**College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board**

**Graadt van Roggenweg 500**
**3531 AH Utrecht**
**The Netherlands**

# DECENTRALISED PROCEDURE

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## Comfortan 10 mg/ml, solution for injection for dogs and cats

**NL/V/0150/001**

**May 2022**

# MODULE 1

## PRODUCT SUMMARY

| | |
|---|---|
| EU Procedure number | NL/V/0150/001/DC |
| Name, strength and pharmaceutical form | Comfortan 10 mg/ml, solution for injection |
| Applicant | Eurovet Animal Health B.V.<br>Handelsweg 25,<br>5531AE Bladel,<br>The Netherlands |
| Active substance(s) | Methadone hydrochloride |
| ATC Vetcode | QN02AC90 |
| Target species | Dogs, cats |
| Indication for use | Analgesia in dogs and cats<br>Premedication for general anaesthesia or neuroleptanalgesia in dogs and cats in combination with a neuroleptic drug |

# 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 | Hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended. |
| Date of completion of the original decentralised procedure | 23 February 2011 |
| Date product first authorised in the Reference Member State (MRP only) | |
| Concerned Member States for original procedure | AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NO, PL, PT, SE, SK, UK |

## I. SCIENTIFIC OVERVIEW

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; the adverse effects 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 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.

## II. QUALITY ASPECTS

### *A. Composition*

The product contains methadone hydrochloride 10 mg per millilitre and excipients methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

The product is packed in uncoloured type I (Ph.Eur.) glass vials closed with Teflon coated chlorobutyl rubber stoppers type I (Ph.Eur.) secured with aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and presence of preservative is justified.

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.

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

## *C. Control of Starting Materials*

The active substance is methadone hydrochloride, an established active substance described in the European Veterinary Pharmacopoeia. 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.

Two active substance suppliers are used and for both suppliers a CEP has been provided.

The excipients comply with compendial requirements.

## *D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies*

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

## *E. Control on intermediate products*

Not applicable.

## *F. 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.

## *G. 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.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The claim of a 28-day stability after broaching has been justified, as well as the storage conditions of the opened product.

## *H. Genetically Modified Organisms*

Not applicable.

### *J. Other Information*

None.

## III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

### *III.A Safety Testing*

#### *Pharmacological Studies*

As this is a hybrid application according to Article 13 (3), and bioequivalence with a reference product (Methadon HCL 10 mg/ml, REG NL 2594) has been demonstrated, results of pharmacological studies are not required.

The pharmacological aspects of this product are identical to the reference product.

#### *Toxicological Studies*

As this is a hybrid application according to Article 13 (3), and bioequivalence with a reference product (Methadon HCL 10 mg/ml, REG NL 2594) has been demonstrated, results of toxicological studies are not required.

The toxicological aspects of this product are identical to the reference product.

#### *User Safety*

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product has typical opioid undesirable effects like respiratory depression and dependency following repeated administration. The product will only be used by highly skilled professionals (veterinarians) therefore the risk of accidental self injection in considered to be low and the risk of dermal exposure is limited as users have access to appropriate personal protective equipment.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

#### *Ecotoxicity*

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

# IV. CLINICAL ASSESSMENT (EFFICACY)

## *IV.A Pre-Clinical Studies*

### *Pharmacology*

The applicant has provided bibliographical data to show that methadone is structurally unrelated to opioid analgesics and exists as a racemic mixture. Each enantiomer has a separate mode of action; the d-isomer noncompetitively antagonizes the NMDA receptor and inhibits norepinephrine reuptake; the l-isomer is a μ-opioid receptor agonist. Methadone has the ability to produce profound analgesia. It can also be used for premedication and it can assist in the production of sedation in combination with tranquilizers or sedatives. The duration of effects may vary from 1.5 to 6.5 hours. Opioids produce a dose-dependent respiratory depression. Very high doses may result in convulsions.

