7 November 2024
EMA/584294/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Carprofen Orion (EMEA/V/C/006249/0000)

INN: Carprofen

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

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Table of contents

Introduction

The Applicant Orion Corporation submitted on 28 February 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Carprofen Orion, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (optional scope).

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

At the time of submission, the Applicant applied for the following indications:

Dog:

For alleviation of inflammation and pain in musculoskeletal and joint disorders (e.g. osteoarthritis) and after surgical operations (tablet).

For perioperative alleviation of pain and inflammation especially in orthopaedic and soft tissue (including ocular) operations (solution for injection).

Cat:

For perioperative alleviation of pain (solution for injection).

The active substance of Carprofen Orion is carprofen, a non-steroidal antiinflammatory drug (NSAID) belonging to the group of 2-arylpropionic acids. Carprofen possesses analgesic and anti-inflammatory activity. The effect of carprofen is partly based on its inhibitory effect on the cyclo-oxygenase and lipoxygenase enzyme action. As a result, detrimental prostaglandins related to the inflammatory reaction are not produced. However, the inhibition of prostaglandin production by carprofen is so slight that it does not explain the full effect of the substance.

The target species are cat (solution for injection) and dog (solution for injection and chewable tablet).

Carprofen Orion chewable tablets contain 25, 50 or 100 mg of carprofen and are presented in packs containing 10 tablets, 20 tablets, 60 tablets and 180 tablets.

Carprofen Orion solution for injection contains 50 mg/ml of carprofen and is presented in packs of 5 vials of 20 ml volume.

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 (for 50, 100 mg tablets and 50 mg/ml solution for injection)

Article 19 of Regulation (EU) 2019/6 – a hybrid application (for 25 mg tablets - change in strength)

On 7 November 2024, the CVMP adopted an opinion and CVMP assessment report.

On 19 December 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Carprofen Orion.

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 V006249, 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

Manufacture of the active substance takes place within the EEA. The GMP certificates and a valid QP declaration is provided. The QP declaration states that the active substance is manufactured in compliance with EU GMP. The declaration is based on on-site audits which were performed in 2022.

Manufacturing, primary and secondary packaging and quality control of the finished product takes place outside the EEA. A valid GMP certificate is available.

Chemical, physical, microbiological testing and EU re-analysis takes places within the EEA.

GMP certification for the testing sites has been provided, which confirms the date of the last inspection and shows that the sites are authorised for the activities indicated above.

Batch release takes place at Orion Corporation, Orionintie 1, Espoo, Finland. The site has GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the batch release of such veterinary dosage forms. The site holds a manufacturing authorisation issued by Finnish Medicines Agency (Fimea).

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

Chewable Tablet

Carprofen 25 mg, 50 mg and 100 mg chewable tablets are immediate release chewable tablet preparations for veterinary use containing carprofen (Ph. Eur.). The 25 mg tablets are brown, round, biconvex, uncoated tablets debossed with “C 148” on one side and a score line on the other side. The tablets have a smoky, meaty aroma and can be divided into two equal doses. The 50 mg tablets are

brown, round, biconvex, uncoated tablets debossed with "C 146" on one side and a score line on the other side. The tablets have a smoky, meaty aroma and can be divided into two equal doses. The 100 mg tablets are brown, square, flat, uncoated tablets debossed with "C" on one side and a double score line on both sides. The tablets have a smoky, meaty aroma. The tablets can be divided into four equal doses. The subdivision tests were done according to Ph. Eur. 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. Stearic acid 50% is used. Amounts on % basis are depicted in the composition table. In the SPC and PL there is a description of a score line of all strengths.

Other ingredients are: Povidone, Lactose monohydrate, Microcrystalline cellulose, Stearic acid, Silica colloidal anhydrous, Sodium starch glycolate, Chicken liver powder, Smoke flavour, Light brown sugar. Numbers of Ph. Eur. monographs are included. Microcrystalline cellulose is used. Current monographs for the product excipients monographed in Ph. Eur. include functionality-related characteristics. The particle size of cellulose microcrystalline and lactose monohydrate is controlled. The content of remaining pharmacopoeial excipients is small and thus control of their particle size is not deemed necessary.

Description of the manufacturing process for the chicken liver powder has been provided. Viral risk assessment is included and is acceptable. Microbiological purity and IR identification test is included in specification as well. References to the used methods are provided for chicken liver powder, smoke flavour and light brown sugar. Manufacturer's declaration of compliance with EU regulation 1069/2009 has been provided. Applicant's own results of analysis for chicken liver powder were provided.

Solution for Injection

Carprofen 50mg/ml solution is a clear pale yellow to yellow solution. The ingredients of the solution for injection are: carprofen, L-arginine, glycocholic acid, lecithin, benzyl alcohol, sodium hydroxide, hydrochloric acid and water for injection. Except for lecithin (complies with USP) and glycocholic acid (in-house specification), all other excipients comply with Ph. Eur. Information provided is sufficient.

Containers and closure system

Chewable Tablet

Tablets are packed in high-density polyethylene bottles closed with child-resistant polypropylene closures. The bottles are further packaged into cartons (secondary packaging). Proposed specifications of the containers are based on USP monographs. However, the specifications show that the requirements of Ph. Eur. 3.1.3. and Ph. Eur. 3.1.5. are fulfilled. The technical documentation, release specifications based on Ph. Eur. and a sample certificate of analysis are presented for all package sizes.

