



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 July 2024
EMA/341805/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Cepeloron (EMA/V/C/006254/0000)

INN: Spironolactone

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



Table of contents

Introduction	4
Part 1 - Administrative particulars	4
Summary of the Pharmacovigilance System Master File	4
Manufacturing authorisations and inspection status	4
Overall conclusions on administrative particulars	5
Part 2 - Quality	5
Composition	5
Containers and closure system	5
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.....	9
Overall conclusions on quality.....	10
Part 3 – Safety documentation (Safety tests)	11
Safety tests.....	12
Pharmacology.....	12
Toxicology	12
Other requirements.....	12
Excipients	13
User safety	13
Environmental risk assessment.....	14
Overall conclusions on the safety documentation: safety tests.....	14
Part 4 – Efficacy.....	15
Pre-clinical studies	16
Pharmacology.....	16
Dose determination and confirmation	18
Tolerance in the target animal species.....	18
Clinical trial(s).....	19
Overall conclusions on efficacy	19
Part 5 – Benefit-risk assessment	20
Introduction	20
Benefit assessment	20
Direct benefit	20
Additional benefits	21
Risk assessment	21
Risk management or mitigation measures.....	21

Evaluation of the benefit-risk balance21

Conclusion21

Introduction

The applicant CP-Pharma Handelsgesellschaft mbH submitted on 22 May 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Cepeloron, 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 18 January 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:

Treatment of congestive heart failure caused by degenerative mitral valve disease, in combination with standard therapy (including diuretic support, where necessary) in dogs.

The active substance of Cepeloron is spironolactone, an aldosterone antagonist, natriuretic drug, which inhibits the aldosterone-induced sodium retention leading to an increase in sodium and subsequently water excretion and potassium retention.

Cepeloron chewable tablets contain 10 mg, 40 mg or 80 mg of spironolactone and are presented in packs containing 10 tablets, 30 tablets, 50 tablets or 100 tablets.

The rapporteur appointed is Paul McNeill and the co-rapporteur is Anna Wachnik-Świącicka.

The dossier has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 (a generic application) for the 10 mg strength and Article 19 of Regulation (EU) 2019/6 (a hybrid application) for the 40 mg and 80 mg strengths.

On 18 July 2024, the CVMP adopted an opinion and CVMP assessment report.

On 12 September 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Cepeloron.

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, quality control testing, primary packaging, secondary packaging and storage and/or distribution of the active substance spironolactone takes place outside of 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 on-site audit by a third party.

Finished product

Manufacture of the dosage form, quality control testing (chemical/physical), primary and secondary packaging of the finished product takes place within the EEA. The site has an up to date GMP certificate by the corresponding competent authority which is available in EudraGMDP. The certificate confirms the date of the last inspection and shows that the site is authorised for the activities indicated above.

Batch release (certification) of the finished product takes place at CP-Pharma Handelsgesellschaft mbH, Germany. The site has a manufacturing authorisation issued on 6 January 2022 by the competent authority of Germany. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the activities indicated above, is available in EudraGMDP.

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

The products are off-white to light brown chewable tablets with brown spots. They are round and convex in shape and bear a cross-shaped break line on one side. The tablets contain either 10 mg, 40 mg or 80 mg of the active substance spironolactone. The other ingredients are lactose monohydrate, microcrystalline cellulose, sodium laurilsulfate, crospovidone, type A, silica colloidal hydrated, magnesium stearate, chicken flavour and dried yeast.

The product is presented in blisters consisting of a top foil constructed from oPA/Alu/PVC and a bottom foil made from aluminium, placed in a cardboard box.

The pack sizes are consistent with the dosage regimen and duration of use.

Containers and closure system

The primary packaging is blisters consisting of a top foil constructed from oPA/Alu/PVC and a bottom foil made from aluminium. The material of the top foil complies with the EU Regulation 10/2011 and its amendments and the contact PVC film additionally complies with Ph. Eur. 3.1.11 "Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration" and Ph. Eur. 3.2.2 "Plastic containers and closures for pharmaceutical use". The aluminium bottom foil complies with the EU Regulations 1895/2005, 1935/2004, 2023/2006 and 10/2011. Technical drawings of the container-closure system are provided in the dossier.

Each blister strip contains 10 tablets. Blisters are packaged in a cardboard box. Each cardboard box contains 10, 30, 50 or 100 tablets per box.

The choice of the container closure system has been demonstrated by stability data to be adequate for the intended use of the product.

Product development

Cepeloron 10 mg chewable tablets for dogs has been submitted as a generic application in accordance with Article 18 of Regulation (EU) 2019/6 and Cepeloron 40 mg and 80 mg chewable tablets for dogs have been submitted as hybrid applications in line with Article 19 of Regulation (EU) 2019/6. The reference product cited in this application, and with which bioequivalence of the 10 mg tablet is claimed by means of an in vivo bioequivalence study, is Prilactone Next 10 mg chewable tablets for dogs (MAH Ceva Santé Animale; authorised by decentralised procedure on 15 June 2012). Whilst the reference product is also available in 50 mg and 100 mg strengths, equivalent strengths of the reference product do not exist for the remaining strengths of the candidate formulation, Cepeloron 40 mg chewable tablets for dogs and Cepeloron 80 mg chewable tablets for dogs, and as such, dissolution data have been provided to demonstrate in vitro equivalence for the 40 mg and 80 mg tablet strengths.