In dogs methadone is absorbed very rapidly (Tmax 5-15 min) following intramuscular injection of 0.3 to 0.5 mg/kg. Tmax tends to be later at the higher dose levels indicating that an increase in dose tends to prolong the absorption phase. The rate and extent of systemic exposure of dogs to methadone appears to be characterised by dose-independent (linear) kinetics following intramuscular administration. The bioavailability is high and ranges between 65.4 and 100%, with a estimated mean of 90 %. Following subcutaneous administration of 0.4 mg/kg methadone is absorbed slower (Tmax 15 – 140 min) and bioavailability is 79 ± 22%. In dogs volume of distribution at steady state (Vss) was 4.84 and 6.11 L/kg in males and females respectively. The terminal half-life is in the range 0.9 to 2.2 hours following intramuscular administration, and is independent of dose and sex. The terminal half-life may be slightly longer following intravenous administration. The terminal half-life ranges from 6.4 to 15 hours following subcutaneous administration. Total plasma clearance (CL) of methadone following intravenous administration is high 2.92 to 3.56 L/h/kg or 70% to 85% of the cardiac plasma output in dogs (4.18 L/h/kg).

In cats methadone is also rapidly absorbed following intramuscular injection (peak values occur at 20 min), however when the product is administered subcutaneously (or in another poorly vascularised area) absorption will be slower. The terminal half-life is in the range of 6 to 15 hours. Clearance is medium to low with a mean (sd) value of 9.06 (3.3) ml/kg/min.

Methadone is extensively protein bound (60 to 90%). The opioids are lipophilic and weak bases. These physiochemical properties favour intracellular accumulation. Consequently, opioids have a large volume of distribution, which greatly exceeds total body water. A small amount (3 to 4% in the dog) of the administered dose is excreted unchanged in the urine; the remainder is metabolized in the liver and subsequently excreted.

### *Tolerance in the Target Species of Animals*

As this is a hybrid application according to Article 13 (3), and bioequivalence with a reference product (methadon HCL 10 mg/ml, REG NL 2594) has been demonstrated, target animal tolerance studies are not required. The tolerance claims for this product are equivalent to those of the reference product.

The applicant has conducted tolerance studies, using multiples of the recommended dose, for the new target species, cats.

In a study in cats doses up to 0.9 mg/kg were shown to have minimal adverse effects.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

### *IV.B Clinical Studies*

#### *Laboratory Trials*

As this is a hybrid application according to Article 13 (3), and bioequivalence with a reference product (methadon HCL 10 mg/ml, REG NL 2594) has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

The applicant has provided bibliographical data and has conducted dose determination and confirmation studies in order to support the addition of the target species cat.

In a dose response study in cats, doses between 0.1 mg/kg and 0.9 mg/kg induced significant effects on thermal and mechanical nociception thresholds. Maximum effects were seen at 0.6 and 0.9 mg/kg.

In a dose confirmation study in cats, efficacy of a dose of 0.6 mg/kg was confirmed.

#### *Field Trials*

As this is a hybrid application according to Article 13 (3), and bioequivalence with a reference product (methadon HCL 10 mg/ml, REG NL 2594) has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

The applicant performed a controlled field trial in the new target species cats. The use of the product in combination with acepromazine or medetomidine as a premedication regimen was evaluated. Buprenorphine and butorphanol were used as control products. Additionally the product was administered as an analgesic post-operatively. Sedation as well as analgesia provided by the product was not inferior to the controls. No adverse events were recorded.

## 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 risk benefit profile for the target species 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 Vetrinary 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.

### Safety/efficacy changes

| **Summary of change**<br>**(Type; application number)** | **Section updated in Module 3** | **Approval date** |
|---|---|---|
| Addition of target species - cats<br>(NL/V/0150/001/II/001) | IV | 24 July 2012 |

### Other changes

| **Summary of change**<br>**(Type; application number)** | **Section updated** | **Approval date** |
|---|---|---|
| One-off alignment of the product information with version 9.0 of the QRD templates<br>(NL/V/0150/001/A/009) | NA | 10 August 2023 |
| Subsequent Recognition Procedure - addition of BG as CMS<br>(NL/V/0150/001/E/002) | NA | 30 May 2022 |
| Renewal – NL RMS<br>(NL/V/0150/001/R/002) | Module 2 | 23 January 2021 |
| Change of ATCvet code<br>(NL/V/0150/001/IA/005) | Module 1 and 2 | 26 July 2017 |
| Repeat Use Procedure - addition of CMSs: CZ, EE, EL, FI, HU, IE, LT, LU, LV, NO and SK<br>(NL/V/0150/001/E/001) | NA | 22 June 2016 |
| Renewal – NL RMS<br>(NL/V/0150/001/R/001) | Module 2 | 9 February 2016 |