Solution for Injection

Carprofen 50 mg/ml solution for injection is packed in 20 ml type I amber glass vials closed with bromobutyl rubber stoppers (which are secured with an aluminium over seal with a grey plastic lid). The labelled glass vials are further packed into cartons together with a leaflet. Drawings have been provided for the flip-off seals, rubber stoppers and glass vials, whereas specifications (including description, critical dimensions, and identity) have been presented for the rubber stoppers and glass vials. Analytical method descriptions for the testing of rubber stoppers and glass vials, respectively, have been included. It is stated that the rubber stoppers comply with Ph. Eur. 3.2.9. Thus, no further information on potential migration is necessary. Information on container closure system is acceptable.

Product development

Chewable Tablet

This application is in accordance with Article 18 of Regulation (EU) 2019/6 - Generic application for 50 mg, 100 mg tablets and Article 19(1)(a) of Regulation (EU) 2019/6 - Hybrid application – change in strength for 25 mg tablet. The reference product Rimadyl vet, nationally authorised in Finland, is a scored, uncoated, immediate release tablet.

The physicochemical characterisation of the reference product was performed by the Applicant. For Carprofen chewable tablets critical quality attributes were identified and included content uniformity, dissolution and related substances. The effect of different machine speed on uniformity of dosage units and the effect of hardness on physical and chemical attributes of tablets was studied.

The excipients were selected for the generic product development based on the literature. The level of excipients used in the formulation was studied in subsequent formulation development studies.

The guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.4)) states that test methods should be developed which are product-related and based on general and/or specific pharmacopoeial requirements. It has been shown that the general principles given in the BEQ guideline and also Ph. Eur. 2.9.3 and 5.17.1 are followed.

Comparative dissolution profiles and f2 values are presented for the 25, 50 and 100 mg strength at pH 1.0, 4.5 and 7.5.

The dissolution profile of the 50 mg biobatch was compared with a 25 mg Carprofen Orion batch and were found to be similar As such bioequivalence can be claimed for the 25mg strength.

The dissolution profile of the 50 mg biobatch was compared with a 100 mg Carprofen Orion batch and between test (100 mg) and reference (100 mg) products. Based on the results the bioequivalence can be claimed. The discriminatory power of the method used was shown. The suitability of the test conditions of the dissolution was demonstrated.

The functionality of the tablet break line is confirmed by the Ph. Eur. test Subdivision of tablets as described in the monograph 0478 “Tablets”.

As the proposed packaging is a bottle with 10, 20, 60 or 80 tablets, friability of tablets during storage is studied.

Solution for Injection

This application is in accordance with Article 18 of Regulation (EU) 2019/6 - Generic application for Carprofen 50 mg/ml solution for injection. A summary on the pharmaceutical development is given. Studies that have been performed as part of the product development are listed. The reference product Rimadyl (Carprofen) Injectable Solution, nationally authorised in Finland, is described and details on composition and physicochemical characterisation are discussed. Details on proposed test product composition, Quality Target Product Profile (QTPP) and identification of Critical Quality Attributes (CQAs) are included. Information on physicochemical characteristics, potential residual solvents, and organic impurities of the drug substance has been provided. A risk assessment on drug substance attributes that may impact the drug product critical quality attributes (CQAs) has been performed. In the initial risk assessment, solubility, related substances and microbiological limit have been found medium risk for impact on the drug product. In an updated risk assessment of the aforementioned drug substance attributes, the lowering of the medium risk to low risk has been justified. This is acceptable.

The formulation has been optimised to achieve complete dissolution in oil phase of emulsion. For the micelle composition and its characteristics, the requirements for generic products described in the

"Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (EMA/CHMP/QWP/799402/2011)" have been considered. It has been demonstrated that the composition of the micelle injection is qualitatively and quantitatively the similar the reference product. All excipients of the formulation are shortly described and considerations on selection are discussed. The selection of excipient grade and supplier was based on previous formulation experience and knowledge about excipients that have been used successfully in approved products. This is acceptable.

Excipient compatibility studies were not performed. This is justified based on the similarity of the qualitative and quantitative composition of excipients in the proposed generic product and the reference product and the compatibility can be assumed indirectly from the stability data available from various batches. It is accepted that the material attributes of the excipients do not directly impact the quality attributes of the finished product.

No overages are added in this product. An excess fill volume is proposed for the 20 ml fill volume (according to the application form only 20 ml glass vials will be marketed). This was calculated based on USP 1151. This is acceptable.

The physicochemical and biological properties are sufficiently discussed.

Information on manufacturing process development has been presented. The method of manufacture of the drug product is briefly described and a justification for selection of each manufacturing process step has been provided. It is stated that "to solubilize carprofen emulsification step was included" and that the "order of addition for each ingredient was defined based on API solubility of each ingredient and required temperature and stirring conditions". Considerations regarding order of addition of the ingredients and selection of API solubility, temperature and stirring conditions in relation to the micellar system of the DP have been discussed. Information on lipophilicity, solubility, in vivo disposition and pH stability of the drug substance has been presented and is acceptable. The role/effect of each excipient in the micellar system of the DP has been sufficiently discussed.

Potential drug precipitation has been discussed it is concluded that the samples stored at 5 °C and 25°C/60%, respectively, were found to be stable without drug precipitation.