Formulation development for the candidate products is based on the formulation of the reference product. Information on the reference product SPC allowed the applicant to determine the qualitative composition of the reference product with respect to excipients. The excipient profile of the candidate product is qualitatively similar to that of the reference product, with the exception of 'silica, colloidal hydrated' used in the generic products as opposed to 'silica, colloidal anhydrous' used in the reference product and an additional excipient 'maltodextrine' which is omitted from the candidate products. Additionally, the generic formulation includes 'cellulose, microcrystalline' and not 'cellulose, silicified microcrystalline' as per the reference product. A series of trial batches were manufactured in order to optimise excipient quantities in the formulation and to develop the manufacturing process. The information provided on the formulation development demonstrates that an optimal final formulation has been achieved with a dissolution profile highly comparable to the reference product.

The tablets are to be manufactured in a process involving dry mixing, dry granulation and compression. The suitability of this process was established during the manufacture of the development batches based on satisfactory physical, chemical and dissolution properties.

Parameters liable to affect bioavailability such as particle size and polymorphism of the active substance have been addressed and are considered adequately controlled.

As part of the development pharmaceuticals, the development of the dissolution method for quality control testing is described. The dissolution method is considered to have been satisfactorily developed and its discriminatory power has been demonstrated. The specification limit for dissolution at time of release and shelf-life has been set with reference to results obtained for dissolution using the biobatch and as such is in line with the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017).

Bioequivalence with the 10 mg strength of the reference product has been demonstrated for Cepeloron 10 mg chewable tablets in an in vivo bioequivalence study presented in Part 4 of the dossier. In vitro dissolution studies were used to extrapolate the in vivo bioequivalence findings for the 40 mg tablet strength and the 80 mg tablet strengths (see Part 4).

The tablets are described as 'chewable tablets' and whilst no justification is provided with respect to why the tablets can be considered 'chewable', given that the reference product is also described as

chewable and in the absence of any confirmative tests prescribed by the Ph. Eur. no further information is required.

The tablets bear a break line on one side to enable accurate dosing of both half and quarter fractions. Compliance with the test on subdivision of tablets in the Ph. Eur. dosage form monograph has been suitably demonstrated.

Compatibility of the finished product with the container-closure system is demonstrated by the supporting stability data.

Description of the manufacturing method

The finished products are chewable tablets which are manufactured in a dry granulation process involving the preparation of a pre-blend which is granulated and finally compressed into tablets. The process is considered to be a standard manufacturing process. The proposed commercial batch size range of the powder blend and a calculation for potency adjustment is provided.

The manufacturing process is adequately described providing sufficient detail of all the different steps and process parameters.

In-process controls (IPCs) are defined for the mixing, tableting and packaging stages of the manufacturing process. The IPCs and limits are adequate for the manufacture of tablets using a dry granulation followed by compression process and are based on available supporting batch data and/or Ph. Eur. requirements.

The manufacturing process (including all listed in-process control tests) has been validated using two consecutive batches of powder blend from which tablets of each strength have been manufactured. This meets the requirements for solid oral dosage forms as specified in the Guideline on process validation for finished products – information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev 1, Corr.1). The process validation report includes results for tests carried out on the powder blend and tests carried out during both the tableting and blistering process. All results comply with specifications and demonstrate that the manufacturing process is capable of producing a finished product of intended quality in a reproducible manner.

An appropriate hold time for the bulk tablets has been set. Acceptable results from the validation of the hold time have been provided.

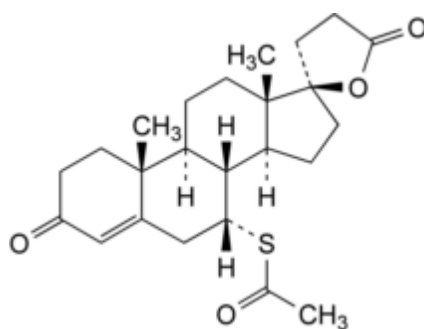
Control of starting materials

Active substance

The active substance is spironolactone Ph. Eur.

The chemical names of spironolactone is 4-Hydroxy-2-methyl-*N*-(5-methylthiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamine 1,2-dioxide and *S*-[2'*R*]-3,5'-Dioxo-3',4'-dihydro-5'*H*-spiro[androst-4-ene-17,2'-furan]-7*α*-yl] ethanethioate.

Spironolactone has the following structure:



Spironolactone is a white or yellowish-white powder, practically insoluble in water and soluble in ethanol (96%).

Polymorphism has been observed for the active substance. Using XPRD analysis it has been demonstrated that the same polymorphic form of spironolactone is consistently produced by the proposed active substance supplier. Active substance polymorphic form is controlled in the dossier.

There is a monograph of spironolactone in the Ph. Eur. The finished product manufacturer sources the active substance from a single manufacturer. The manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for spironolactone, 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.

