13 March 2024
EMA/129987/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Trilorale (EMEA/V/C/006124/0000)

INN: Trilostane

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 AXIENCE submitted on 6 October 2022 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Trilorale, 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 12 May 2022 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

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

For the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs.

The active substance of Trilorale is trilostane, an antiadrenal substance which selectively and reversibly inhibits the enzyme system 3 beta hydroxysteroid isomerase, thus blocking the production of cortisol, corticosterone and aldosterone. The target species is dogs.

Trilorale oral suspension for dogs contains 10 mg/ml or 50 mg/ml of trilostane. The 10 mg/ml strength would be available in bottles containing 30 ml or 90 ml of oral suspension. The 50 mg/ml strength would be available in bottles containing 10 ml, 25 ml, 36 ml, 50 ml, 72 ml or 100 ml of oral suspension. One bottle is packed into a cardboard box together with 2 measuring syringes of 1 ml and 5 ml.

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

The rapporteur appointed is Mary O'Grady and the co-rapporteur is Anna Wachnik-Święcicka.

The dossier has been submitted in line with the requirements for submissions under Article 19 of Regulation (EU) 2019/6 – a hybrid application.

On 13 March 2024, the CVMP adopted an opinion and CVMP assessment report.

On 6 May 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Trilorale.

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) has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

Manufacture, micronisation, quality control testing, primary packaging, secondary packaging and storage and/or distribution of the active substance trilostane takes place outside the EU. A GMP declaration for the active substance manufacturing site and for the active substance intermediate site

from the Qualified Person (QP) at the EU batch release site and manufacturer of dosage form was provided. The declaration was based on an audit of both sites by a third-party following inspection.

Finished product

Manufacture of dosage form, quality control testing (chemical/physical), primary and secondary packaging takes place within the EU and appropriate certification has been provided. Batch release (certification) of the finished product takes place at LelyPharma B.V., The Netherlands and the site has a manufacturing authorisation issued on 7 November 2023 by the competent authority of The Netherlands. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the activity indicated above, is also 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 the active substance and finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Composition

The products are aqueous, white to off-white, oral suspensions containing either 10 mg/ml or 50 mg/ml of the active substance trilostane. The other ingredients are sodium benzoate, sorbitol liquid (non-crystallising), saccharin sodium, glycerol, xylitol, sodium dihydrogen phosphate dihydrate, silica, colloidal anhydrous, xanthan gum, citric acid monohydrate or citric acid anhydrous, vanillin, purified water (minimum grade). The inclusion of the preservative at the proposed level is considered as both safe and adequate to ensure the required antimicrobial activity for the drug product.

The 10 mg/ml oral suspension is packaged in 30 ml or 100 ml capacity high density polyethylene bottles containing 30 ml and 90 ml of oral suspension, respectively.

The 50 mg/ml oral suspension is packaged in 10 ml, 30 ml, 40 ml or 60 ml capacity high density polyethylene bottles containing 10 ml, 25 ml, 36 ml and 50 ml of oral suspension respectively. High density polyethylene bottles of 100 ml capacity are used for the presentations containing 72 ml or 100 ml of product.

Each bottle is closed with a polypropylene/high density polyethylene child resistant stopper with a polyethylene plug placed in the bottle. Each bottle is packed in a cardboard box which will also contain a 1 ml and a 5 ml polypropylene measuring syringe.

Containers and closure system

The primary packaging is high density polyethylene bottles closed with polypropylene/high density polyethylene child resistant stoppers with a polyethylene plug placed in the bottle. The bottles of the 10 mg/ml strength contain 30 ml or 90 ml of oral suspension. The bottles of the 50 mg/ml strength contain 10 ml, 25 ml, 36 ml, 50 ml, 72 ml or 100 ml of oral suspension. Taking into consideration the proposed dosage regimen, each package will be supplied with both a 1 ml and a 5 ml polypropylene measuring syringe. As part of the product development, studies were also carried out to establish the

suitability of the dosing syringes provided with the finished product and compliance of the product with the requirements of Ph. Eur. 2.9.27 'Uniformity and accuracy of delivered doses from multidose containers' was demonstrated for the minimum and maximum doses for both syringe scales for the 1 ml and 5 ml syringes.

Declarations of the compliance with the relevant European Pharmacopoeia (Ph. Eur.) requirements have been provided for the syringes along with suitable specifications for the respective components of the syringes.

Product development

The product was developed as a hybrid formulation (Article 19 (1)(a) of Regulation (EU) 2019/6 - hybrid application – change in strength) of the reference product Vetoryl 30 mg hard capsules; IE/V/0514/002 from Dechra Regulatory B.V., Europe. Given that the proposed product and reference product are considerably different in their pharmaceutical form (hard capsule versus an oral suspension) and strengths (30 mg/capsule versus 10 mg/ml and 50 mg/ml in the respective suspensions), bioequivalence has been demonstrated via a bioequivalence study comparing one of the candidate formulations (10 mg trilostane/ml oral suspension) with the reference formulation. The extrapolation of bioequivalence data from the 10 mg/ml strength of the candidate product to the 50 mg/ml strength has been justified by the applicant. See part 4 of this report.