Surface characteristics of the reference product and Carprofen Orion have been analysed by different techniques. It is concluded that the surface characteristics of the test and reference product are very similar.

It is concluded that the drug product is similar/comparable to the reference product with regard to particle size trend, absolute size range, average size and span values.

The impact of the process parameters on CQAs is discussed.

The results of a forced degradation study on DP vials are presented. It is concluded that carprofen is significantly affected by sunlight and peroxide stress.

An "Oxygen sensitivity Study-Effect of Dissolved oxygen and headspace oxygen on the drug product stability" is presented where the effect of oxygen (whether with reduced or without reduced oxygen) during bulk manufacturing has been evaluated.

The presented "pH Related Solution Stability Study" was performed to select and justify the pH range for the manufacturing of the DP.

The choice of the sterilisation method has been sufficiently justified.

Considerations regarding scale up from exhibit batch to commercial batch, an updated risk assessment of drug product manufacturing process attributes, and control strategy parameters involved in the manufacturing are provided and considered acceptable.

The container closure system fulfils the requirements of Ph. Eur. monograph for parenteral preparations (0520). Fragmentation of the rubber stoppers has been discussed with regard to intended application procedure in the SmPC.

Efficacy testing according to Ph. Eur. 5.1.3 (at the end of shelf life) has been presented.

In view of the presented preservative efficacy test data, it can be concluded that benzyl alcohol is required, as without preservative, the preservative efficacy criteria are not met

The integrity of the container closure system with regards to microbial contamination has been sufficiently discussed. Studies with regard to excipient compatibility, filter compatibility, tubing compatibility, stainless steel compatibility, container closure compatibility have been addressed.

Description of the manufacturing method

Chewable Tablet

For the manufacturing of production scale batches one batch of common blend is manufactured and used to manufacturer tablets of different strengths. The batch formula corresponds proportionally to the product composition. The manufacturing process can be considered a standard process consisting of sequential steps of mixing, blending, screening, milling and compression. The final blend is compressed into Carprofen 25 mg, 50 mg and 100 mg chewable tablets. The description of the manufacturing process includes the quantity of each ingredient added during the process**.**

Validation data of the manufacturing process from two pilot batches is provided. Each batch was divided to manufacture all strengths. A process validation scheme for production-scale batches is provided.

The In-process control tests are done according to Ph. Eur. Monographs 2.9.8.and 2.9.7 when applicable. Additionally, in-house methods are used. The flow sheet of the manufacturing process includes all the in-process controls showing at each stage what materials enter the process. The respective IPC acceptance criteria are included in the flow sheet.

Solution for Injection

The batch formula is in line with the finished product composition formula in P.1., except for the amounts of sodium hydroxide and hydrochloric acid where the amounts are indicated with q.s. Information on overage of the drug substance (no overage is used) and quality standard of each component is given. No overages have been mentioned for the excipients.

A flow diagram and a narrative description of the manufacturing process has been provided. In-process controls (IPCs) are indicated.

Information regarding the hold times has been presented in this section.

There are no reprocessing steps.

Critical steps of the manufacturing process have been declared and a justified.

The DP manufacturing process is considered a standard process with terminal sterilisation. Process validation data have been included for the batch sizes. Potential extractables/leachables (E/L) originating from the filters have been discussed and justified with adequate analytical methods. Potential sorption of solution compounds has been discussed. It is concluded that there is no sorption on the filters. This is acceptable.

Terminal sterilisation is performed in accordance with the Ph. Eur.

In the validation report on product specific integrity test parameters the proposed acceptance criteria of integrity testing have been justified product specifically for the chosen filter type.

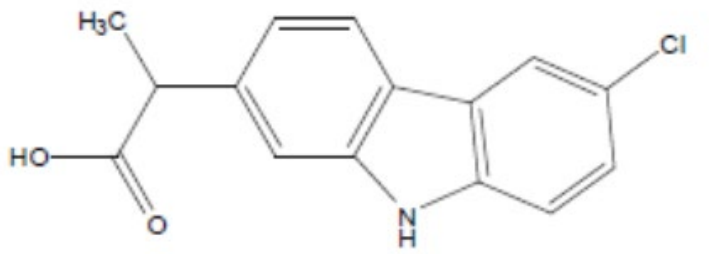
Control of starting materials

Chewable Tablet

Active substance

The chemical name of carprofen is (2RS)-2-(6-chloro-9H-carbazol-2-yl)propanoic acid;

9H-carbazole-2-acetic acid, 6-chloro- α -methyl-, (±)-;(±) 6-chloro-α-methyl-9H-carbazole-2-acetic acid. and has the following structure:



The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Carprofen is described in the Ph. Eur. monograph (01/2023:2201) and the substance is controlled by the Applicant accordingly. In addition, specifications for microbiological impurities and residuals solvents have been set. Additional tests are applied on residual solvents that reflects the requirements established in the ASMF. The limits are compliant with the VICH GL18.

Particle size is controlled by the active substance manufacturer and by the final product manufacturer. Validation of the method used to control particle size is provided**.** A sufficient number of batches were tested by the Applicant. References to Ph. Eur. monographs are included. Particle size results were provided.

Excipients

The excipients described in Ph. Eur. are controlled according to their relevant monographs. References to Ph. Eur. monograph numbers are included. There is a control for particle size for the main excipients cellulose microcrystalline and lactose monohydrate.