Additional specifications have been set for residual solvents and particle size. The specifications for residual solvents are consistent with those listed on the CEP. Non-compendial methods have been adequately validated and described according to VICH GL1: *Validation of analytical procedures: definition and terminology* and VICH GL2: *Validation of analytical procedures: methodology*. The CEP indicates the acceptable re-test period when stored in specific containers.

The working standard used for the analysis of spironolactone is the same standard as used in the finished product.

Certificates of analysis are provided for three batches of active substance manufactured by the active substance supplier. These batches were tested by both the CEP holder and by the dosage form manufacturer with results demonstrating consistency and compliance with the requirements of the active substance specification.

Excipients

The product excipients consist of a number of well-known pharmaceutical ingredients whose quality is compliant with Ph. Eur. Additional parameters are controlled in the case of cellulose microcrystalline, lactose monohydrate and magnesium stearate. A control of microbial quality is not performed for every excipient, however, where absent these excipients are present in low amounts and as such omission of microbial control is considered justified for a product of this nature.

The two flavouring agents, yeast and chicken flavour comply with in-house specifications which are acceptable. Higher limits for microbial purity than specified in Ph. Eur. 5.1.4 for substances for pharmaceutical use are suitably justified for both non-pharmacopoeial excipients. A declaration is provided that the chicken flavour is permitted for use in the EU according to Regulation (EC) No 1334/2008, Regulation (EC) No 2065/2003 and Regulation (EC) No 1333/2008.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

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

With the exception of lactose monohydrate, the product does not contain any materials derived from human or animal origin.

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.

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, diameter, tightness of blister, average mass, uniformity of dosage units (content uniformity, Ph. Eur.), resistance to crushing (Ph. Eur.), friability (Ph. Eur.), loss on drying (Ph. Eur.), active substance identification, related substances, dissolution, and microbial purity.

The proposed specifications for release are acceptable, and whilst the tablet appearance for all strengths are described as "Off-white to light brown, with brown spots, round and convex" the applicant has proposed different coloured packaging and a large prominent declaration of tablet strength on the labelling to avoid the end user mistaking the different strengths.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the CVMP guidance on risk management requirements for elemental impurities in veterinary medicinal products. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines where applicable. Information regarding the reference standards used for assay testing has been presented and deemed suitable.

Certificates of analysis are provided for 2 batches of powder blend, compressed into all three strengths, 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. The parameters tested are the same as those proposed at release with the following differences: Tightness of blister, uniformity of dosage units and identification of spironolactone are included on the shelf-life specification but for the purposes of marketplace testing only which is acceptable as these tests are not considered as stability indicating. Tests for subdivision of tablets and resistance to crushing are additional tests added to the shelf-life specification to only be performed on the first two validation batches.

Stability data were provided for batches of the 10 mg and 80 mg tablet strengths, stored under long term conditions for 24 months at 25 °C/60% RH and for up to 6 months under accelerated conditions at 40 °C/75% RH according to the VICH GL3 *Stability testing of new veterinary drug*

substances and medicinal products. The batches are identical to those proposed for marketing and 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 specification limits. Results for microbial quality complied with requirements when tested at the initial and the 18-month time-point under long-term conditions and at the initial and 6-month time-point under accelerated conditions. No increasing trend was observed in loss on drying results.

An in-use stability study was performed to simulate a “worst-case” scenario with respect to tablet exposure and no precautionary storage statement is considered necessary. Results from a photostability study show that the product packaging can be considered to impart sufficient protection from light and inclusion of a warning, of this nature, on the SPC and product literature is not considered necessary.

Based on the available stability data, the proposed shelf-life of 36 months is supported.

Overall conclusions on quality

The finished product is presented as a chewable tablet containing spironolactone as the active substance at a concentration of 10 mg/tablet, 40 mg/tablet or 80 mg/tablet.

The product is presented in blisters constructed of top foil made from oPA/Alu/PVC and a bottom foil made from aluminium. One blister strip contains 10 tablets and each blister strip is placed into cardboard boxes with 1, 3, 5 or 10 blister strips per box.

Formulation development for the candidate products is based on the formulation of the reference product ‘Prilactone Next 10 mg chewable tablets for dogs’ as authorised in the EU. The candidate tablets are qualitatively similar to the reference products, with reference to publicly available information on the SPC of the reference products. Pharmaceutical development trial batches were manufactured to optimise the formulation quantitatively with respect to excipients and also allowed evaluation of dry mixing, dry granulation and compression as the method of manufacture. Data has been presented which demonstrates that the dissolution test has been satisfactorily developed and is supported by the demonstration of the discriminatory power of the dissolution assay.

The manufacturing process is considered to be a standard process and involves dry mixing of product ingredients to obtain a pre-blend which is granulated and finally compressed into tablets. A comprehensive description of the manufacturing process has been provided and in-process controls have been proposed and are considered adequate. The manufacturing process has been satisfactorily validated using two consecutive batches of powder blend from which tablets of each strength have been manufactured. A commitment to carry out process validation on larger batch sizes at time of manufacture is provided and any scale-up required changes to critical process parameters will be registered by way of variation with appropriate supporting data.

