate monohydrate.



The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. There are two manufacturers of the active substance.

Maropitant citrate is not monographed in the Ph. Eur. and so is tested by the applicant against an in-house monograph. Quality and testing standards outlined in the ASMF must be met by the API manufacturers. The applicant has proposed a common specification for the active substance which differentiates the residual solvent testing to be carried out dependant on the ASMF source.

Certificates of analysis according to the applicant's overall specification are provided and are acceptable. The applicant has incorporated the test for Microbiological purity for the purpose of life cycle management and oversight in the applicant's overall API specification. The non-routine Ph. Eur. method has been described and validated.

The applicant has included a test for polymorphism in the MAH overall specification for the purpose of life cycle management and oversight.

An internal method to control the content and related substances in all sources of maropitant citrate monohydrate was developed by the applicant. The method includes a system suitability test that meets the repeatability requirements as defined in Ph. Eur., 2.2.46. Certificates of Analysis test are presented and show that specifications are appropriate, and the results are acceptable.

With regard to the storage of the active, the active is packed into either polyethylene bags placed into a polyester/aluminium/polyethylene bag or a double polyethylene bag placed in a polyethylene drum. The container closure system is acceptable. Confirmation that the bags in immediate contact with the active complies with the requirements of EU regulations on plastic materials and articles intended to come into contact with food (EU 10/2011) is provided.

Excipients

All the excipients, except for chicken flavour, are described in Ph. Eur. and are controlled to the specification of their respective monographs. Current monographs for the product excipients monographed in Ph. Eur. include functionality-related characteristics. Functionality-related characteristics are used to control the excipients. Particle size for the excipients is controlled.

Chicken flavour is controlled by an in-house monograph. An identification test for chicken flavour is included according to guideline EMEA/CVMP/004/98. A description of manufacturing of chicken flavour (manufacturing flow-chart) is provided. Microbiological purity is included into specifications of chicken flavour. Viral safety assessment is provided. Manufacturer's declaration of compliance with EU Regulation 1069/2009 (Animal by-products) is provided. Applicant's own results of analysis for chicken flavour were provided. Proposed specifications for the excipients are acceptable.

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

A declaration from the lactose manufacturer was provided stating that the milk from which it is produced, has been sourced from healthy cows in the same conditions as milk collected for human consumption. Viral safety evaluation for chicken flavour was provided. A TSE declaration for was provided.

Control tests on the finished product

The tests include appearance, tightness of blister, uniformity of dosage unit, identification of maropitant, assay of maropitant, related substances (each individual, total), dissolution, microbiological purity. In the release tests references to the Ph. Eur. monographs and general methods used were provided. Appearance and tightness of the Blister were done according to in house requirements. In house methods are used for assay, related substances and content uniformity. All the tests are validated in accordance with VICH GL2. The sizes of the different strengths of chewable tables are detailed in the specifications and subject to a visual inspection.

The proposed release specification for total related substances in the finished product is justified

The test "Uniformity of mass of subdivided tablets" for halved and quartered tablets are included in finished products specifications at release. The limits for microbiological quality comply with the Ph. Eur. 5.1.4 for non-aqueous preparations for oral use. The are no non-routine tests used. Certificates of Analysis are provided and are acceptable.

Resistance to crushing and friability are included in the release tests. The long-term stability study is currently set to run for 60 months, however only 24 months have currently elapsed. A decrease of resistance to crushing has been seen under accelerated conditions. For a chewable tablet hardness and friability can be considered critical quality attribute. Resistance to crushing is an important specification for chewable tablets. Chewable tablets are designed to be easily crushed by chewing, ensuring that they are not too hard to chew and not too soft that they crumble immediately. Resistance to crushing is included in the specifications.

The applicant uses commercially available impurity reference standards and standards from the ASMF holder.

Stability

The stability protocol follows the principles established in the VICH and CVMP guidelines on stability studies. A declaration was provided stating that the shelf-life of the product will comply with the requirements of the "Note for Guidance on Start of Shelf-life of the Finished Dosage Form" EMEA/CVMP/453/01.