The data presented on formulation development are considered rather limited but acceptable. The applicant has provided justification for the use of the flavouring agent, vanillin and also some data for trial batches manufactured to demonstrate stability of the finished product with the proposed formulation. Comparative batch analysis data is provided for a number of test product batches to demonstrate that the test product used in the bioequivalence study is representative of typical batches with respect to physico-chemical properties including, but not limited to physical parameters such as pH, density, viscosity and dissolution, and functionality related physical characteristics such as particle size.

Description of the manufacturing method

The manufacturing process consists of sequential mixing of the excipients followed by addition of the active substance and homogenisation of the suspension.

The level of detail provided with respect to the manufacturing process is acceptable.

Process validation data has been provided for two finished product batches of each product strength of the minimum proposed batch size. Confirmation is provided that the batches of active substance used in the validation batches had been subjected to micronisation. Compliant results are provided for tests performed on the bulk suspension and on bottled samples taken at the beginning, middle and end of the filling process. Results for in-process control tests during manufacture of these batches are provided.

In line with the *Guideline on process validation for finished products – information and data to be provided in regulatory submission* EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1, a justification is provided as to why the manufacturing process is considered as a standard process and consequently, why the process validation data provided for only the lower end of the production scale batches is acceptable at time of regulatory submission. This justification is considered acceptable and is accompanied by a process validation scheme for the largest proposed batch size. A bulk hold time is proposed and considered acceptable.

Control of starting materials

Active substance

The active substance trilostane is not monographed in the Ph. Eur. and data on the active substance is provided according to the Active Substance Master File (ASMF) procedure. The active substance specification as applied by the dosage form manufacturer includes tests for appearance, identification, specific optical rotation, loss on drying, residue on ignition, particle size distribution, related substances, assay and residual solvents. Non-routine tests for polymorphism and melting point are additionally included. The specification is considered to be acceptable. The test methods used for the control of the active substance are as per those of the ASMF. Batch analysis data and a justification for the proposed active substance specification are provided. Characterisation data is provided for the reference standard batch to be used by the applicant which differs to that used by the ASMF holder. The Applicant's Part of the ASMF is provided based on a manufacturing process consisting of two synthetic steps and an additional particle size reduction step to produce trilostane. The structure of trilostane active substance is generally well characterised. Of the three potential organic impurities discussed, two are controlled within the active substance specification and one on the specification of the starting material, with no genotoxic impurities identified. All potential residual solvents are controlled within the active substance or methanol solvent raw material specification. An elemental impurity risk assessment is provided, where compliance with ICH Q3D is demonstrated.

Detailed information on the manufacture of the active substance has been provided in the restricted part of the ASMF, with a brief description also included in the applicant's part of the ASMF.

The active substance specification includes tests for description, identification by IR, specific optical rotation, assay, loss on drying, residue on ignition, related substances, residual solvents, microbial quality and particle size.

The control tests were carried out to comply with Ph. Eur. Substances for Pharmaceutical Use.

Batch analysis data for three batches of active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability data on three batches of active substance from the proposed manufacturer(s) stored to simulate the commercial packaging, were provided for 60 months under long term conditions at 25 ºC/60% RH and for six months under accelerated conditions at 40 ºC/75% RH according to the VICH guidelines. Results on stress conditions including heat, humidity, light, refrigeration, acid and base hydrolysis and oxidation were also provided on a single active substance batch.

The following parameters were tested during the stability study: description, solubility, loss on drying, related substances and assay. The parameters tested are the same as in the active substance specification. The analytical methods used were the same as for the active substance specification and the HPLC assay method has shown to be stability-indicating.

All tested parameters were within the specification. Degradation products increased slightly under accelerated conditions but remained within the specification.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container of double LDPE bags, with an additional storage statement of statement of 'Store in the original container' required.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. These include sodium benzoate, sorbitol liquid, glycerol, saccharin sodium, xylitol, sodium dihydrogen phosphate dihydrate, silica, colloidal anhydrous, xanthan gum, citric acid monohydrate (or citric acid, anhydrous), vanillin and purified water. The specification for Xanthan gum lists an additional test for the functionality related characteristics, viscosity, as recommended by the Ph. Eur. monograph. The option to use either citric acid monohydrate or citric acid anhydrous to formulate the products is considered acceptable given that neither should affect bioavailability or the quality of the product. Likewise, the proposal to use either purified water or water for injections is acceptable as different qualities of water will not impact on the quality of the product and purified water is specified as the minimum grade to be used.