Information on the control of starting materials has been provided. The active substance spironolactone is monographed in Ph. Eur. and data on the active substance is provided by way of a Certificate of Suitability of the European Pharmacopoeia (CEP). The dossier includes a specification for spironolactone applied at the dosage form manufacturing site. The specification demonstrates compliance with the Ph. Eur. monograph for spironolactone and includes additional acceptance criteria for particle size and residual solvents. The product excipients consist of a number of well-known pharmaceutical tableting excipients whose quality is compliant with Ph. Eur. In addition, the flavouring agents, chicken flavour and yeast, comply with in-house specifications.

With the exception of lactose monohydrate, the product does not contain any materials derived from human or animal origin. The lactose monohydrate has been declared to be produced from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption.

The specifications proposed at release are appropriate to control the quality of the finished product. Non-routine control of microbiological quality is proposed and considered acceptable. The analytical methods have been described and validated in accordance with the VICH guidelines. Batch analysis results are provided for 2 batches of powder blend, compressed into all three strengths, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The specifications proposed at the end of shelf-life are appropriate to control the quality of the finished product. The parameters tested and limits differ somewhat to those proposed at release.

Stability data for 2 batches of the 10 mg and 80 mg tablet strengths has been provided for studies conducted under VICH long term and accelerated storage conditions. The 40 mg tablet strength is omitted from stability studies by way of a bracketing approach. Results across both VICH stability storage conditions are within the proposed shelf-life specification. An in-use stability study was performed to simulate a "worst-case" scenario with respect to tablet exposure. Based on the available stability data, the proposed shelf-life of 36 months is accepted without any storage warnings.

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner.

Part 3 – Safety documentation (Safety tests)

This application has been submitted in accordance with Articles 18 (10 mg tablet – generic application) and 19(1) (40 mg and 80 mg tablets – hybrid, change in strength) of Regulation (EU) 2019/6.

The active substance in Cepeloron chewable tablets is spironolactone, an aldosterone antagonist. Spironolactone is a natriuretic drug. In the kidney, spironolactone inhibits aldosterone-induced sodium retention, thereby leading to an increase in sodium and subsequently water excretion, and potassium retention. The renal effects of spironolactone and its metabolites lead to a decrease in extracellular volume and consequently to a decrease of cardiac preload and left atrial pressure. The result is an improvement of heart function.

The cited reference product is "Prilactone Next 10 mg chewable tablets for dogs" (Ceva Santé Animale), which was first granted a marketing authorisation following a decentralised procedure on 15 June 2012 based on a full dossier. Therefore, Prilactone Next 10 mg chewable tablets for dogs is accepted as a suitable reference product for this application. Prilactone Next chewable tablets are authorised and marketed in three different strengths: 10 mg, 50 mg and 100 mg (that is, the middle and higher strengths of the candidate product are different to those of the reference product).

The applicant claims bioequivalence between the 10 mg chewable tablet formulation of the candidate veterinary medicinal product and the corresponding strength of the reference product, based on the results of an in vivo bioequivalence study. Extrapolation of the results of this study to the 40 mg and 80 mg formulations is also claimed based on in vitro dissolution study data.

Safety tests

Pharmacology

Pharmacodynamics

No new pharmacodynamic data have been provided. Given that bioequivalence with the reference product can be accepted and that the product is intended to be administered to the same target species, for the same indications, at the same posology and using the same route of administration as the reference product, the pharmacodynamics of spironolactone in the target species are not expected to differ between the candidate and reference formulations and, consequently, the omission of pharmacodynamic data can be accepted. The applicant proposes to include the same text under section 4.2 of the SPC as that included in the equivalent section of the SPC for Prilactone Next 10 mg chewable tablets for dogs.

Pharmacokinetics

The applicant has conducted an in vivo bioequivalence study in the target species, dogs, in which bioavailability of the candidate product is compared to Prilactone Next 10 mg chewable tablets for dogs using the lower strength (10 mg) tablet of the candidate product. In vitro dissolution studies were also conducted to demonstrate equivalence for the 40 mg and 80 mg strengths of the candidate formulation. Please refer to Part 4 for assessment of these studies. Based on the results obtained in the in vivo and in vitro studies, bioequivalence is claimed.

The applicant proposes to include the same text under section 4.3 of the SPC as that included in the equivalent section of the reference VMP SPC.

Toxicology

No data relating to the toxicological profile of the product have been provided as bioequivalence with the reference product has been claimed. Given the legal basis of this application and given that bioequivalence between Cepeloron and the reference product can be accepted, the omission of toxicological data can be accepted.

Other requirements

Special studies

No data was presented. Given the legal basis of this application and given that bioequivalence between candidate and reference products can be accepted, there is no requirement for the applicant to provide 'special studies' specific to the candidate formulation.

Regarding the potential for the candidate product to have local effects in the event of dermal or ocular exposure, it is noted that:

- the candidate and reference formulations contain the same or comparable concentrations of active substance (spironolactone);
- the candidate and reference formulations contain comparable excipients; and

- those excipients included in the candidate formulation that are not included in the reference formulation (cellulose microcrystalline and silica colloidal hydrated) are considered safe at the concentrations used and are considered to have limited irritation or sensitisation potential.