The long-term studies (25 °C ±2 °C /60%±5% RH) are pending, the data is available up to 24 months with no significant changes observed. The shelf-life can thus be extrapolated up to 36 months according to the Guideline on Stability Testing, EMEA/CVMP/QWP/846/99. No significant changes were observed in the accelerated studies (40 °C ±2 °C /75%±5% RH) except for a decrease in resistance to crushing. The data provided by the applicant supports a shelf life of 36 months with no special storage conditions.

A decrease in resistance to crushing was observed under accelerated conditions. The long-term stability data (t=24 months) shows no significant trend in resistance to crushing. The resistance to

crushing and uniformity of mass for whole tablets are included in the stability specifications. The test for uniformity of mass of divided quarters does not need to be performed routinely during the shelf-life. The in-use stability studies were performed as follows: "After the first opening the samples of product were stored, inside their cardboard box, for 3 days at 25 °C and 60% RH.". Consequently, 5.2 of the SPC includes "If the tablets are divided, the remaining part should be kept in the blister pack and used at the next administration. Any halved or quartered tablets remaining after 3 days should be discarded."

Overall conclusions on quality

The data provided in Part II of the dossier is satisfactory. Information on the development, manufacture, control of the active substance, control of the finished product and stability have been presented.

The results of tests carried out indicate consistency and uniformity of important product characteristics which leads to the conclusion that the quality of the product can be considered to be acceptable when used in accordance with the conditions defined in the SPC.

The active substance maropitant citrate monohydrate is not monographed in the Ph. Eur. and so is controlled by an in-house specification applicable to both manufacturers of the active substance. Particle size is controlled in the in-house specification.

The manufacturing process of the finished process is a standard process of direct compression and sufficient validation data and data on the in-process controls have been provided to demonstrate that the process is controlled.

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. Based on the review of the data on quality, the manufacture and control of the product could be acceptable.

The finished product is packaged in Aluminium [PVC/Alu/oPA]-Aluminium blisters, containing 10 chewable tablets each. The packaging complies with the requirements as stated in the current version of the EU-food directive 2002/72/EC.

Stability data has been provided for the active substance and finished product. A declaration has been provided that the shelf-life of the product will comply with the requirements of the "Note for Guidance on Start of Shelf-life of the Finished Dosage Form" EMEA/CVMP/453/01. Long term stability data from two pilot batches over 24 months were provided. The results demonstrated that the batches were within the specifications. No changes to the polymorphic form were observed. A decrease of resistance to crushing has been seen under accelerated conditions. Chewable tablets are designed to be easily crushed by chewing, ensuring that they are not too hard to chew and not too soft that they crumble immediately.

Part 3 – Safety documentation (Safety and residues tests)

The active substance of Emevet is maropitant, a neurokinin 1 (NK1) receptor antagonist, which acts by inhibiting the binding of substance P, a neuropeptide of the tachykinin family. Substance P is found in significant concentrations in the nuclei comprising the emetic centre and is considered the key neurotransmitter involved in vomiting. By inhibiting the binding of substance P within the emetic centre, maropitant is effective against neural and humoral (central and peripheral) causes of vomiting.

This application has been submitted in accordance with Article 18 (EU) 2019/6 (generic veterinary medicinal product). The reference product is Cerenia tablets for dogs, MA number EU/2/06/062/001-004.

Safety tests

This application has been submitted as a generic application in accordance with Article 18 of Regulation (EU) 2019/6 (generic/hybrid veterinary medicinal product). An application for a marketing authorisation for a generic veterinary medicinal product does not need to contain the documentation on safety and efficacy if all the conditions listed in the Article are fulfilled.

The applicant has cited a suitable reference product, Cerenia tablets for dogs. Emevet and Cerenia are of the same pharmaceutical form (tablet/chewable tablet) and are intended for use via the same route (oral administration) to the same target species (dog) for the same indication and at the same dosage. The active substance (maropitant) is the same and only a difference in excipient composition is noted. These differences are not expected to present any toxicological risk since the excipients are well-known excipients commonly used in pharmaceutical products.

