MEB agency / Veterinary Medicinal Products Unit

The Netherlands

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Insistor 10 mg/ml solution for injection for dogs and cats (NL/V/0235/001/DC)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0235/001/DC
Name, strength and pharmaceutical form	Name: Insistor. Strength: 10mg/ml. Pharmaceutical form: solution for injection.
Applicant	Richter Pharma AG Feldgasse 19 4600 Wels Austria
Active substance(s)	Methadone hydrochloride
ATC Vetcode	QN02AC90
Target species	Dogs and cats.
Indication for use	Analgesia. Premedication for general anaesthesia or neuroleptanalgesia in combination with a neuroleptic drug.

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	28 March 2018.
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	AT, BE, DE, DK, EE, ES, FI, FR, HR, IE, LT, LV, NO, PT, SE, SI, UK.

1. SCIENTIFIC OVERVIEW

Insistor 10 mg/ml solution for injection for dogs and cats 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 specie.
Insistor 10 mg/ml solution for injection for dogs and cats is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

The safety and efficacy aspects of *Insistor 10 mg/ml solution for injection for dogs and cats* are based on bioequivalence with the reference product *Methadon HCl 10 mg/ml,* which has been authorized in the Netherlands since 20 September 1995 (REG NL 2594). The marketing authorisation holder of the reference product is Eurovet Animal Health B.V.

Eurovet Animal Health B.V. has also marketed a hybrid of *Methadon HCl 10 mg/ml* on the European market (*Comfortan 10 mg/ml solution for injection for dogs and cats*; procedure NL/V/0150/001/DC, REG NL 107389). *Comfortan* has been authorized for an extra target animal (cat), an extra route of administration in the dog (intravenous) and a dose range instead of a single dose. In addition, the following claims were added to the existing indication: '*premedication in combination with a neuroleptic drug'*. This has been properly underpinned by full data, i.e. additional safety and clinical studies, included in the hybrid dossier of *Comfortan.*

The product that is currently applied for, *Insistor 10 mg/ml solution for injection for dogs and cats*, has an almost identical composition to *Comfortan* and has an identical SPC. The reference product, *Methadon HCl*, and the hybrid product *Comfortan* (with inclusion of approved variations) belong to the same Global Marketing Authorization (Eurovet Animal Health B.V.). Therefore, the product applied for, *Insistor*, have been matched with their originator product, *Comfortan 10 mg/ml*.

Warnings statements and precautions are adopted from the reference products. Additional statements have been added, based on increased knowledge and the current state of science.

2. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The proposed product is a aqueous veterinary medicinal product for parenteral administration. The product contains 10 mg/mL methadone hydrochloride as active substance and the following excipients: methyl-parahydroxybenzoate, propyl-parahydroxybenzoate, sodium chloride, and water for injections. Hydrochloric acid (diluted) and sodium hydroxide are used for pH adjustment. The use of methyl-parahydroxybenzoate and propyl-parahydroxybenzoate and the used quantity has been adequately justified by the applicant.

The product is packed in clear type I glass vials of 10, mL, closed with chlorobutyl rubber stoppers and aluminium pull flip off cap. The glass vials and rubber stoppers are in conformity with Ph. Eur. requirements.

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

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured using conventional manufacturing techniques. Process validation results for five batches are given. The tests performed during production are described.

The maximum holding times between the subsequent individual production steps, maximum total holding time and total holding time of the sterile part of the process are provided. Furthermore, the chemical stability of the product during the total holding has been demonstrated.

The in-process control tests and acceptance criteria given are generally deemed adequate.

C. Control of Starting Materials

The active substance is methadone hydrochloride, an established active substance described in the European Pharmacopoeia. For the active substance the CEP procedure is followed. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The applicant only refers to the Ph. Eur. monograph for his drug substance specification. In addition, microbiological quality and 2-chloropropane are controlled in the drug substance.

Batch analytical data demonstrating compliance with this specification have been provided.

No materials of animal origin are contained or used in the manufacturing process of the veterinary medicinal product.

D. Control on intermediate products

Not applicable.

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 the corresponding acceptance criteria are considered acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been submitted, demonstrating compliance with the finished product specification.

F. Stability

A re-test period of 4 years for the active substance is indicated on the CEP when stored in double polyethylene bags placed in sheet-steel barrels.

The limits for single and total impurities at shelf-life is considered acceptable.

For the chlorobutyl rubber stopper sufficient stability data (12 months) is available so far, demonstrating adequate stability without adsorption to the stoppers. Based on the submitted stability data for the drug product, the proposed shelf-life of 24 months without any temperature precautions can be granted.

The product is sensitive to light and the vial should be stored in the outer carton in order to protect from light. In addition, adequate in-use stability data have been provided that support the proposed inuse storage claim of 28 days.

Furthermore, it has been adequately demonstrated that the product remains stable for 24 hours when diluted (1: 5) with Sodium Chloride 0.9%, Glucose 5% and Ringer's Solution (protected from light).

G. Other Information

Not applicable.

3. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13(1), and bioequivalence with the reference product has been demonstrated, results of toxicological, pharmacological and clinical tests tests are not required.

Warning statements and precautions as listed in the product literature are based on those of the reference products and supplemented with additional statements, based on increased knowledge and the current state of science. This information is considered adequate to ensure safety of the product to users and the environment.

3.A User Safety

User Safety

Being a generic procedure the applicant refers to the reference product for information on this section. Additionally, the applicant has provided a user safety assessment. Warnings statements and precautions are adopted from the reference products, ensuring safety to users of the product.

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Ecotoxicity

Phase 1

The environmental risk assessment can stop in Phase 1, because the product will be used only in nonfood animals.

Conclusion

Based on the data provided, the ERA can stop at Phase 1. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

4. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13(1), and bioequivalence with the reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are based on increased knowledge and the current state of science.

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 risk benefit profile for the target specie is favourable and the quality and safety of the product for humans and the environment is acceptable.

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

None.