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

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Control tests on the finished product

The finished product release specification controls relevant parameters for the dosage form, including tests for appearance of the product, net content, pH, density, viscosity, identification and assay of the active substance, identification and assay of the preservative, related substances, resuspendability, uniformity of mass of delivered doses and microbial quality. The finished product specifications are acceptable.

The analytical methods are well described and, have been validated in accordance with VICH GL1 *Validation of analytical procedures: definition and terminology* and VICH GL2 *Validation of analytical procedures: methodology.*

Acceptable comparative batch analysis data has been provided for two batches of the 10 mg/ml oral suspension filled into 30 ml and 90 ml bottles and two batches of the 50 mg/ml oral suspension filled into 10 ml, 25 ml, 36 ml, 50 ml, 72 ml and 100 ml bottles. The results for all three batches comply with the proposed specifications and are comparable between batches, confirming the consistency of the manufacturing process and its ability to manufacture to the proposed product specification. Satisfactory information has been provided for the reference standards.

A summary report of the risk management to justify the presence/absence of control strategy for elemental impurities in line with the CVMP guidance on risk management requirements for elemental impurities in veterinary medicinal products is provided and considered compliant with the aforementioned guidance document.

Stability

The proposed shelf-life of the veterinary medicinal product as packaged for sale is 3 years, with no special storage conditions. The proposed in-use shelf-life is 6 months. The proposed shelf-life specification is the same as that for release except for the lower limit for sodium benzoate. The analytical procedures used are stability indicating.

Stability data is provided for batches of the 10 mg/ml oral suspension and for batches of the 50 mg/ml oral suspension. The formulation of the batches of product is the same as that proposed for marketing, and products were packed in the same primary packaging proposed for marketing. Testing in the stability studies was carried out on both pack sizes (30 ml and 90 ml) for the 10 mg/ml product and on the 10 ml, 72 ml and 100 ml bottles for the 50 mg/ml product with the 25 ml, 36 ml and 50 ml bottles omitted from the study. However, this is justified given that the extremes of the container sizes were tested. Samples were stored at long-term conditions of 25 °C/60% RH and accelerated conditions of 40 °C/75% RH.

The parameters monitored on stability are appearance, pH, density, viscosity, sodium benzoate identification and assay, trilostane identification and assay, trilostane related substances and resuspendability. The test for microbiological quality was carried out at the initial and 24-month timepoints at 25 °C/60% RH and at the initial and 6-month timepoints at 40 °C/75% RH. Microbiological quality will be tested at the end timepoint (36 months) at 25 °C/60% RH. VICH GL 3 compliant data has been provided to 24 months on long-term conditions of 25 °C/60% RH and to 6 months on accelerated conditions of 40 °C/75% RH.

No trending in assay of trilostane is apparent with minor fluctuations observed at 25 °C/60% RH. Although some variability in results was observed with the lower strength 10 mg/ml product under accelerated conditions of 40 °C/75% RH these values were considered anomalous. Results for preservative content showed a decreasing trend over time, with a widening of the lower shelf-life assay limit for sodium benzoate to 80% being deemed appropriate. Very little variation is seen for pH and for viscosity. Microbiological quality and resuspendability (where tested), appearance and density are all within specification at all timepoints. All results for related substances (known, unknown and total) are within the specification.

The proposed shelf-life of 3 years is considered acceptable for both the 10 mg/ml and 50 mg/ml strengths with no storage precautions.

An in-use stability study was performed on 2 batches of each strength of the finished product at time of release and will be repeated again on products following 36 months storage. The parameters monitored on in-use stability at all time-points are appearance, pH, density, viscosity, sodium benzoate identification and assay, trilostane identification and assay, trilostane related substances and microbiological quality. Additionally, testing for efficacy of antimicrobial preservation, in line with the requirements of Ph. Eur. 5.1.3, was performed at the end of the study on the remaining quantities of product in the containers. Testing for viscosity was performed at the 3 and 6 month time points only (50 mg/ml product) and microbiological quality at the final timepoint exclusively (both strengths). The results for the physico-chemical testing were within specification for both batches throughout the study, with no obvious trending. The results for the physico-chemical testing were within specification for all batches throughout the study, with no obvious trending. All related substances results were within specification. Results for preservative efficacy at the 6-month testing timepoint are all reported to conform. An in-use shelf-life of 6 months is considered justified.

A photostability study was conducted on a single batch of each strength of product. Parameters tested included appearance, identity, assay, pH, density, viscosity and related substances. All results were within specification requirements with negligible differences observed between the various controls.

Although little detail has been provided with respect to the photostability study undertaken given that the primary packaging material (high density polyethylene) will allow only minimum exposure of the product to light and that the products will be stored in a cardboard box no precautionary warnings with respect to light exposure are deemed necessary for inclusion on the product information.