Bioequivalence between Emevet and Cerenia is accepted and Emevet meets the requirements of Article 18 of Regulation (EU) 2019/6 for generic veterinary medicinal products.

Pharmacology

Pharmacodynamics

The applicant has referred to a suitable reference product (Cerenia tablets for dogs). No new data relating to pharmacodynamics of the product have been provided. Since bioequivalence between formulations has been demonstrated this approach is acceptable.

The applicant has proposed to include the same information in section 4.2 'Pharmacodynamics' of the SPC as in section 4.2 of the SPC of the reference product Cerenia tablets for dogs. This is considered acceptable.

Pharmacokinetics

The applicant has referred to a suitable reference product (Cerenia tablets for dogs) in this application. No new data relating to pharmacokinetics of the product have been provided.

The applicant has provided two *in vivo* bioequivalence studies to evaluate the bioequivalence between the test product Emevet chewable tablet and the reference product Cerenia tablets for dog. A two way,

two treatments, two periods, cross-over design with Beagle female and male dogs is presented. Please refer to Part 4 for the assessment of these studies.

The applicant has proposed to include the same information in section 4.3 'Pharmacokinetics' of the SPC as is contained in section 4.3 of the SPC of the reference product. This approach is acceptable.

Toxicology

No data relating to toxicological profile of Emevet has been provided as bioequivalence with the reference product is claimed. Emevet and Cerenia tablets for dogs contain the same concentration of active substance (maropitant) and the omission of toxicological (including reproductive and developmental toxicity), genotoxicity and carcinogenicity data can be accepted (see Part 4).

All excipients used in Emevet are well-known and commonly used in pharmaceutical products. Thus, the minor differences noted are not expected to present a risk in terms of the toxicological profile of the candidate product Emevet.

Other requirements

Special studies

As the bioequivalence between Emevet and Cerenia is accepted, the omission of additional data on potential dermal irritation and sensitisation as well as eye irritation of Emevet can be accepted.

The SPC section 3.5 contains the same information as in the reference product, including a warning to avoid eye/skin exposure. This is accepted.

Observations in humans

Maropitant is not used in human medicinal products.

Excipients

The excipients are well-known and widely used in human medicinal products. No toxicological concern is identified. Therefore, the toxicity of the finished product for the user can be assessed solely based on the toxicity of the active substance.

User safety

The applicant has presented a brief user risk assessment (URA). According to Section IV.1 of the Annex II to Regulation (EU) 2019/6, a review of the user safety risk assessment is required which should focus on differences between the generic and reference veterinary medicinal products (for example, composition in excipients). As previously noted, the only differences between the candidate and reference product are in terms of the excipient composition. These differences do not present a toxicological concern.

The Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) has been followed in the applicant's assessment. The exposure has been assessed in normal conditions of use (non-professional users) as well as foreseeable accidents: pre-application phase (hand contact when subdividing product), application phase (hand contact during administration) and accidental ingestion (adult/child).

There are no remarkable differences between the candidate and the reference product, and therefore the URA conclusions of the reference product are valid also for Emevet.

The applicant has identified two possible routes of exposure: dermal and oral. The inhalation and ocular exposure are assessed as unlikely. The quantitative user risk assessment revealed an MOE well below 100, however, the user safety warnings provided by the applicant are considered sufficient to mitigate the identified risks. Overall, the risk management are in line with those of the reference product and deemed acceptable.

Environmental risk assessment

The applicant has conducted an environmental risk assessment (ERA) in accordance with the CVMP 'Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38' (EMA/CVMP/ERA/418282/2005-Rev.1-Corr.1).

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 producing species.

No additional environmental warnings are considered necessary for inclusion in the SPC of Emevet. It can be concluded that Emevet will not present an unacceptable risk for the environment when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.