Solution for Injection

Active substance

See information as presented and assessed for the drug substance in the summary for Carprofen 25 mg, 50 mg and 100 mg chewable tablets.

Excipients

All excipients, except for glycocholic acid (in-house specification) and lecithin (USP), comply with the current version of the respective Ph. Eur. monograph. Consequently, an in-house specification (which includes parameters, i.a. identity and assay) for glycocholic acid has been provided. Functionality-related characteristics and other potential parameters, which could influence the micelle formation/stability have been sufficiently discussed.

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

Chewable Tablet

Manufacturer of Carprofen declares that they do not use any material of human or animal origin during the manufacture of API. The finished product contains lactose and chicken flavour, which are both of animal origin. Declaration from the lactose manufacturer is 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.

Solution for Injection

There are no excipients of animal origin, except for glycocholic acid which is derived from bovine bile. Nevertheless, it is stated that it is "manufactured in compliance with the revised "Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01 rev.03) in force since July 1st, 2011 and the monograph 5.2.8 "Minimising the risk of transmitting TSE via medicinal products", Ph. Eur. current edition". According to the respective NfG, bovine bile belongs to the category IB tissues (i.e. lower-infectivity tissues).

Control tests on the finished product

Chewable Tablet

The finished product release specification includes tests for description, identification, average weight, loss on drying, assay, dissolution, uniformity of dosage units, content uniformity test, related substances, Impurities, total aerobic microbial count, total combined yeasts and moulds count.

In the release and shelf-life tests references to the used methods are included. The size of the chewable tablet of different strengths is provided in the description. The requirement for assay ±5 % of nominal content is in-line with the requirements established in the legislation. The Applicant´s justification of limit for total impurities at release and at the end of shelf-life is acceptable.

The limits for dissolution are based on the results from development section. Discriminatory power of the chosen dissolution method has been shown. It has been shown that the final product specification requirement is compliant with the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017).

Friability and hardness are included into in-process specifications and are also be included into shelf-life specifications. Justification not to control optical rotation in stability studies has been provided. The limits for microbiological quality comply with the Ph. Eur. 5.1.4 for non-aqueous preparations for oral use. Elemental impurities risk assessment is acceptable.

Analytical results have been provided for a number of batches. Certificates of analysis will be available for commercial batches. A method suitability report is provided.

The methods used are described in a satisfactory manner. References to the methods used are included. Method to identify related substances of carprofen is described. Validation data of Identification of Carprofen assay, related substances and dissolution follows guidelines VICH GL1 and GL2.

Solution for Injection

The specified parameters for the control of the drug product have been set up primarily according to the Ph. Eur. requirements for this dosage form and according to respective ICH guidelines.

The method descriptions and validation data provided for analytical methods, assay of carprofen, assay of benzyl alcohol and content of benzaldehyde, and related substances are in accordance with the requirements of the relevant ICH guidelines. The provided validation data are considered satisfactory.

Batch analysis data have been presented for two commercial scale batches produced by the finished product manufacturer. Drug substance batches. are indicated. All results comply with the specifications.

Impurity discussion: Ph. Eur. impurities, A, B, C, D, E, F, G and H (of which Impurities B, C, D and H are degradation products) have been listed tabularly. Information on characterisation of potential impurities is acceptable.

All parameters of the drug product specification have been justified.

Information regarding reference standards, used for identification, related substances and assay tests, has been presented. It is stated that the "working standard batch has been checked against the carprofen reference standard". A CoA (including identity and impurity testing results) has been included for the working standard. This is sufficient.

Stability

Chewable Tablet

The stability protocol follows the principles established in the VICH and CVMP guidelines on stability studies. The long-term studies are pending, the data is available up to 18 months with no significant changes observed. The shelf-life can thus be extrapolated up to 24 months according to the guideline on Stability Testing: Stability testing of existing active substances and related finished products (EMA/CVMP/QWP/709423/2022). No significant changes were observed in the accelerated studies. As the submission includes data from stability studies on two production batches, confirmation was provided that an additional production batch would be placed on long term stability studies through the proposed shelf life and on accelerated studies for 6 months. The hold time period of compressed tablets has been studied and is confirmed. No in-use stability studies have been provided, since there seems to be no stability issues. The final product is not light sensitive. Compliance with the Note for Guidance on Start of Shelf-life of the Finished Dosage Form (EMEA/CVMP/453/01) is confirmed by the finished product manufacturer.

Solution for Injection

Up to 24 months long-term (5 ± 3°C; upright and inverted) and 6 months accelerated (25 ± 2°C / 60 ± 5 %RH; upright and inverted) stability data have been presented for each of two commercial batches with drug substance from the finished product manufacturer. The Applicant confirmed that:

- One additional carprofen solution for injection production batch will be put in long term stability studies through the approved shelf life and on accelerated studies for 6 months.
- The first three production batches of the bigger commercial batch size will be put in long term stability studies through the approved shelf life and on accelerated studies for at least 6 months.
- One additional validation batch at proposed commercial scale and with a different API batch and one additional validation batch will be put on long-term stability to the registered shelf-life.

Degree of coloration results have been additionally presented for two batches (upright and inverted) up to the 24 months timepoint. The proposed shelf life of 24 months with storage condition "Store in a refrigerator (2°C-8°C)" is acceptable.