Overall conclusions on quality

The products are aqueous, white to off-white, oral suspensions containing either 10 mg/ml or 50 mg/ml of the active substance, trilostane. The 10 mg/ml strength is packaged in high density polyethylene bottles containing 30 ml or 90 ml of oral suspension whilst the 50 mg/ml strength is packaged in high density polyethylene bottles containing 10 ml, 25 ml, 36 ml, 50 ml, 72 ml or 100 ml of oral suspension. All bottles include a polypropylene/high density polyethylene child resistant stopper with a polyethylene plug placed in the bottle. Each package will be presented with a 1 ml and a 5 ml polypropylene measuring syringes.

Information on the development, manufacture and control of the active substance and the finished product is satisfactory.

In the development pharmaceutics section, the applicant provides a brief summary of the development of the formulation with some details of the optimisation of the formulation with respect to compatibility with and stability of the active substance. Comparative batch analysis data is provided to demonstrate that the test product used in the bioequivalence study is representative of typical batches. Data to demonstrate the compliance of the product with the requirements of Ph. Eur. 2.9.27 'Uniformity and accuracy of delivered doses from multidose containers' is provided and deemed acceptable.

The manufacturing process consists of sequential mixing of the excipients followed by addition of the active substance and homogenisation of the suspension. In-process controls are listed for each step of the process. Process validation data has been provided for two finished product batches, per product strength, of the minimum proposed batch size which has been justified and accompanied by a process validation scheme which will be used to perform process validation on the largest proposed batch size at a later date.

The active substance trilostane is not monographed in the Ph. Eur. and data on the active substance is provided in the form of Active Substance Master File (ASMF) procedure. The specification to control the material is considered suitable and satisfactory batch analysis data is provided. Satisfactory data demonstrating the stability of the active substance is provided in the ASMF.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. Information on the container-closure systems for the active substance and the finished product is provided. Data has been presented to give reassurance on TSE safety.

The finished product release specification controls relevant parameters for the dosage form. Analytical methods and validation have been provided. Acceptable comparative batch analysis data has been provided, along with information on the reference standards. An elemental impurities risk assessment is presented and deemed acceptable.

Finished product stability data in compliance with VICH GL 3 has been provided. A shelf-life of 3 years is acceptable for both strengths.

An in-use shelf-life of 6 months is considered justified and based on the provided photostability data, no precautionary warnings with respect to light exposure are deemed necessary for inclusion on the product information.

Part 3 – Safety documentation

This application has been submitted in accordance with Article 42 (a centralised application) and Article 19 of Regulation (EU) 2019/6 (a hybrid application).

Trilorale oral suspension contains the active substance trilostane and two strengths are proposed in this application: Trilorale 10 mg/ml oral suspension for dogs and Trilorale 50 mg/ml oral suspension for dogs. The product is intended for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs.

The reference product cited is Vetoryl 30 mg hard capsules (VPA22622/023/002), which was first granted a marketing authorisation in Ireland (current reference member state) following a mutual recognition procedure (IE/V/0514/002) on 1 October 2010.

Whilst the candidate product, Trilorale, has a different pharmaceutical form to the reference product Vetoryl (oral suspensions and oral capsules respectively) and the products are of different strengths (10 mg trilostane/ml and 50 mg trilostane/ml vs 30 mg per capsule respectively), both the candidate and reference products are immediate release pharmaceutical forms, intended to be administered to the same target species (dogs), at the same posology (2 mg trilostane/kg bw with titration to effect) using the same route of administration (oral) and for the same indications (for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism [Cushing's disease and syndrome] in dogs).

In order to claim bioequivalence between the candidate and reference product formulations, the applicant has submitted the results of an *in vivo* bioequivalence study in the target animal species, dogs, and an *in vitro* dissolution study comparing the 10 mg trilostane/ml and 50 mg trilostane/ml candidate formulations (see Part 4).

Safety tests

Pharmacology

Pharmacodynamics

No pharmacodynamic data has been presented. 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 routes of administration as the reference product, the pharmacodynamics of trilostane 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 pharmacodynamic properties of the active substance are adequately described in section 4.2 of the SPC.

Pharmacokinetics

An *in vivo* bioequivalence study in the target animal species, dogs, was provided (assessed under Part 4), in which bioequivalence between Trilorale 10 mg/ml oral suspension and Vetoryl 30 mg hard capsules was investigated. Based upon the results of that study, bioequivalence between Trilorale and the reference product (Vetoryl) can be accepted. The applicant proposes to include the same information on pharmacokinetics as included in section 4.3 of the SPC of the reference product.

Toxicology

No data relating to the toxicological profile of the product has been provided. Given that this application has been submitted in accordance with Article 19 of Regulation (EU) 2019/6, a hybrid application and bioequivalence with the reference product can be accepted, the results of toxicological studies are not required as this information can be extrapolated from the reference product.