Therefore, the omission of additional data on potential local effects (dermal and ocular irritation as well as sensitisation) of the candidate formulation specifically can be accepted. That said, it is noted that spironolactone, while non-irritating, has the potential to cause skin sensitisation (based on the user safety warnings agreed for the reference product). The same user warnings and risk mitigation measures are proposed for inclusion under section 3.5 of the proposed SPC as for the reference product. This is considered appropriate.

Observations in humans

Spironolactone is used in human medicine as an anti-diuretic. The applicant refers to the SmPC of an authorised human medicinal product which has the following therapeutic indications: congestive cardiac failure, hepatic cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, and in the diagnosis and treatment of primary aldosteronism. Dose rates in adults vary from 25–400 mg/day, while it is recommended that paediatric patients receive an initial daily dose of 1–3 mg/kg bw/day, and only under the guidance of a paediatric specialist. It is noted that the most frequently reported adverse effect observed with use of the tablets in humans is hyperkalaemia.

Warnings have been included in section 3.5 of the proposed SPC regarding the potential for hypersensitivity reactions, and the measures to be taken (urgent medical attention) in the event of such a reaction occurring, which is considered to be appropriate.

Excipients

The candidate and reference formulations differ qualitatively and quantitatively in terms of the included excipients, with the candidate formulations containing cellulose, microcrystalline and silica, colloidal hydrated while the reference product contains cellulose, silicified microcrystalline and silica, colloidal anhydrous as well as maltodextrine. All excipients used in the candidate product, with the exception of chicken flavour and dried yeast, are of Ph. Eur. standard. It is accepted that the excipients proposed for inclusion in the candidate formulations can be considered as safe at the concentrations used.

User safety

A brief user safety assessment was provided.

It can be accepted that Cepeloron and the reference formulation are of the same pharmaceutical form (tablet) and are intended for administration in the same manner (oral administration) to the same target species (dogs) for the same indications and at the same dose rate.

Furthermore, the candidate and reference formulations are qualitatively and quantitatively comparable in respect of the active substance, spironolactone. The candidate veterinary medicinal product does, however, differ from the reference product with regard to excipient composition. These differences are not expected to present a change to the user risk profile of the candidate formulation, as all excipients are commonly used in pharmaceutical products.

In addition, it is noted that the candidate product is presented in aluminium foil blister packs in an

outer container (that is, similar to the reference product).

In light of the above, no difference in exposure to candidate and reference formulations is anticipated, and the CVMP considers that a full user safety assessment (in accordance with current guidance) specific to the candidate product to be unnecessary in this instance, as the risk posed to the user by the candidate product is not expected to differ from that posed by the reference product. The same user safety warnings as approved by for the reference product have been proposed for Cepeloron, and this is considered appropriate. Regarding the risk to children specifically (from ingestion of full or part-used tablets), it is noted that the product will be packaged in aluminium foil blisters in an outer carton, and that the labelling will include warnings to store out of sight and reach of children.

Provided the product is stored, handled, administered, and disposed of in accordance with the recommendations included in the proposed SPC, it can be accepted that the candidate VMP will not present an unacceptable risk to the user.

Environmental risk assessment

An environmental risk assessment has been provided in accordance with VICH GL6 on environmental impact assessments for veterinary medicinal products - Phase I (CVMP/VICH/592/98-Final) and 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 applicant has followed the phase I decision tree outlined in VICH GL6 and concludes that the environmental risk assessment can stop at question 1, as the candidate VMP is exempt from this requirement in accordance with Article 18(7) of Regulation (EU) 2019/6. The reference veterinary medicinal product, Prilactone Next 10 mg chewable tablets for dogs, has been authorised in the Union since June 2012. On this basis, the applicant's conclusion is considered to be acceptable.

Furthermore, based on question 3 of the decision tree outlined in VICH GL6, the candidate VMP is intended only for use in non-food-producing animals, and so the ERA can stop at Phase I.

As is the case for the reference product, no specific environmental warnings are considered necessary and the standard text relating to disposal of unused product is proposed for inclusion in the SPC of the candidate product and this is considered acceptable. It can be accepted that the candidate formulation 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

This application has been submitted in accordance with Articles 18 (10 mg tablet – generic application) and 19(1) (40 mg and 80 mg tablets – hybrid, change in strength) of Regulation (EU) 2019/6.

In this application, a suitable reference product, Prilactone Next 10 mg chewable tablets for dogs, has been cited, and comparative bioavailability between the candidate and reference veterinary medicinal products has been investigated by means of an in vivo bioequivalence study and in vitro dissolution studies. The applicant claims bioequivalence between the candidate and reference VMPs.

It can be accepted that the candidate and reference formulations are of the same pharmaceutical form (tablet) and are intended for administration in the same manner (oral administration) to the same target species (dogs) for the same indications and at the same dose rate.

The candidate and reference formulations are qualitatively and quantitatively comparable in respect of the active substance, spironolactone. The candidate veterinary medicinal product does, however, differ from the reference product with regard to excipient composition. These differences are nonetheless not expected to present a change to user risk profile of the candidate formulation as all excipients used are commonly used and well-known excipients in pharmaceutical products.