Overall conclusions on the safety documentation: safety tests

According to Article 18 of Regulation (EU) 2019/6, an application for a marketing authorisation for a generic veterinary medicinal product does not need to contain the documentation on safety and efficacy if all the conditions listed are fulfilled. The applicant has cited to Cerenia tablets for dogs as reference product. Emevet and Cerenia are of the same pharmaceutical form (chewable tablet/tablet) and are intended for use via the same route (oral administration) to the same target species (dog) for the same indication of use and the same dosage. The active substance (maropitant) is the same and only differences in the excipient composition are noted. These differences are not expected to present any toxicological concern since the excipients are well-known and commonly used in pharmaceutical products. Bioequivalence between Emevet and Cerenia is accepted (see Part 4).

Pharmacology:

No pharmacodynamic or pharmacokinetic studies were presented as bioequivalence with the reference product is claimed. The omission of these data are accepted since the requirements for a generic veterinary medicinal product are fulfilled. The texts in the SPC sections 4.2 and 4.3 are aligned with the reference product and this is acceptable.

Toxicology:

No data relating to toxicological profile of Emevet has been provided as bioequivalence with the reference product has been claimed. The omission of the toxicological data can be accepted, despite the qualitative and quantitative differences in the excipients noted between these two products. These

differences are not expected to present any toxicological concern. The excipients are well-known and commonly used in pharmaceutical products.

The information in the proposed SPC is in line with the reference product.

User safety:

Based on the assessment presented, the product does not pose an unacceptable risk to the user when used in accordance with the SPC. Appropriate warnings for the user have been included in the product literature in line with those of the reference product.

The quantitative user risk assessment resulted an estimated MOE below 100. Appropriate safety advice/warning statements are included in the SPC to mitigate the risks.

Environmental risk assessment:

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pre-clinical studies

Emevet chewable tablets contains 16mg, 24mg, 60mg and 160mg of maropitant and are intended for the following indication:

- Prevention of nausea induced by chemotherapy in dogs.
- Prevention of vomiting induced by motion sickness in dogs.
- Prevention and treatment of vomiting, in conjunction with maropitant solution for injection and in combination with other supportive measures in dogs.

The dose for prevention of vomiting induced by motion sickness is 8 mg/kg. For other indications, the dose is 2 mg/kg.

The active substance of Emevet is maropitant, an anti-emetic, which is a neurokinin-1 (NK1) receptor antagonist, which acts in the central nervous system by inhibiting Substance P, the key neurotransmitter involved in vomiting.

The application has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 – a generic application. The reference product is Cerenia (EMEA/V/C/000106), 24, 60 and 160 mg tablets for dogs.

Pharmacology

Pharmacodynamics

See part 3

Pharmacokinetics

See part 3

Bioequivalence studies

Two GLP-compliant bioequivalence studies were conducted in accordance with current guidance (CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products, EMA/CVMP/016/2000-Rev.4*). The first study was performed to demonstrate bioequivalence for the 60 mg strength, using the test product Emevet 60 mg chewable tablets and the reference product Cerenia 60 mg tablets (8 mg/kg) in fasting state. Due to abundant vomiting and diarrhoea in the beagle dogs a second bioequivalence study was performed to demonstrate bioequivalence with the lower 24 mg strength, using the test product Emevet 24 mg chewable tablets and the reference product Cerenia 24 mg tablets (2 mg/kg) in fasted dogs.

Study 1

The design of the study was a single-dose, randomised, two-period, two-sequence, laboratory blind cross-over study balanced in relation to body weight. After an overnight fast of at least 12 hours the test dogs (n=36) received two tablets (120 mg) either of the test product Emevet 60 mg chewable tablets or reference product Cerenia 60 mg tablets, corresponding to a dose of 8-12mg/kg. A wash-out period of 7 days was held between the treatments. The dose of maropitant administered is in line with the intended dose for prevention of vomiting induced by motion sickness, this is considered acceptable.

