SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Comfortan 10 mg/ml solution for injection for dogs and cats
Spain, Italy, Portugal: Semfortan 10 mg/ml solution for injection for dogs and cats
France: Comfortan solution for injection for dogs and cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

Active substance:

Methadone	8.9 mg
equivalent to methadone hydrochloride	10 mg

Excipients:

Methyl parahydroxybenzoate (E218)	1.0 mg
Propyl parahydroxybenzoate	0.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
A clear colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

- Analgesia in dogs and cats.
- Premedication for general anaesthesia or neuroleptanalgesia in dogs and cats in combination with a neuroleptic drug.

4.3 Contraindications

Do not use in known cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in animals with advanced respiratory failure.
Do not use in animals with severe liver and renal dysfunction.

4.4 Special warnings for each target species

Due to the variable individual response to methadone, animals should be monitored regularly to ensure sufficient efficacy for the desired duration of effect.
Use of the product must be preceded by a thorough clinical examination.
In cats, pupil dilation is seen long after the analgesic effect has disappeared. It is therefore not an adequate parameter to assess clinical efficacy of the administered dose.
Greyhounds may require higher doses than other breeds to achieve efficacious plasma levels.

4.5 Special precautions for use

Special precautions for use in animals
Methadone may occasionally cause respiratory depression and, as with other opioid drugs, care should be taken when treating animals with impaired respiratory function, or animals that are receiving drugs that can cause respiratory depression. To ensure safe use of the product, treated animals should be monitored regularly, including examination of heart rate and respiratory rate.

As methadone is metabolised by the liver, its intensity and duration of action may be affected in animals with impaired liver function.
In case of renal, cardiac or hepatic dysfunction, or shock, there may be greater risk associated with the use of the product.
The safety of methadone has not been demonstrated in dogs less than 8 weeks and cats less than 5 months of age.
The effect of an opioid on head injury is dependent on the type and severity of the injury and the respiratory support supplied.
Safety has not been fully evaluated in clinically compromised cats.
Due to the risk of excitation, repeated administration in cats should be used with care.
The benefit/risk ratio for using the product should be made by the attending veterinarian.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
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.

4.6 Adverse reactions (frequency and seriousness)

In very common cases (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment), the following reactions have been observed after administration of the product:

Cats: Respiratory depression may be seen. Mild excitatory reactions have been observed: lip licking, vocalisation, urination, defaecation, mydriasis, hyperthermia and diarrhoea. Hyperalgesia has been reported. All reactions were transient.

Dogs: Respiratory and bradycardia depression may be seen. Mild reactions have been observed: panting, lip licking, salivation, vocalisation, irregular breathing, hypothermia, fixed stare and body tremors. Occasional urination and defaecation can be seen within the first hour post dose. All reactions were transient.

4.7 Use during pregnancy, lactation or lay

Methadone diffuses across the placenta.
Studies in laboratory animals have shown adverse effects on reproduction.
The safety of the product during pregnancy and lactation has not been assessed in the target species. The use of the product is not recommended during pregnancy or lactation.

4.8 Interaction with other medicinal products and other forms of interaction

For concurrent use with neuroleptics refer to section 4.9.
Methadone can potentiate the effects of analgesics, central nervous system inhibitors and substances that cause respiratory depression. Concomitant or subsequent use of the veterinary medicinal product with buprenorphine may lead to lack of efficacy.

4.9 Amounts to be administered and administration route

Before administration the body weight should be accurately determined.

Analgesia
Dogs: 0.5 to 1 mg Methadone HCl per kg bodyweight, SC, IM or IV (corresponding to 0.05 to 0.1 ml/kg)
Cats: 0.3 to 0.6 mg Methadone HCL per kg bodyweight, IM (corresponding to 0.03 to 0.06 ml/kg)
To ensure accuracy of dosing in cats, an appropriately calibrated syringe should be used to administer the product.

As the individual response to methadone is varied, and depends partly on the dosage, the age of the patient, individual differences in pain sensitivity and general condition, the optimal dosing regimen should be individually based.
In dogs, onset of action is 1 hour following subcutaneous administration, approximately 15 minutes following intramuscular injection and within 10 minutes following intravenous injection. Duration of effect is approximately 4 hours following intramuscular or intravenous administration.
In cats, onset of action is 15 minutes following administration, and the duration of effect is 4 hours on average.
The animal should be examined regularly to assess if additional analgesia is subsequently required.

Premedication and/or neuroleptanalgesia

Dogs:

- Methadone HCl 0.5-1 mg/kg bodyweight, IV, SC or IM (corresponding to 0.05 to 0.1 ml/kg)

Combinations e.g.:

- Methadone HCl 0.5 mg/kg bodyweight, IV (corresponding to 0.05 ml/kg), + e.g. midazolam or diazepam
  Induction with propofol, maintenance on isoflurane in oxygen.