Pharmacology:

No pharmacodynamic studies were presented. As bioequivalence between Cepeloron and the reference product can be accepted, the omission of this data is considered acceptable given the legal basis of the application. The text in sections 4.2 (pharmacodynamics) and 4.3 (pharmacokinetics) of the SPC is consistent with that of the reference product. This is considered acceptable.

Toxicology:

No data relating to the toxicological profile of the product have been provided. Given the legal basis of the application, this can be accepted.

User safety:

The applicant has conducted a brief user risk assessment in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1). Based on the similarities between Cepeloron and the reference product, no difference in exposure to the candidate formulation compared to the reference product is anticipated.

The risk posed to the user by Cepeloron is not expected to differ to that posed by the reference product. The same user safety warnings as approved for the reference product have been proposed for Cepeloron. This is considered appropriate. If the product is stored, handled, administered and disposed of in accordance with the recommendations included in the proposed SPC, it can be accepted that Cepeloron will not present an unacceptable risk to the user.

Environmental risk assessment:

An environmental risk assessment has been provided in accordance with VICH GL6 (CVMP/VICH/592/98-Final) and 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). It is concluded that the environmental risk assessment can stop at Phase I.

It can be accepted that the candidate formulation 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.

Part 4 – Efficacy

This application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 (generic veterinary medicinal product) for the 10 mg chewable tablet formulation, and Article 19(1) of regulation (EU) 2019/6 (hybrid - change in strength) for the 40 mg and 80 mg chewable tablet formulations.

Cepeloron chewable tablets are proposed for use in the target species dogs, with the following therapeutic indication:

“Treatment of congestive heart failure caused by degenerative mitral valve disease, in combination with standard therapy (including diuretic support, where necessary) in dogs.”

The proposed dose rate is 2 mg spironolactone/kg bodyweight once daily, orally. It is anticipated that the treatment will be lifelong.

The reference product cited is Prilactone Next 10 mg chewable tablets for dogs (Ceva Santé Animale), which was first granted a marketing authorisation following a decentralised procedure on 15 June 2012.

The candidate and reference formulations are of the same pharmaceutical form (chewable tablet) and are intended for the same route of administration (oral) to the same target species (dogs) for the same indications and at the same dose rate (2 mg spironolactone/kg bodyweight once daily). Furthermore, the candidate and reference 10 mg formulations are qualitatively and quantitatively the same in respect of the active substance, spironolactone, and the excipients proposed for the candidate product can be considered as safe at the concentrations included. The proposed 40 mg and 80 mg tablets are produced from the same common blend.

In accordance with Article 18 of Regulation (EU) 2019/6, a pivotal in vivo bioequivalence study in the target species, dogs, has been conducted using the 10 mg tablet strength (see below).

Pre-clinical studies

Pharmacology

Pharmacodynamics and pharmacokinetics

Please refer to Part 3.

Bioequivalence studies

The applicant has provided a well-designed, GLP-compliant in vivo bioequivalence study, which was conducted in accordance with the current CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4). The purpose of this study was to demonstrate bioequivalence between the reference veterinary medicinal product (Prilactone Next 10 mg chewable tablets for dogs) and the generic product (Cepeloron 10 mg chewable tablets for dogs) at the recommended dose of 2 mg spironolactone/kg bw.

The test item used in the in vivo bioequivalence study was the final formulation of the candidate VMP as intended for marketing.

The lowest (10 mg) strength tablets were used in the study. on the grounds that the study animals (Beagle dogs) weighed between 5.8 and 11.4 kg and therefore 2 or 3 of the 10 mg tablet strength is most appropriate for provision of a dose at or close to the recommended treatment dose of 2 mg spironolactone/kg bw.

A randomised, two-period, two-sequence single dose crossover study was performed, with a sufficiently long wash-out period. Administration of the test and reference items in the fed state was justified by the applicant on the grounds that feeding significantly increases the oral bioavailability of all measured metabolites resulting from treating dogs with spironolactone. As the products were

administered in a manner consistent with the SPC of the reference product, the approach used by the applicant is considered acceptable.

The number of study animals (n=24) was appropriate, and it can be accepted that the animals were clinically healthy and suitably representative of the target animal population. The animals were allocated to each of the test groups randomly and groups were balanced for bodyweight and gender.

The dose range of the candidate product and the reference product was identical, although it is noted that the recommended treatment dose of 2 mg/kg bw was exceeded for both test and reference items (actual dose administered ranged from 2.63-3.45 mg/kg bw). According to the aforementioned CVMP guideline, bioequivalence studies should be conducted at the highest labelled dose as significant formulation differences are more easily detected. Furthermore, the applicant states that linear pharmacokinetics apply to the 2 – 4 mg/kg bw dosing interval. This is supported by the EPAR for the Prilactone product, which states that the metabolites evaluated showed linear kinetics over the dose range 1 - 4 mg/kg bw and the clearance for both also remained constant, suggesting first-order kinetics over the dose range tested. As the recommended treatment dose approved for the reference product is 2 mg/kg bw, the approach to dosing used in this study is acceptable.