According to the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4*), fasting conditions are recommended in bioequivalence studies for canine immediate-release oral formulations, unless recommended by the SPC of the reference veterinary medicinal product (for cases where feeding may interfere with drug absorption and increase the inter- and intra-individual variability in the rate and extent of drug absorption). Based on the EPAR of the reference product and literature provided, food has no impact on the pharmacokinetics of maropitant.

Maropitant has been studied in the abovementioned bioequivalence study during fasting state with the dose 8 mg/kg. Vomiting is a common adverse event of the reference product that is usually observed within hours after the administration of the 8 mg/kg dose. Therefore, the SPC of the reference veterinary medicinal product recommends a light meal or snack before dosing of maropitant for motion sickness and prolonged fasting before administration should be avoided. As the recommendation about a light meal can be considered as a safety precaution, the applicant's rationale and justification to follow the relevant guideline and to conduct the bioequivalence study in fasted state can be accepted, although it can be anticipated that less animals would have had diarrhoea or vomiting if a light meal had been provided.

Plasma samples were analysed for concentrations of maropitant by an appropriately validated LC-MS/MS method. The lower limit of quantitation (LLOQ) was 5.0 ng/ml. Sample stability is considered to have been adequately investigated in terms of storage, and the stability of the samples at the time of analysis can be assured.

Non-compartmental methods were used for evaluation of the pharmacokinetic parameters. Analysis of variance (ANOVA) was performed using ln-transformed AUC_t and C_{max} parameters, and this is considered acceptable and in line with relevant guidelines. The applicant specified that bioequivalence could be concluded if the 90% confidence interval for the ratio of the means of AUC was included within interval 80 – 125% and if the 90% confidence interval for the ratio of the means of C_{max} was included within interval 70% – 143%.

Results

Table 4.1: Mean Pharmacokinetic Parameters of Maropitant after Oral Administration (exclusion of vomiting animals No. 3, 6, 8, 9, 10, 21, 22, 23, 24, 25, 26, 34, 35 and 36) (n=22)

Parameter	**Test Item**		**Reference Item**	
	Mean	**SD**	**Mean**	**SD**
Cmax ($ng.mL^{-1}$)	727.44	314.17	698.14	359.21
AUCt ($ng.hr.mL^{-1}$)	9 222.64	4 274.90	8 837.83	5 182.23

Table 4.2: Mean Pharmacokinetic Parameters of Maropitant after Oral Administration (exclusion of vomiting and diarrhea animals No. 3, 6, 8, 9, 10, 12, 13, 15, 16, 21, 22, 23, 24, 25, 26, 34, 35 and 36) (n=18)

Parameter	Test Item		Reference Item	
	Mean	SD	Mean	SD
Cmax (ng.mL^{-1})	765.92	301.70	768.47	330.35
AUCt (ng.hr.mL^{-1})	9 861.95	3 938.16	9 721.56	4 884 45

Table 4.3: Calculated 90% Confidence Limits for the Treatment Effect Ratio of Test and Reference Item (after exclusion of vomiting animals) (n=22)

Parameter	90% Confidence Limits (%)		Acceptance Bounds (%)
Cmax	Upper	141.2	143
	Lower	95.3	70
AUCt	Upper	144.6	125
	Lower	101.0	80

Table 4.4: Calculated 90% Confidence Limits for the Treatment Effect Ratio of Test and Reference Item (after exclusion of vomiting animals and diarrhea animals) (n=18)

Parameter	90% Confidence Limits (%)		Acceptance Bounds (%)
Cmax	Upper	120.2	143
	Lower	87.1	70
AUCt	Upper	121.2	125
	Lower	96.6	80

According to the study plan if an animal vomits up to the 3 hours sampling point, then it is excluded from bioequivalence determination. However, also dogs with diarrhoea have been excluded from calculations of the 90% confidence intervals, resulting in a final 18 evaluable animals for the study. The analysis in the table 4.4 shows bioequivalence between the test and reference product. Despite the high number of animals excluded, which may hamper the study reliability, the analysis supports bioequivalence between the test and reference product (table 4.4). The applicant does not appear to have calculated the sample size as the "minimum number of animals" needed to perform bioequivalence analysis. Considering the recommendations set in the VICH bioequivalence guideline (VICH GL52), a minimum of 12 evaluable animals should be included per treatment. For a crossover study, this implies that at least 6 animals per sequence should be included, thus the analysis conducted with 18 animals can be accepted.