- Methadone HCl 0.5 mg/kg bodyweight, IV (corresponding to 0.05 ml/kg), + e.g. acepromazine
  Induction with thiopentone or propofol to effect, maintenance on isoflurane in oxygen or induction with diazepam and ketamine.

- Methadone HCl 0.5 -1.0 mg/kg bodyweight, IV or IM (corresponding to 0.05 to 0.1 ml/kg), + α_2-agonist (e.g. xylazine or medetomidine)
  Induction with propofol, maintenance with isoflurane in combination with fentanyl or total intravenous anaesthesia (TIVA) protocol: maintenance with propofol in combination with fentanyl.

TIVA protocol: induction propofol, to effect. Maintenance with propofol and remifentanil. Chemical-physical compatibility has only been demonstrated for dilutions 1:5 with the following solutions for infusion: sodium chloride 0.9%, Ringer's solution, and glucose 5%.

Cats:

- Methadone HCl 0.3-0.6 mg/kg bodyweight, IM (corresponding to 0.03 to 0.06 ml/kg)
  - Induction with benzodiazepine (e.g. midazolam) and dissociative (e.g. ketamine).
  - With a tranquiliser (e.g. acepromazine) and NSAID (meloxicam) or sedative (e.g. α_2-agonist).
  - Induction with propofol, maintenance with isoflurane in oxygen.

Doses are dependent on the desired degree of analgesia and sedation, desired duration of effect and the concurrent use of other analgesics and anaesthetics.
When used in combination with other products, lower dosages can be used.
For safe use with other veterinary medicinal products, reference must be made to the relevant product literature.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

A 1.5 fold overdose resulted in the effects described in section 4.6.
Cats: In case of overdoses (>2 mg/kg) the following signs can be observed: increased salivation, excitation, hind leg paralysis and loss of righting reflex. Seizures, convulsion and hypoxia were also recorded in some cats. A dose of 4 mg/kg could be fatal in cats. Respiratory depression has been described.
Dogs: Respiratory depression has been described.
Methadone can be antagonised by naloxone. Naloxone should be given to effect. A starting dose of 0.1 mg/kg intravenously is recommended.

4.11 Withdrawal periods

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Diphenylpropylamine derivatives.
ATCvet code: QN02AC90.

5.1 Pharmacodynamic properties

Methadone is structurally unrelated to other opium-derived analgesics and exists as a racemic mixture. Each enantiomer has a separate mode of action; the d-isomer non-competitively antagonises the NMDA receptor and inhibits norepinephrine reuptake; the l-isomer is a μ-opioid receptor agonist.
There are two subtypes μ_1 and μ_2. The analgesic effects of methadone are believed to be mediated by both the μ_1 and μ_2 subtypes, whereas the μ_2 subtype appears to mediate respiratory depression and inhibition of gastrointestinal motility. The μ_1 subtype produces supraspinal analgesia and the μ_2 receptors produce spinal analgesia.
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 tranquilisers or sedatives. The duration of effect may vary from 1.5 to 6.5 hours. Opioids produce a dose-dependent respiratory depression. Very high doses may result in convulsions.

5.2 Pharmacokinetic particulars

In dogs, methadone is absorbed very rapidly (T_{max} 5-15 minutes) following intramuscular injection of 0.3 to 0.5 mg/kg. T_{max} 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 mean estimate of 90%. Following subcutaneous administration of 0.4 mg/kg, methadone is absorbed slower (T_{max} 15-140 minutes) and bioavailability is 79 ± 22%.

In dogs, the volume of distribution at steady state (V_{ss}) 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 ca 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 minutes), however, when the product is administered inadvertently 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%). 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 metabolised in the liver and subsequently excreted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E 218)
Propyl parahydroxybenzoate
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Do not mix with any other veterinary medicinal products, except for the infusion solutions indicated in section 4.9.
The product is incompatible with injection fluids containing meloxicam, or any other non-aqueous solution.

6.3 Shelf life

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.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and composition of immediate packaging

- Vials of uncoloured glass type I filled with 5 ml, 10 ml, 20 ml, 25 ml, 30 ml and 50 ml.
- Teflon-coated chlorobutyl rubber stopper type I secured with an aluminium cap.

1 vial in a cardboard box.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eurovet Animal Health B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

8. MARKETING AUTHORISATION NUMBER

Vm 16849/4022

9. DATE OF FIRST AUTHORISATION

30 March 2011

10. DATE OF REVISION OF THE TEXT

August 2017

PROHIBITION OF SALE, SUPPLY AND/OR USE

This product falls within the regime of controlled drugs Schedule II.

Approved: 15 August 2017