The sampling schedule was considered appropriate in that it allowed for a reliable estimate of the primary PK parameters, C_{max} and AUC.

The evaluation of bioequivalence was based upon measurement of the major metabolites of the active substance spironolactone (i.e. 7 α -thiomethyl-spironolactone and canrenone) in plasma, which is appropriate.

The applicant specified a priori that bioequivalence may be concluded if the 90% confidence interval for the ratio of the means of the parameter AUC_t are included within the interval 80 – 125%, and if the 90% confidence interval for the ratio of the means of the parameter C_{max} are included within the interval 70-143%. The applicant provided limited justification for the widened acceptance criteria for C_{max} , citing the potential for high, though clinically irrelevant variability of the parameter (from the SPC of the reference product). However, as both lower and upper bounds of the 90% CI for C_{max} of both measured metabolites (91.7 – 111% for 7 α -thiomethyl-spironolactone and 93.5 – 104% for canrenone) fell within the narrower standard acceptance limits of 80 – 125%, further discussion of the wider limits for C_{max} is unnecessary.

Significant treatment and period effects were observed for the AUC as determined for both 7 α -thiomethyl spironolactone and canrenone. The CVMP accepts the applicant's conclusion that these effects do not impact on the overall interpretation of the study. It is noted that a sequence effect was not detected.

The results of this study indicate that the 90% confidence intervals for the least-square mean differences (Test-Reference) of the ln-transformed means for both pivotal pharmacokinetic parameters lie within the pre-specified limits.

Therefore, based on the results of this study, it can be accepted that the test item Cepeloron 10 mg chewable tablets is bioequivalent to the 10 mg strength of the reference product Prilactone Next.

The applicant has presented a validation study report for the LC-MS/MS method used in the determination of the spironolactone metabolites. From the data provided, it appears that the applicant has used an appropriately validated LC-MS/MS method for the determination of two metabolites in canine plasma in accordance with the relevant guidelines: the method was found to be suitably selective, accurate and precise as well as being appropriately robust. 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.

In vitro dissolution data have been provided to permit extrapolation of the findings from the in vivo bioequivalence study conducted using the 10 mg tablet strength, to the higher strengths 40 mg and 80 mg tablets and this is considered acceptable given that the three strengths of the product are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and the composition of the strengths is quantitatively proportional.

Suitable buffers were selected in order to evaluate dissolution across a pH range relevant for the target species (pH 1.2, 4.5 and 7.5), which is acceptable.

In order to evaluate dissolution, a paddle apparatus was used, with 900 ml of dissolution medium, which is in accordance with current guidance. A paddle speed of 50 rpm was used, as recommended in the CVMP bioequivalence guideline. This is considered appropriate.

Twelve replicates of each product were evaluated for the comparison between 1 x 10 mg tablet and 1 x 40 mg tablet, and 1 x 10 mg and 1 x 80 mg tablet of the candidate formulation. As the calculated f_2 values were all less than 50, the applicant concludes that the dissolution profiles are not similar and that this is due to the fact that sink conditions were not achieved at all pH values 1.2, 4.5 and 7.5.

Following the guideline recommendations, the applicant has compared the dissolution profiles of the 40 mg and 80 mg strengths of the candidate product with the same dose of spironolactone using the 10 mg tablet candidate formulation (i.e. 4 tablets of 10 mg versus one tablet of 40 mg and 8 tablets of 10 mg versus one tablet of 80 mg). Based on the findings, it can be accepted that the low dissolution observed appears indeed to be active substance rather than formulation related.

However, it was noted that the range of the dissolution profile compared is rather limited and, therefore, the applicant subsequently conducted additional in vitro dissolution studies using a surfactant in order to better characterise the dissolution profiles. It can be accepted that the concentrations used permit the dissolution profiles to be satisfactorily characterised whilst retaining sufficient discriminatory power across the range of physiologically-relevant pH conditions.

Based on the results of these additional dissolution studies, it is accepted that the dissolution profiles of Cepeloron chewable tablets 40 and 80 mg are similar to the biobatch of the 10 mg tablet strength and therefore the findings of the in vivo bioequivalence study conducted using the 10 mg tablet strength may be extrapolated to the 40 mg and 80 mg tablet strengths.

Dose determination and confirmation

No data were presented, however given that bioequivalence with a suitable reference product has been demonstrated, and the proposed posology for the candidate product is the same as that of the reference product, the omission of dose determination and confirmation data is considered acceptable. The applicant has proposed to include largely the same text as that already approved for the reference veterinary medicinal product in section 3.9 of the SPC.

Tolerance in the target animal species

No data were presented.

Given that bioequivalence between the reference and candidate products can be accepted, the omission of data in support of tolerance in the target animal species, dogs, is considered acceptable.

Indeed, an acceptable tolerance profile was demonstrated in the in vivo bioequivalence study using the 10 mg tablet strength, where no treatment-related adverse events were noted after oral administration of the test or reference items.

It is noted in the reference product SPC that the adverse event prostatic atrophy is classified as 'often observed', while the applicant for the generic product has included this adverse event with the frequency descriptor 'common'. This is considered acceptable.