Photostability studies according to VICH GL5 have been performed on two batches. All results comply with the specifications. It is concluded that the product is photostable.

In-use stability data have been presented. In view of the presented data, the in-use stability statement, "once broached the product can be used for 28 days when stored below 25°C" is acceptable. The finished product manufacturer confirmed the compliance with the Note for Guidance on Start of Shelf-life of the Finished Dosage Form".

Overall conclusions on quality

Carprofen Orion chewable tablets contain 25, 50 or 100 mg of carprofen and are presented in packs containing 10 tablets, 20 tablets, 60 tablets and 180 tablets.

Carprofen Orion solution for injection contains 50 mg/ml of carprofen and is presented in packs of 5 vials of 20 ml volume.

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

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

Part 3 – Safety documentation (Safety and residues tests)

This application has been submitted in line with the requirements for submissions under Article 18 of Regulation (EU) 2019/6 – a generic application (for 50, 100 mg tablets and 50 mg/ml solution for injection), and Article 19 of Regulation (EU) 2019/6 – a hybrid application (for 25 mg tablets - change in strength). The reference product is Rimadyl 20 mg, 50 mg and 100 mg chewable tablet and Rimadyl 50 mg/ml solution for injection. The active substance of Carprofen Orion is carprofen, a non-steroidal anti-inflammatory drug (NSAID) belonging to the group of 2-arylpropionic acids.

No new pharmacological or toxicological data are provided in the dossier and the Applicant refers to data from the reference product. A user risk assessment (URA) has been included in Part 3.A.5 of the dossier.

Safety tests

In accordance with 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 the conditions for a generic veterinary medicinal product are met. Further, according to Article 19 of Regulation (EU) 2019/6 appropriate pre-clinical studies or clinical trials shall be required when the veterinary medicinal product does not meet all the characteristics of a generic veterinary medicinal product, e.g. when there are changes in the strength.

Chewable tablets:

Based on the published SPC of the reference product it could be accepted that Carprofen Orion and the reference product are qualitatively and quantitatively the same in respect of the active substance in strengths 50 mg and 100 mg. Further the Applicant claims that the smallest strengths 20 mg (Rimadyl vet) and 25 mg (Carprofen Orion vet) can be considered comparable. As the candidate product differs in the excipient formulation, comparative bioavailability between the reference product and Carprofen Orion 50 mg chewable tablets has been investigated by means of an in vivo bioequivalence study according to guideline EMA/CVMP/016/2000-Rev.4, and bioequivalence is claimed.

Further, the Applicant has claimed a biowaiver for other tablet strengths (25 mg and 100 mg) according to guideline EMA/CVMP/016/2000-Rev.4, Biowaiver 7.2 'comparisons between strengths'.

Biowaiver for the other strengths 25 mg and 100 mg has been justified as

- the products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the composition of the strengths is quantitatively proportional,
- the dissolution profiles of the different strengths are similar.

The bioequivalence can be considered demonstrated (see part 4).

Solution for injection:

It is accepted that based on the published SPC of the reference product, injectable formulations of Carprofen Orion and the reference product are qualitatively and quantitatively the same in respect of the active substance, carprofen, and qualitatively the same in respect of the excipients. Carprofen Orion solution for injection complies with all the requirements for a biowaiver 7.1. 'comparisons between formulations' listed in the guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4). Furthermore, Carprofen Orion is intended for use in the same manner to the same target species (dogs and cats) for the same indications and at the same dose rate as the reference product.

Bioequivalence can be considered demonstrated.

Pharmacology

Pharmacodynamics

It can be accepted that the Applicant has cited a suitable reference product in this application, i.e. Rimadyl vet chewable tablets and solution for injection.

The Applicant has claimed bioequivalence of the tablet formulation by means of an in vivo bioequivalence study (assessed in Part IV A.1.2) and a biowaiver in accordance with the relevant guideline (EMA/CVMP/016/2000-Rev.4). Bioequivalence for the chewable tablets has been demonstrated. For the injectable formulation, due to the comparability of the formulation between products and its administration via intravenous or subcutaneous injection, no pharmacodynamic or bioequivalence studies were conducted with the injection formulation and a biowaiver is also claimed. As bioequivalence between candidate and reference injectable formulation can be accepted, and given the legal basis of this application, the omission of pharmacodynamic data could be considered acceptable.

The information included in section 4.2 'Pharmacodynamics' of the SPC is the same as is contained in section 5.1 of the SPC of the reference product and this is considered acceptable. The PI is in line with the updated version of the reference product PI.

Pharmacokinetics

The Applicant has provided an in vivo bioequivalence study with the 50 mg chewable tablets. Additionally in vitro dissolution data has been presented to support the biowaiver claimed for other tablet strengths. Please refer to Part 4 for assessment of the bioequivalence study.

With regards to the solution for injection formulation, no pharmacokinetic or bioequivalence studies were conducted. A biowaiver is claimed. Omission of bioequivalence study is acceptable, and bioequivalence can be considered demonstrated.

Toxicology

No data relating to the toxicological profile of the product have been provided as bioequivalence with the reference product has been claimed. Although there are differences in qualitative and quantitative composition in excipients between tablet and injection formulations of test and reference products, all excipients used in the candidate product are well-known and commonly used in veterinary pharmaceutical products. Thus, differences are not expected to present a safety concern in terms of the toxicological profile of the candidate formulation, as the excipients fulfil applicable European Pharmacopoeia standards (see Part 2).

