Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Methadyne 10 mg/ml Solution for Injection for Dogs and Cats

Date Created: September 2018

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Methadyne 10 mg/ml Solution for Injection for Dogs and Cats
Applicant	Jurox (UK) Limited Second Floor, Richmond House 105 High Street Crawley West Sussex RH10 1DD United Kingdom
Active substance	Methadone Hydrochloride
ATC Vetcode	QN02AC90
Target species	Dogs, cats
Indication for use	Analgesia. Premedication for general anaesthesia or neuroleptanalgesia in combination with a neuroleptic drug.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic 'hybrid' application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	20th September 2018

I. SCIENTIFIC OVERVIEW

The application was for a generic 'hybrid' product, Methadyne 10 mg/ml Solution for Injection for Dogs and Cats. The product is indicated for use as an analgesic and for premedication for general anaesthesia, or neuroleptanalgesia, in combination with a neuroleptic drug. The Summary of Product Characteristics (SPC) provides extensive information on dose and administration.

The reference products are: Methadon HCL 10 mg/ml (REG NL 2594), authorised in The Netherlands since April 2007. (Not authorised in the UK), and Comfortan 10 mg/ml Solution for Injection for Dogs, authorised in the UK since March 2011.

This was determined a generic 'hybrid' application because there were changes to the indication: cats were added to the authorisation. The new indication was acceptable when compared with Methadon HCL 10 mg/ml. The SPC for the proposed product is based on that of the UK reference product. The applicant claimed an exemption from the requirement for bioequivalence studies in accordance with exemptions 7.1 a) and 7.1 b) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev 2).

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC. The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy[1] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 10 mg/ml methadone hydrochloride, equivalent to 8.9 mg/ml methadone, and the excipients methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate, sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections.

The container/closure system consists of either a 5 ml or 10 ml amber, Type I glass vial with a teflon-coated chlorobutyl rubber stopper, and a 20 mm aluminium collar with a flip-off cap. One vial is presented in a cardboard box. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

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

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of: adding and mixing of active substances and excipients, heating and cooling as appropriate, pH adjustment if required, making up to volume with water, sterilisation of filled vials and quality control analysis.

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

II.C. Control of Starting Materials

The active substance is methadone hydrochloride, an established active substance described in the European Pharmacopoeia, (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice.

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

All excipients are supplied in accordance with Ph. Eur monographs and acceptable Certificates of Analysis were provided.

All relevant packaging materials carried acceptable Certificates of Suitability (active substance container), or a relevant Ph. Eur monograph, (finished product packaging).

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product are: appearance, clarity, identity of active and associated substances, degradation products, pH, sterility and volume of injection in the container.

II.F. Stability

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

G. Other Information

Do not mix with any other veterinary medicinal products, except as directed n section 4.9 of the SPC.
The product is incompatible with injection fluids containing meloxicam, or any other non-aqueous solution.
Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after first opening the immediate packaging: 28 days.
Chemical and physical stability of the dilutions has been demonstrated for 4 hours at 25°C, protected from light. From a microbiological point of view the dilutions should be used immediately.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Due to the nature of the application, no pharmacological or toxicological studies were required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The following applicant's user recommendations are appropriate:

- Methadone can cause respiratory depression following spillage onto the skin or accidental self-injection. Avoid skin, eye and mouth contact, and wear impermeable gloves when handling the product. In cases of spillage onto the skin, or splashing into the eyes, wash immediately with large amounts of water. Remove contaminated clothes.

- People with known hypersensitivity to methadone should avoid contact with the veterinary medicinal product. Methadone has the potential to cause stillbirths. Pregnant women are advised not to handle the product.

- In the case of accidental self-injection, seek medical advice immediately and show the package leaflet to the physician but DO NOT DRIVE as sedation may occur.

- ADVICE TO DOCTORS: Methadone is an opioid whose toxicity may cause clinical effects including respiratory depression or apnoea, sedation, hypotension and coma. When respiratory depression occurs controlled ventilation should be installed. Administration of the opioid antagonist naloxone to reverse the symptoms is recommended.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH[2] and CVMP[3] guidelines.

[2] VICH – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.
[3] CVMP – Committee for Medicinal Products for Veterinary Use.

The applicant provided an ERA which ended at Phase I, (Question 3 of the VICH decision tree) for non-food animals, and therefore exposure of the environment from the product is not considered significant. The product is not expected to pose a risk to the environment when used as recommended.

IV. CLINICAL DOCUMENTATION

The product contains the same qualitative and quantitative composition as the reference products in terms of active substance, and is presented in the same pharmaceutical form. Any differences in excipients are not expected to alter the bioavailability of the active substance. The applicant did not provide any clinical documentation and a waiver was sought from the requirement to demonstrate *in vivo* bioequivalence, in accordance with sections 7.1 a) and 7.1 b) of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).

The product is to be given by the intravenous, subcutaneous and intramuscular routes and so waivers 7.1 a) and 7.1 b) were considered appropriate. There are no differences in the qualitative or quantitative composition of the active substance or excipients that are expected to impact on the bioavailability, therefore, bioequivalence to the reference products was accepted. No further data were required.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product is favourable.

MODULE 4

POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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