Other requirements

Special studies

No data was presented. Given that this application has been submitted in accordance with Article 19 of Regulation (EU) 2019/6, a hybrid application and bioequivalence with the reference product can be accepted, the results of toxicological studies are not required as this information can be extrapolated from the reference product.

Excipients

Whilst the excipients included in the candidate formulation differ from those included in the reference formulation, from the information provided it can be accepted that the excipients included in Trilorale are either included in other oral/topical pharmaceutical preparations, are consumed naturally in the diet or are regarded as essentially non-toxic. Whilst no special studies have been conducted specifically evaluating the irritation or sensitisation potential of the final formulation of the candidate product, it is noted, based on the information provided, that local effects such as ocular irritation, contact dermatitis, urticaria, anaphylaxis and bronchospasm have been reported for certain excipients (sorbitol, sodium benzoate and vanillin). Therefore, the applicant has proposed that risk mitigation measures (RMMs) be included in the SPC. While, ideally, studies evaluating the potential of the final formulation to cause local effects should have been provided, the proposed RMMs are considered adequate to address the risks posed by the inclusion of these excipients and the irritation/sensitisation potential of the final formulation generally.

User safety

The applicant has submitted a user risk assessment in line with the European Guideline on User Safety for Veterinary Medicinal Products (EMA/CVMP/543/03-Rev.1). Notwithstanding the legal basis of the application (Article 19 of Regulation (EU) 2019/6, a hybrid application), a comprehensive user safety assessment is considered necessary given that the pharmaceutical form, strength and the excipients included in the candidate formulations, Trilorale 10 mg/ml and 50 mg/ml oral suspensions, differ from the reference formulation, Vetoryl 30 mg hard capsules.

Toxicity data for the active substance and the excipients have been considered in the risk characterisation for the candidate formulations. The candidate formulations are intended for administration on a daily basis by the owner in the home environment and the most likely route of accidental user exposure is considered to be dermal exposure, however, a risk of indirect oral or ocular exposure via hand-to-mouth or hand-to-eye contact is also possible, albeit this risk is considered low.

The qualitative risk characterisation conducted by the applicant took into consideration the toxicity data presented and the potential exposure scenarios, and consequently risk mitigation measures were proposed for section 3.5 of the SPC, such as warnings regarding potential skin and eye irritation and sensitisation, with the user advised to wash the in-contact area immediately with water and seek

medical advice should irritation persist. The information provided in the URA is considered sufficient to conclude upon the potential for local effects posed by the final formulation and no further information relating to the potential for local effects is required.

A quantitative risk characterisation has been provided which considered the risks posed to both the adult user and children, consequent to oral and dermal exposure. Only limited toxicological data and the lowest effective dose used in humans (120 mg/day) were available for the derivation of a toxicological reference value (TRV). When conducting exposure calculations, the applicant considered accidental oral exposure of an adult to 0.1 ml of either product (i.e. 10 mg/ml or 50 mg/ml formulation, that corresponds with exposure to 1 mg or 5 mg trilostane, respectively), with 100% bioavailability as a worst-case scenario, whereas for a child, oral exposure to 2 ml of either product (that corresponds with 20 mg or 100 mg trilostane, respectively) directly from a syringe, with 100% bioavailability, also considered a worst-case scenario. Based on this exposure, a risk can already be identified when compared to the lowest effect dose in humans (margins of exposure of 6 or 1.2 for children and 100 or 24 for adults, for 10 mg/ml or 50 mg/ml, respectively). Based upon this data and with the consequent exposure calculations identifying a risk, mitigation measures have been proposed for the product information, both reflecting those of the reference product but also taking into consideration the different pharmaceutical form for the candidate product (the candidate product is an oral suspension whereas the reference product is presented as hard capsules). Additionally, and in relation to potential risks to children, it is noted that the product is to be supplied in bottles with child-resistant closures and the applicant has provided appropriate certification of compliance with the relevant standards (ISO 8317). In conclusion, Trilorale is not expected to pose a risk for the user when used according to the SPC.

Environmental risk assessment

An environmental risk assessment conducted in accordance with the relevant guidelines, VICH GL6 (CVMP/VICH/592/98-Final) and the 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), has been provided. As the candidate product is intended for use in dogs, a non-food animal, the ERA can stop at Phase I and a Phase II assessment is not required.

Trilorale is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation: safety tests

This application has been submitted in accordance with Article 42 (a centralised application) and Article 19 of Regulation (EU) 2019/6 (a hybrid application).

Trilorale oral suspension contains the active substance trilostane and is intended for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs.

The reference product cited is Vetoryl 30 mg hard capsules (VPA22622/023/002) and bioequivalence between Trilorale 10 mg/ml oral suspension and Vetoryl has been investigated by means of an *in vivo* bioequivalence study (see Part 4).