Bioequivalence for the chewable tablets has been accepted. As bioequivalence for the injectable formulation can also be accepted, and given the legal basis of this application, the omission of toxicological (including reproductive and developmental toxicity), genotoxicity and carcinogenicity data could be accepted.

Other requirements

Special studies

No data have been provided.

Noting that the injection formulations of the candidate and the reference product contain the same active substance in the same concentration and comparable excipients in comparable amounts no special studies are required for injection formulation.

Bioequivalence between tablet formulations of the candidate and the reference products is accepted. Given the legal basis of this application and the fact that the candidate and reference formulations contain the same concentration of active substance (carprofen), and the excipients are well-known and commonly used the omission of additional data on potential dermal irritancy and sensitisation, and ocular irritancy of the candidate tablet formulation can be accepted.

Observations in humans

No proprietary data have been provided, which is acceptable. The Applicant states that carprofen is currently not used in human medicine. Previously, carprofen was used for human therapy at daily oral doses in the range of 150 – 600 mg (approximately 2.5 – 10 mg/kg bw/day). In clinical trials, carprofen

was well tolerated and majority of adverse effects were transient and mild, such as gastrointestinal discomfort or pain and nausea. The incidence of adverse effects in humans were similar to other non-steroidal anti-inflammatory drugs.

Excipients

No data have been provided. As stated above, excipients are well-known and commonly used in veterinary pharmaceutical products, and any difference between candidate and reference products are not expected to present a safety concern.

User safety

A user safety assessment was provided in line to the applicable Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1).

Chewable tablets:

The Applicant considers accidental ingestion of one tablet of the highest strength (100 mg carprofen) by a child as the worst-case scenario. The resulting exposure level is above the ADI but within the dose level that had been used for human therapy. However, it should be borne in mind that the therapeutic dose cannot be used as a reference value to estimate the risk for the user since the user (the child in this case) is not getting any benefit from the exposure to the product. Considering that the NOAEL on which the ADI is based has been obtained in a repeated dose toxicity study while the user exposure is expected to be occasional, it is accepted that the risk can be mitigated by putting in place adequate risk mitigation measures like keeping the product out of the sight and reach of children and a childproof container.

Furthermore, published reports indicate that carprofen may cause photosensitisation in humans. The Applicant has proposed to add the following warning in the SPC:

"In case of accidental ingestion of the tablets, seek medical advice if symptoms occur and show the package leaflet or the label to the physician."

In accordance with the legal framework of this application, the summary of the product characteristics of the generic veterinary medicinal product shall be essentially similar to that of the reference veterinary medicinal product (Article 18(6) of Regulation (EU) 2019/6) and no updates can be implemented.

The SPC section 3.5 'special precautions to be taken by the person administering the veterinary medicinal product to animals', is in line with the reference product SPC.

Solution for injection:

The Applicant considers the risk for skin irritation or skin sensitization after dermal exposure towards carprofen injection negligible, as neither carprofen nor the excipients have skin irritating or skin sensitizing properties at their concentrations in the final product formulation. The risk for eye irritation is regarded to be low, as only benzyl alcohol may be irritating to the eye. However, the substance is not classified as an eye irritant and makes up only a small amount of the product composition. Nevertheless, the Applicant proposes to add general warning sentences:

"Avoid contact with skin and eyes. Wash off any splashes immediately with water. Seek medical attention if symptoms (irritation) occur. Care should be taken to avoid self-injection. If accidental self-injection occurs, seek medical attention immediately and show the package leaflet or the label to the physician. People with known hypersensitivity to carprofen should administer the veterinary medicinal product with caution."

It is noted that, according to the Annex to the European Commission Guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) EMA/CHMP/302620/2017, the excipient benzyl alcohol can produce local irritation and sensitization.

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

Environmental risk assessment

The Applicant has conducted an environmental risk assessment 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 Applicant has followed the Phase I decision tree and concludes that the environmental risk assessment can stop in Phase I (at Question 3) as the candidate product will be used only in non-food producing species. This conclusion is acceptable.

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 concluded that the candidate formulations 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 Article 18 of Regulation (EU) 2019/6 (generic application) and Article 19 of Regulation (EU) 2019/6 (hybrid application - change of strength).

The Applicant has cited suitable reference products, "Rimadyl vet solution for injection" and "Rimadyl vet chewable tablets". No bioequivalence studies were conducted with the injection formulation and biowaivers are claimed. An in vivo bioequivalence study with supporting in vitro dissolution studies were performed with the tablet formulation. This approach is acceptable.

Bioequivalence for the tablet formulation has been claimed by means of an in vivo bioequivalence study and a biowaiver in accordance with the relevant guideline (EMA/CVMP/016/2000-Rev.4), and it is accepted (see Part 4). For the injectable formulation, a biowaiver is also claimed. Bioequivalence can also be accepted for the injectable formulation.

Pharmacology:

No pharmacodynamic studies were presented and this is acceptable. The text in section 4.2 'Pharmacodynamics' of the SPC is consistent with that of the reference product and is therefore acceptable.

It is noted that the Applicant has revised the information in section 4.3 'Pharmacokinetics' of the SPC for both the tablet and the injectable formulations to be in line with the information of the SPC of the reference product. Given the legal basis of this application, this is acceptable.