When comparing individual plots in the study 1 report it is seen that plasma concentrations are clearly decreased in case the animal had vomited or suffered from diarrhoea. Vomiting occurred both after the administration of the test and reference product in Periods 1 or 2. Diarrhoea was seen in four animals after administration of the reference product. For animals that did not vomit or suffer from diarrhoea, the plasma concentration time curves were similar for the test and reference product. The study was poorly designed as so many animals had to be excluded from the analysis due to vomiting. Due to the high exclusion rate due to vomiting, the additional animals with outlying bioavailability results due to diarrhoea likely led to a failed study. Although bioequivalence could not be concluded in the pre-specified analysis, the bioavailability is similar for the test and reference product in the absence of vomiting/diarrhoea. It is reasonable to assume, that bioequivalence could have been shown if fewer animals had been excluded from the study.

Although reliability of the study was questioned given the high animal exclusion, the applied product Emevet 60 mg chewable tablet can be considered bioequivalent with the reference product Cerenia 60 mg tablets at a dose of 8 mg/kg. The applicant's justification for conducting the study in fasting state instead of light meal is acceptable.

Study 2

The design of the study was a single-dose, randomised, two-period, two-sequence, laboratory blind cross-over study balanced in relation to body weight and sex. The dogs (n=36) received either the test product Emevet 24 mg chewable tablets or reference product Cerenia 24 mg tablets after an overnight fast of at least 12 hours. Animals with 8.1 – 12.0 kg received one tablet (24 mg) of the test or reference product, and animals in the bodyweight range 12.1 – 17.0 kg received two tablets (48 mg). This dose corresponded to 2.0 – 3.3 mg of maropitant per kg, which is the recommended dose for the prevention of nausea induced by chemotherapy and treatment and prevention of vomiting (except motion sickness) and is considered acceptable. A wash-out period of 7 days was held between the treatments.

Plasma samples were analysed for concentrations of maropitant by an appropriately validated LC-MS/MS method. The lower limit of quantitation was (LLOQ) 0.5 ng/ml. Sample stability is considered to have been adequately investigated in terms of storage, and the stability of the samples at the time of analysis can be assured.

Non-compartmental methods were used for evaluation of the pharmacokinetic parameters. Analysis of variance (ANOVA) was performed using ln-transformed AUC_t and C_{max} parameters. The statistical design was appropriate and in line with relevant guidelines. The applicant specified that bioequivalence could be concluded if the 90% confidence interval for the ratio of the means of AUC was included within interval 80 – 125% and if the 90% confidence interval for the ratio of the means of C_{max} was included within interval 70% – 143%.

Results

The pivotal parameters to demonstrate bioequivalence between test product Emevet and reference product of maropitant were AUC_t and C_{max}. The dogs, No. 1, 23, 27 and 33, with significant vomiting within 3 hours after administration were excluded from evaluation of bioequivalence. Mean values (±SD) without excluded animal are presented below:

Table 4.6. Mean pharmacokinetic Parameters of Maropitant after Oral Administration (24 mg) (n=32)

Parameter	Test product		Reference product	
	Mean	**SD**	**Mean**	**SD**
C_{max} (ng/mL)	139.36	62.81	142.01	62.57
AUC_t (ng.hr/mL)	838.93	436.49	839.92	483.99
AUC_i	856.39	434.71	854.63	482.08
T_{max}	2.0 *	1.0-3.0**	1.5*	1.0-3.0**
$t_{1/2}$	5.29	2.26	4.94	1.46
Residual area	2.41	2.81 (0.19-16.23)**	2.14	1.51 (0.25-6.24)**

*median, ** range

The assessment of bioequivalence was based upon 90% confidence limits for the ratio of the geometric means of the candidate and reference products which fell within the pre-stated acceptance bounds of 70 – 143% and also the standard bounds 80% - 125% for C_{max} and 80% - 125% for AUC_t.