Clinical trial(s)

No data was presented.

Given that bioequivalence with the reference product, Prilactone Next, is accepted based on the results of an in vivo bioequivalence study between the 10 mg strengths of both the candidate and the reference products, the provision of clinical trial data is unnecessary as this can be extrapolated from the reference product. Bioequivalence between the different strengths of the candidate product is demonstrated via in vitro dissolution studies.

Overall conclusions on efficacy

This application has been submitted in accordance with Article 18 (10 mg strength tablet) and Article 19(1) (40 mg and 80 mg strength tablets) of Regulation (EU) 2019/6.

The applicant has cited a suitable reference product 'Prilactone Next 10 mg chewable tablets for dogs' and has demonstrated bioequivalence of the candidate product with this reference product by means of an in vivo bioequivalence study conducted using the 10 mg tablet strength. Bioequivalence for the higher 40 and 80 mg strengths has been supported by means of in vitro dissolution study data.

Pharmacology (pharmacodynamics and pharmacokinetics)

Please refer to Part 3.

Bioequivalence

A well-designed in vivo bioequivalence study that was conducted to GLP standard and was designed in accordance with current guidance (CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4)) is provided. The purpose of this study was to demonstrate bioequivalence between the reference product Prilactone Next 10 mg chewable tablets for dogs and the generic product Cepeloron 10 mg chewable tablets for dogs when administered at the recommended treatment dose of 2 mg spironolactone/kg bw.

The applicant used an appropriately validated LC-MS/MS method for the determination of spironolactone metabolites in canine plasma in accordance with the relevant guidelines.

Based on the findings of this study, the 10 mg strength of Cepeloron has been demonstrated to be bioequivalent to the equivalent strength of the reference product: the 90% confidence intervals for the ratio of the means of the parameters C_{max} and AUC_t are included within the interval 80 - 125%.

In vitro dissolution data have been provided in order to permit extrapolation of data from the in vivo bioequivalence study investigating the 10 mg tablet strength, to the 40 mg and 80 mg tablet formulations and results are considered acceptable.

In light of the above, bioequivalence between the candidate and reference products is considered to have been demonstrated.

Dose determination and confirmation

No data were presented, however given that bioequivalence with a suitable reference product has been demonstrated, and the proposed posology for the candidate product is the same as that of the reference product, the omission of dose determination and confirmation data is considered acceptable.

Tolerance in the target animal species

No data were presented. As bioequivalence with a suitable reference product has been demonstrated, the omission of data in support of tolerance in the target animal species, dogs, is considered acceptable.

Clinical trials

No data was presented. Given that bioequivalence between the reference and candidate products can be accepted, the provision of clinical trial data is unnecessary as this can be extrapolated from the reference product.

Part 5 – Benefit-risk assessment

Introduction

Cepeloron chewable tablets contain 10 mg, 40 mg, or 80 mg of spironolactone as active substance. The active substance is well-known.

Spironolactone is an aldosterone antagonist, natriuretic drug, which inhibits the aldosterone-induced sodium retention leading to increase in sodium and subsequently water excretion and potassium retention.

The product is intended for use in dogs for the treatment of congestive heart failure caused by degenerative mitral valve disease, in combination with standard therapy (including diuretic support, where necessary). The proposed effective dose of 2 mg spironolactone/kg bw once daily, administered orally, has been confirmed.

The application has been submitted in accordance with Article 18 of Regulation (EU) 2019/6 (a generic application) for the 10 mg strength and Article 19 of Regulation (EU) 2019/6 (a hybrid application) for the 40 mg and 80 mg strengths.

Benefit assessment

Direct benefit

The benefit of Cepeloron is considered established considering that bioequivalence to the reference product has been demonstrated when administered at the same dose, route of administration and dosing interval as recommended in the marketing authorisation for the reference product. On this basis, Cepeloron is expected to be as efficacious as the reference product and, therefore, beneficial

for the treatment of dogs with congestive heart failure caused by degenerative mitral valve disease, in combination with standard therapy (including diuretic support, where necessary).

Additional benefits

No additional benefits for this generic veterinary medicinal product are expected other than the availability of an alternative product on the marketplace.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and 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 Cepeloron chewable tablets are expected to be the same as those associated with the reference product. On this basis, it is concluded that Cepeloron is not expected to present an unacceptable risk to the target animal, the user or the environment when used as recommended and in accordance with the SPC.

Risk management or mitigation measures

Given that bioequivalence between the reference and candidate products is accepted, it is considered appropriate that the warnings and risk mitigation measures proposed for inclusion in the candidate product SPC reflect those approved for the reference product. For the risks identified in the SPC approved for the reference product, the same, appropriate risk mitigation measures have been proposed for this product.

Evaluation of the benefit-risk balance

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

- Treatment of congestive heart failure caused by degenerative mitral valve disease, in combination with standard therapy (including diuretic support, where necessary) in dogs.

Since the benefit-risk balance of the reference product has previously been judged to be favourable, it is expected that the benefit-risk balance for this product will also be favourable.

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 Cepeloron is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 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.