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, the omission of toxicological data is considered acceptable. Differences in qualitative and quantitative composition of the excipients

between the candidate and reference tablet formulations, are not expected to present a safety concern. Therefore, no further toxicological data about the excipients are required.

User safety:

A user safety assessment was provided in line with current guidelines. Based on the similarities between Carprofen Orion and the reference product as outlined above, no difference in exposure to Carprofen Orion compared to the reference product is anticipated. The proposed worst-case exposure scenarios (accidental self-injection or accidental ingestion by a child) as justified by the Applicant, can be accepted. Child resistance report/s for the 33 mm, 38 mm and a declaration for the 53 mm closures were provided. Therefore, the claim for child-resistant packaging in the SPC and its consideration as a risk mitigation measure can be accepted.

In accordance with the legal framework of this application, the summary of the product characteristics of the generic veterinary medicinal product shall be essentially similar to that of the reference veterinary medicinal product (Article 18(6) of Regulation (EU) 2019/6).

It can be accepted that the user safety warnings are adequate, provided that the product is stored, handled, administered, and disposed of in accordance with the recommendations included in the proposed SPC.

Environmental risk assessment:

An environmental risk assessment (ERA) according to the CVMP/VICH guidelines was provided. It is concluded that Carprofen Orion 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

Pre-clinical studies

Pharmacology

Pharmacodynamics

See part 3.

Pharmacokinetics

See part 3.

Bioequivalence studies

Carprofen Orion chewable tablets

Bioequivalence between the candidate product Carprofen Orion 50 mg chewable tablets and the reference product Rimadyl vet 50 mg chewable tablets was investigated after a single oral dose administered to 24

male Beagle dogs. This bioequivalence study was designed as a single-dose, randomised, two-period, two-sequence, cross-over study. The dogs received either the test product Carprofen Orion 50 mg chewable tablets (1 tablet of 50 mg) or the reference product Rimadyl 50 mg chewable tablets (1 tablet of 50 mg) after an overnight fast of at least 12 hours. A wash-out period of two weeks was held between the treatments.

The dose for the test and reference products used in the bioequivalence study targets the highest approved dose of the reference product (4 mg/kg bw). The reference product is authorized in the European Union (Finland) and is in line with the guideline EMA/CVMP/016/00-Rev.4.

Plasma samples were analysed for determination of carprofen concentrations using a validated HPLC/MS/MS method. The bioanalytical analysis has been done according to the relevant guidelines and GLP and are found appropriate.

Non-compartmental methods were used for evaluation of the pharmacokinetic parameters. Pharmacokinetic parameters (C_{max} and AUC_t) were analysed using ANOVA with factors for sequence, subject within sequence, period, and formulation as fixed effects. The data was transformed prior to analysis using a logarithmic transformation.

The results show that the 90% confidence intervals are within the pre-specified acceptance range of 80-125% between the candidate product Carprofen Orion 50 mg chewable tablets and the reference product Rimadyl vet 50 mg chewable tablets. Lower and upper limits of the 90% CI for C_{max} are 89.9-112% and 95.3-106% for AUC_t.

The bioequivalence study was conducted with the 50 mg strength. Biowaivers for the other strengths (25 mg and 100 mg) have been requested according to guideline EMA/CVMP/016/2000-Rev.4, 7.2 Comparisons between strengths.

Biowaiver for the other strengths 25 mg and 100 mg has been justified as:

- the products are manufactured by the same manufacturing process (a common blend is used to manufacture the tablets)
- the qualitative composition of the different strengths is the same.
- the composition of the strengths is quantitatively proportional.
- the dissolution profiles of the different strengths are similar.

The similarity of the dissolution profiles of Carprofen 25 mg and 50 mg has been demonstrated in three buffers (pH 1.2, 4.5 and 6.8) and the f2 value is over 50 in all media. The biowaiver claim for Carprofen 25 mg is acceptable.

The dissolution profile of the 50 mg biobatch was compared with a 100 mg Carprofen Orion batch and between test (100 mg) and reference (100 mg) products. Based on the results the bioequivalence can be claimed.

*Conclusions***:** Based on the 90% confidence intervals which are within the pre-specified acceptance range of 80-125%, the candidate product Carprofen Orion 50 mg chewable tablets and the reference product Rimadyl vet 50 mg chewable tablets are bioequivalent. Biowaiver of Carprofen Orion 25 mg and 100 mg chewable tablets is acceptable.

Carprofen Orion solution for injection

It can be accepted that the candidate product Carprofen Orion solution for injection contains the same active substance in the same concentration and comparable excipients in comparable amounts as the reference product 'Rimadyl vet solution for injection'. Due to the comparable formulation of the products and administration via intravenous or subcutaneous injection, no pharmacodynamic or bioequivalence

studies were conducted. This could be acceptable according to guideline EMA/CVMP/016/2000-Rev.4. Biowaiver 7.1. Comparisons between formulations. Since the questions from the quality part have been properly addressed, bioequivalence can be considered demonstrated.

Dose determination and confirmation

Dose justification

No data have been presented.