Table 4.7. Calculated 90% Confidence Limits for the Treatment Effect Ratio of Test and Reference product (n=32)

Parameter	90% Confidence Limits (%)		Acceptance Bounds (%)
C_{max}	Upper	110.2	143

	Lower	86.1	70
AUCt	Upper	111.5	125
	Lower	90.5	80

Based on the results from study 2, it can be accepted that the 24 mg strength Emevet is bioequivalent to the 24 mg strength reference product, at a dose of 2 mg of maropitant/kg.

Biowaiver

In vivo bioequivalence studies have been performed with test product Emevet at 24 mg and 60 mg maropitant strengths. For the lower strength (16 mg) and higher strength (160 mg), the applicant claims a biowaiver based on '7.2. Comparison between strengths in line with the Guideline on the conduct of bioequivalence studies (EMA/CVMP/016/2000-Rev.4*). The biowaiver is justified if all the following conditions are fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process;

b) the qualitative composition of the different strengths is the same;

c) the composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths;

d) appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing;

Points a, b and c are fulfilled for biowaiver. In addition, dissolution studies between the different strengths (16 mg, 24 mg, 60 mg and 160 mg) have been presented at three pHs in accordance with the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4*), and the results are considered acceptable. The biowaiver for the strengths 16 mg and 160 mg can be accepted, based on data provided with the 24 mg and 60 mg strengths used in the bioequivalence studies.

In conclusion, bioequivalence was demonstrated *in vivo* between the test product Emevet (24 mg chewable tablets) and the reference product (24 mg tablets) at a maropitant dose of 2 mg/kg. Bioequivalence was also seen for the 60 mg strength tablet when vomiting animals and those suffering from diarrhoea were excluded after the formulation was administered at a maropitant dose of 8 mg/kg. The dissolution data shows that all the formulations (16 mg, 24 mg, 60 mg and 160 mg) are similar in three different pHs. Despite the non-proportional pharmacokinetics of maropitant (AUC increases more than proportionally with increasing dose), no difference was seen after different doses used in the presented *in vivo* bioequivalence studies (24 mg and 60 mg), supporting that these are equivalent with each other. Thus, despite the flaws in the conduct of Study 1, the bioequivalence of the 60 mg strength between the test and reference product, with exclusion of animals vomiting and suffering from diarrhoea, can be accepted when taking into the consideration the totality of the data.

The bioequivalence between the test product and Emevet and the reference product is considered to have been demonstrated for all product strengths.

Dose determination and confirmation

Dose justification

No data have been presented.

Given that bioequivalence with a suitable reference product is accepted and the proposed posology for the test product Emevet is the same as that of the reference product, the omission of dose determination and confirmation data is considered acceptable. The same text as that already approved for the reference product has been proposed for inclusion in section 3.9 of the SPC, which is considered acceptable.

Tolerance in the target animal species

No data have been presented.

It can be accepted that the test and reference product formulations are of the same pharmaceutical forms (chewable tablet and tablet) and are intended for use in the same manner (oral administration) to the same target species (dogs) for the same indications and at the same dose rate. The test and reference product tablet formulations are qualitatively and quantitatively comparable in respect of the active substance. The formulation of the test product Emevet slightly differs in excipient composition, but all excipients used are common and well-known excipients in pharmaceutical products and are not expected to pose any safety issues. Consequently, no difference in tolerance between test and reference formulations is anticipated.

Considering the above and as bioequivalence is accepted, the omission of data in support of tolerance in the target animal species is considered acceptable.

Clinical trial(s)

No data have been presented.

Given that bioequivalence with a suitable reference product is accepted, the omission of clinical trials is acceptable. The same text as that already approved for the reference product has been proposed for inclusion in section 3.9 of the SPC, which is considered acceptable.