Whilst the candidate product has a different pharmaceutical form to the reference product (oral suspension and oral capsules respectively) and is of a different strength (10 mg trilostane/ml and 50 mg trilostane/ml vs 30 mg per capsule respectively), it is noted that the candidate and reference products are oral immediate release pharmaceutical forms, intended to be administered to the same

target species (dogs), at the same posology (2 mg trilostane/kg bw with titration to effect) using the same routes of administration (oral).

Pharmacology:

The applicant has justified the omission of pharmacodynamic and pharmacokinetic data from this submission by claiming bioequivalence with the reference product, which is considered supported by the results of a bioequivalence study comparing one strength of the candidate product (10 mg trilostane/ml oral suspension) to the reference product, Vetoryl 30 mg hard capsules. Given that bioequivalence with the reference product can be accepted and that the candidate and reference products are immediate-release oral pharmaceutical forms and are intended to be administered to the same target species (dogs), at the same posology (2 mg trilostane/kg bw with titration to effect) using the same routes of administration (oral), the pharmacological properties of trilostane in the target species are not expected to differ between candidate and reference formulations and consequently, the omission of pharmacodynamic and pharmacokinetic data can be accepted.

Given that bioequivalence between Trilorale and the reference product can be accepted, the inclusion of text in sections 4.2 and 4.3 of the SPC consistent with that of the reference product is acceptable.

Toxicology:

Given the legal basis of the application (a hybrid application) and that bioequivalence with the reference product can be accepted, the results of toxicological studies are not required as this information can be extrapolated from the reference product.

User safety:

The applicant has submitted a user risk assessment in line with the European Guideline on User Safety for Veterinary Medicinal Products (EMA/CVMP/543/03-Rev.1). Notwithstanding the legal basis of the application, a comprehensive user safety assessment is considered necessary given that the presentation, strength and the excipients included in the candidate formulations, Trilorale 10 mg/ml and 50 mg/ml oral suspensions, differ from the reference formulation, Vetoryl 30 mg hard capsules. Whilst the toxicity data available for the active substance is limited, the applicant has provided a qualitative and a quantitative risk characterisation and consequently proposed risk mitigation measures which comprise warnings for inclusion in the product information and also a child-proof presentation for the candidate product. These measures are considered adequate.

Environmental risk assessment:

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

Part 4 – Efficacy

This application has been submitted in accordance with Article 42 (a centralised application) and Article 19 of Regulation (EU) 2019/6 (a hybrid application).

Trilorale oral suspension contains the active substance trilostane and two strengths are proposed in this application: Trilorale 10 mg/ml oral suspension for dogs and Trilorale 50 mg/ml oral suspension for dogs. The product is intended for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs.

The proposed starting dose for treatment is approximately 2 mg trilostane/kg bw with titration of the dose according to individual response to treatment. The product is to be administered once daily with food.

The reference product cited is Vetoryl 30 mg hard capsules (VPA22622/023/002), which was first granted a marketing authorisation in Ireland following a mutual recognition procedure (IE/V/0514/002) on 1 October 2010.

The candidate product has a different pharmaceutical form to the reference product (oral suspension and oral capsules, respectively) and is of a different strength (10 mg trilostane/ml and 50 mg trilostane/ml vs 30 mg trilostane per capsule, respectively). Both the candidate and reference products are immediate release pharmaceutical forms and are intended to be administered to the same target species (dogs), at the same posology (2 mg trilostane/kg bw with titration to effect) using the same route of administration (oral) and for the same indications (for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome).

In order to demonstrate bioequivalence with the reference product, the applicant has conducted a pivotal *in vivo* bioequivalence study in the target species dog and an *in vitro* dissolution study comparing the 10 mg trilostane/ml and 50 mg trilostane/ml candidate formulations, details of which are summarised below.

Pre-clinical studies

Pharmacology (pharmacodynamics and pharmacokinetics)

Please refer to part 3.

Bioequivalence studies

In order to demonstrate bioequivalence with the reference product Vetoryl 30 mg hard capsules, the applicant has submitted the results of a well conducted GLP study, in accordance with the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4) and VICH GL52 Bioequivalence: blood level bioequivalence study (EMA/CVMP/VICH/751935/2013-Corr).

A 10 mg trilostane/ml oral suspension (final formulation) was used as the test article for the purpose of demonstrating bioequivalence with the reference product Vetoryl 30 mg hard capsules.

The applicant chose a randomised, two period, two sequence, single dose crossover design, with a sufficiently long washout period. Thirty-two beagle dogs were assigned to one of two treatment groups; sample size was considered satisfactorily justified and study animals considered suitably representative of the target species, with regards weight, age and gender.