Given that bioequivalence with a suitable reference product has been claimed and the proposed posology for the candidate product is the same as 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 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 candidate and reference formulations are of the same pharmaceutical forms (chewable tablet and solution for injection) and are intended for use in the same manner (oral administration, subcutaneous and intravenous injection) to the same target species (dog and cat) for the same indications and at the same dose rates. It can be accepted that the solution for injection formulations of the candidate and reference product contain the same active substance in the same concentration and comparable excipients in comparable amounts. Furthermore, the candidate and reference tablet formulations are qualitatively and quantitatively the same in respect of the active substance for 50 mg and 100 mg strengths. Further, the Applicant claims that the smallest strengths 20 mg (Rimadyl vet) and 25 mg (Carprofen Orion) can be considered comparable. Tablet formulation of the candidate product 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 candidate and reference formulations is anticipated. In addition, an acceptable tolerance profile was demonstrated in the in vivo bioequivalence study using the 50 mg tablet strength.

Considering the above and as the bioequivalence has been demonstrated the omission of data in support of tolerance in the target animal species, dogs and cats, is considered acceptable.

Clinical trial(s)

No data have been presented.

It can be accepted that the candidate and reference formulations are of the same pharmaceutical forms (chewable tablet and solution for injection) and are intended for use in the same manner (oral administration, subcutaneous and intravenous injection) to the same target species (dog and cat) for the same indications and at the same posology. Furthermore, the candidate and reference tablet formulations are qualitatively and quantitatively the same in respect of the active substance for 50 mg and 100 mg strengths. Further, the Applicant claims that the smallest strengths 20 mg (Rimadyl vet) and 25 mg (Carprofen Orion) can be considered comparable. Candidate product (tablet formulation) differs in excipient composition, but all excipients used are common and well-known excipients in pharmaceutical

products. Consequently, no difference in efficacy between candidate and reference formulations is anticipated as the bioequivalence is acceptable.

Considering the above, the CVMP considers that omission of clinical data in support of efficacy of the candidate product in the target species, dog and cat, can be accepted.

Overall conclusions on efficacy

This application has been submitted in accordance with Articles 18 and 19 of Regulation (EU) 2019/6 (a generic/hybrid veterinary medicinal product).

In accordance with Article 18 of Regulation (EU) 2019/6, a pivotal in vivo bioequivalence study in the target species dog was conducted with the chewable tablet formulation (50 mg strength). Further in vitro dissolution data was provided to support the biowaivers of other tablet strengths (25 mg and 100 mg). The Applicant claims a biowaiver for the solution for injection formulation, in accordance with the guideline EMA/CVMP/016/2000-Rev.4.

Pharmacology

Please refer to Part 3.

Bioequivalence

A study investigating bioequivalence between the candidate product Carprofen Orion 50 mg chewable tablets and the reference product Rimadyl vet 50 mg chewable tablets has been provided. Additional dissolution data between the different strengths was provided to support biowaiver of Carprofen 25 mg and 100 mg chewable tablets.

As bioequivalence between the proposed generic product and the reference product has been claimed no data on dose determination, tolerance and clinical data has been provided. The omission of data can be accepted since bioequivalence between candidate and reference formulations is satisfactorily addressed.

Part 5 – Benefit-risk assessment

Introduction

Carprofen Orion is a chewable tablet and a solution for injection containing carprofen as active substance which is well-known.

The active substance, carprofen, is an NSAID belonging to the group of 2-arylpropionic acids. Carprofen possesses analgesic and anti-inflammatory activity. The effect of carprofen is partly based on its inhibitory effect on the cyclo-oxygenase and lipoxygenase enzyme action.

The product is intended for use in cat and dog for:

Dog:

For alleviation of inflammation and pain in musculoskeletal and joint disorders and after surgical procedures.

For perioperative alleviation of pain and inflammation especially in orthopaedic and soft tissue (including ocular) procedures.

Cat:

For perioperative alleviation of pain.

The application has been submitted in accordance with:

Article 18 of Regulation (EU) 2019/6 – a generic application. (For 50, 100 mg tablets and 50 mg/ml solution for injection)

Article 19 of Regulation (EU) 2019/6 – a hybrid application. (For 25 mg tablets)

Benefit assessment

Direct benefit

The proposed benefit of Carprofen Orion could be considered established based on bioequivalence to the reference product when administered at the same dose, route of administration and dosing interval as recommended in the marketing authorisation for the reference product. As bioequivalence with the reference product has been claimed, Carprofen Orion is expected to be as efficacious as the reference product and therefore, beneficial in the following indications:

- For alleviation of inflammation and pain in musculoskeletal and joint disorders and after surgical procedures in dogs.
- For perioperative alleviation of pain and inflammation especially in orthopaedic and soft tissue (including ocular) procedures in dogs.
- For perioperative alleviation of pain in cats,

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

The direct therapeutic benefits for Carprofen Orion are expected to be the same as those for the reference product "Rimadyl vet solution for injection" and "Rimadyl vet chewable tablets".

Additional benefits

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

Risk assessment

Quality

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

Safety

The risks associated with the use of Carprofen Orion chewable tablets and solution for injection are expected to be the same as those associated with the reference product. Therefore, Carprofen Orion 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, and 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:

- For alleviation of inflammation and pain in musculoskeletal and joint disorders (e.g., osteoarthritis) and after surgical operations in dogs.
- For perioperative alleviation of pain and inflammation especially in orthopaedic and soft tissue (including ocular) operations in dogs.
- For perioperative alleviation of pain in cats

Based on the data presented, the overall benefit-risk may be considered positive. The product information has been reviewed and is considered to be acceptable.

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 Carprofen Orion 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.