Overall conclusions on efficacy

This application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 – a generic application.

In accordance with Article 18 of Regulation (EU) 2019/6, the applicant has cited a suitable reference product 'Cerenia 24 mg tablets for dogs' and has demonstrated bioequivalence of the test product Emevet with this reference product by means of two pivotal *in vivo* bioequivalence studies in the target species (dogs). Studies were conducted with the chewable tablet formulations (24 mg strength and 60 mg strength). Bioequivalence for the 16 and 160 mg strengths has been supported by means of *in vitro* dissolution study data.

Pharmacology

Please refer to Part 3.

Pharmacokinetics

Please refer to Part 3.

Bioequivalence

Two *in vivo* bioequivalence studies were conducted in beagle dogs. The first study was performed with the test product Emevet 60 mg chewable tablets and the reference product Cerenia 60 mg tablets (8 mg/kg) in fasting state. Due to abundant vomiting and diarrhoea in the test animals a second bioequivalence study was performed with a lower strength and dose, using the test product Emevet 24 mg chewable tablets and the reference product Cerenia 24 mg tablets (2 mg/kg) in fasted dogs.

Bioequivalence is considered demonstrated between the test product Emevet 24 mg chewable tablets and reference product, Cerenia 24 mg tablets, at the lower recommended dose of 2 mg maropitant/kg. Bioequivalence is also considered demonstrated for the 60 mg formulation, administered at the highest recommended dose of 8 mg maropitant/kg, after exclusion of vomiting animals and those suffering from diarrhoea.

In vitro dissolution data has been provided to allow extrapolation of data from the *in vivo* bioequivalence studies (using the 24 mg and 60 mg strengths) to the remaining strengths (16 mg and 160 mg). Based on the data provided, the biowaiver for the 16 mg and 160 mg strengths of Emevet is considered acceptable.

Therefore, bioequivalence for all strengths (16 mg, 24 mg, 60 mg and 160 mg) of the test product Emevet and the reference product is considered to have been demonstrated.

As bioequivalence between the proposed generic product and the reference product has been claimed and accepted, the omission of dose determination, tolerance in the target animal species and clinical data is acceptable.

Part 5 – Benefit-risk assessment

Introduction

Emevet is a chewable tablet containing the antiemetic maropitant, a well-known active substance.

The product is available in four strengths, 16mg, 24mg, 60mg and 160mg and is intended for use in dogs for the following indications:

- Prevention of nausea induced by chemotherapy in dogs.
- Prevention of vomiting induced by motion sickness in dogs.
- Prevention and treatment of vomiting, in conjunction with maropitant solution for injection and in combination with other supportive measures in dogs.

The application has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 – a generic application.

Benefit assessment

Direct benefit

As bioequivalence with the reference product has been claimed, and this is satisfactorily demonstrated, Emevet is expected to be as efficacious as the reference product and therefore, beneficial in the following indications:

- Prevention of nausea induced by chemotherapy in dogs
- Prevention of vomiting induced by motion sickness in dogs
- Prevention and treatment of vomiting, in conjunction with maropitant solution for injection and in combination with other supportive measures in dogs

when administered at the same dose, route of administration and dosing interval as recommended in the marketing authorisation for the reference product.

Additional benefits

Chewable tablet formulation could help administration of the product to some animals and thus improve treatment compliance. Additionally, this generic veterinary medicinal product would provide an alternative product on the market and thus could improve availability.

Risk assessment

Quality

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.

Safety

The risks associated with the use of Emevet chewable tablets are expected to be the same as those associated with the reference product. Emevet is not expected to present an unacceptable risk to the target animal, user or environment when used as recommended and in accordance with the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: "Prevention of nausea induced by chemotherapy in dogs. Prevention of vomiting induced by motion sickness in dogs. Prevention and treatment of vomiting, in conjunction with maropitant solution for injection and in combination with other supportive measures 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 data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Emevet 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.