The test and reference articles were administered 15 minutes after feeding with further feed provided subsequent to dosing, which is consistent with the SPCs for the candidate and reference products which specify administration with food. Animals were orally administered either 3 ml of the test article (equating to 30 mg trilostane) or a 30 mg (trilostane) capsule of the reference product; actual dose ranges administered for the test and reference articles (2.07 – 2.83 and 2.08 – 2.84 mg trilostane/kg bw, respectively) were similar and considered acceptable in line with the SPCs proposed for the candidate product and approved for the reference product, which specify the starting dose for treatment as 2 mg trilostane/kg bw with titration to effect.

Determination of whether bioequivalence could be accepted was based upon AUC_t and C_{max}, with statistical analysis conducted in accordance with guideline recommendations. Bioequivalence for trilostane was to be accepted if the 90% confidence intervals for C_{max} and AUC_t were within an allowable ratio of the test mean to control mean of 80-125% for AUC_t and 70-143% for C_{max}. This is considered acceptable as the CVMP guideline on bioequivalence studies (EMA/CVMP/016/2000-Rev.4) specifies that whilst AUC should be entirely contained within the limits 80-125%, for C_{max}, as this parameter may exhibit a greater intra-individual variability, a maximal widening of the limits to 70-143% is acceptable provided it is prospectively defined in the protocol and justified from a safety and efficacy perspective. The applicant justified the widening of these limits in the study plan by highlighting the high variability for C_{max} observed in a pilot study conducted and noting that the SPC for the reference product specifies that dosing should be titrated to individual response. The justification provided is considered acceptable. Following statistical analysis, plasma trilostane values were observed to fall within the pre-determined confidence intervals for C_{max} (73.6% - 102.8%) and AUC_t (93.7% - 112.6%), thereby demonstrating bioequivalence between the test and reference articles.

In order to extrapolate the data derived from the pivotal bioequivalence study, which evaluated the 10 mg trilostane/ml oral suspension, to the 50 mg trilostane/ml oral suspension, the applicant has referred to section 7.2 of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4), which specifies that for an application concerning several strengths of an active substance, a bioequivalence study investigating only one strength may be acceptable provided *in vitro* equivalence data are presented for the additional strengths. The applicant has presented acceptable data, including the results of an *in vitro* dissolution study comparing the 10 mg trilostane/ml and 50 mg trilostane/ml oral suspensions, which are considered to fulfil the criteria set out under section 7.2 of the aforementioned bioequivalence guideline. Consequently, the extrapolation of bioequivalence data from the 10 mg/ml strength of the candidate product to the 50 mg/ml strength can be accepted.

Dose determination and confirmation

No data was presented. Given that bioequivalence with the reference product, Vetoryl, is accepted based on the results of both a bioequivalence study between the reference product and the 10 mg/ml strength of the candidate product and a dissolution study between both strengths of the candidate product, the omission of dose determination/confirmation data can be accepted as this can be extrapolated from the reference product.

Tolerance in the target animal species

No data was presented. The applicant considers the omission of target animal tolerance data justifiable on account of bioequivalence having been demonstrated for the candidate and reference product formulations. Whilst the candidate product has a different pharmaceutical form to the reference product (oral suspension and oral capsules, respectively) and is of a different strength (10 mg trilostane/ml and 50 mg trilostane/ml vs 30 mg trilostane per capsule, respectively), it is noted that the products are intended to be administered to the same target species, at the same posology, using the same route of administration and therefore, given that bioequivalence has been accepted, it would appear that target animal tolerance for the candidate product should reflect that for the reference product. However, the candidate formulation includes xylitol which is known to be toxic to dogs and consequently may pose a risk to the target species when ingested (hypoglycaemia). Based upon available safety data and a quantitative assessment, a dosing restriction has been applied to the 10

mg trilostane/ml formulation and for animals requiring trilostane doses greater than 2 mg/kg bodyweight, the 50 mg trilostane/ml formulation should be used. Provided this guidance is adhered to, the inclusion of xylitol should not pose a risk to the target animal. The product literature has been adequately updated to reflect this information. Other excipients included in the candidate product are not expected to pose any risk to the target animal.

In support of the omission of target animal tolerance data, the applicant has provided the results of a bioequivalence study comparing one of the candidate formulations (10 mg trilostane/ml oral suspension) with the reference formulation and the results of a dissolution study comparing both strengths of the candidate product, with these studies demonstrating bioequivalence for the candidate formulations and the reference product (that is the risk to the target animal from exposure to the active substance is not expected to differ between the candidate and reference products).

Clinical trials

No data was presented.

Given that bioequivalence with the reference product, Vetoryl, is accepted based on the results of both a bioequivalence study between the reference product and the 10 mg/ml strength of the candidate product and a dissolution study between both strengths of the candidate product, the provision of clinical trial data is unnecessary as this can be extrapolated from the reference product.

Overall conclusions on efficacy

This application has been submitted in accordance with Article 19 of Regulation (EU) 2019/6 (a hybrid application).

The reference product cited is Vetoryl 30 mg hard capsules.

The candidate product has a different pharmaceutical form to the reference product (oral suspension and oral capsules, respectively) and is of a different strength (10 mg trilostane/ml and 50 mg trilostane/ml vs 30 mg trilostane per capsule, respectively). Both the candidate and reference products are immediate release pharmaceutical forms and are intended to be administered to the same target species (dogs), at the same posology (2 mg trilostane/kg bw with titration to effect) using the same route of administration (oral) and for the same indications (for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome).

Pharmacology (pharmacodynamics and pharmacokinetics)

Please refer to Part 3.

Bioequivalence

A well-designed *in vivo* bioequivalence study that was conducted to GLP standard and designed in accordance with current guidance has been provided. The purpose of this study was to demonstrate bioequivalence between the reference product Vetoryl 30 mg hard capsules and the hybrid product Trilorale 10 mg/ml oral suspension, when administered at the recommended treatment dose of approximately 2 mg trilostane/kg bw.

The applicant specified a-priori that bioequivalence for trilostane was to be accepted if the 90% confidence intervals for C_{max} and AUC_t were within an allowable ratio of the test mean to control mean of 80-125% for AUC_t and 70-143% for C_{max}; the applicant provided justification for the widened acceptance criteria for C_{max}. The results of this study demonstrated that plasma trilostane values fell

within the pre-determined confidence intervals for C_{max} (73.6% - 102.8%) and AUC_t (93.7% - 112.6%), thereby demonstrating bioequivalence between the test and reference articles.

In order to extrapolate the data derived from the pivotal bioequivalence study, which evaluated the 10 mg trilostane/ml oral suspension, to the 50 mg trilostane/ml oral suspension, the applicant has presented acceptable *in vitro* equivalence data, including the results of dissolution studies conducted, which are considered to fulfil the criteria set out under section 7.2 of the CVMP guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.4). Consequently, bioequivalence with the reference product can be accepted for the 10 mg trilostane/ml strength of the candidate product and, through the provision of *in vitro* equivalence data, the extrapolation of bioequivalence data from the 10 mg/ml strength of the candidate product to the 50 mg/ml strength can be accepted.

Dose determination and confirmation

No data was presented. Given that bioequivalence with the reference product has been accepted, further dose justification/confirmation data is considered unnecessary as this can be extrapolated from the reference product.

Tolerance in the target animal species

No data was presented. Given that bioequivalence has been accepted, it is expected that target animal tolerance for the candidate product should reflect that for the reference product. However, the candidate formulation includes xylitol which is known to be toxic to dogs and consequently may pose a risk to the target species when ingested (hypoglycaemia). Consequently, a dosing restriction has been applied to the 10 mg trilostane/ml formulation and for animals requiring trilostane doses greater than 2 mg/kg bodyweight, the 50 mg trilostane/ml formulation should be used. Provided this guidance is adhered to, the inclusion of xylitol should not pose a risk to the target animal. The product literature has been adequately updated to reflect this information.

Clinical trials

No data was presented. Given that bioequivalence with the reference product can be accepted for both candidate formulations, the provision of clinical trial data is unnecessary as this can be extrapolated from the reference product.

Part 5 – Benefit-risk assessment

Introduction

Trilorale is an oral suspension for dogs containing 10 mg/ml or 50 mg/ml of trilostane as active substance.

Trilostane is an antiadrenal substance which selectively and reversibly inhibits the enzyme system 3 beta hydroxysteroid isomerase, thus blocking the production of cortisol, corticosterone and aldosterone. It is intended for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs. The proposed starting dose is approximately 2 mg/kg bodyweight, once daily.

The application has been submitted in accordance with Article 19(1) of Regulation (EU) 2019/6 (hybrid application).

Benefit assessment

Direct benefit

The active substance, trilostane, is a well-known antiadrenal substance in veterinary medicine. It is beneficial in the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs.

The evidence for the benefit is considered established on the basis of 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.

Additional benefits

Additional benefits associated with Trilorale include the availability of an alternative product on the marketplace for the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs, which has a different pharmaceutical form compared to the reference product (oral suspension vs hard capsules) and thus may facilitate increased administration compliance.

Risk assessment

Quality

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

Risks for the target animal

Trilorale is not expected to pose a risk to the target animal when used according to the SPC recommendations.

Risk for the user

Trilorale is not expected to pose a risk to the user when used according to the SPC recommendations.

Risk for the environment

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

Risk management or mitigation measures

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, the user and the 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 the treatment of pituitary-dependent and adrenal-dependent hyperadrenocorticism (Cushing's disease and syndrome) in dogs.

Based on the data presented to date, the overall benefit-risk balance is considered positive.

The CVMP accepted the indications as proposed by the applicant.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment.

The product information has been reviewed and is considered to be satisfactory and in line with the assessment.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Trilorale 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.