ANNEX II

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE
OUTER CARTON / 5 ML, 10 ML, 20 ML, 25 ML, 30 ML, 50 ML

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Comfortan 10 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
8.9 mg methadone equivalent to 10 mg methadone hydrochloride

3. PACKAGE SIZE

5 ml 10 ml 20 ml 25 ml 30 ml, 50 ml

4. TARGET SPECIES

Dogs and cats.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Dog: SC, IM or IV use.
Cat: IM use.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp.: {mm/yyyy}
Once broached, use within 28 days. Use by:__/__/__

9. SPECIAL STORAGE PRECAUTIONS

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

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Eurovet Animal Health B.V.

14. MARKETING AUTHORISATION NUMBER

Vm 16849/3005

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

{LABEL / 50 ML}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Comfortan 10 mg/ml solution for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
8.9 mg methadone equivalent to 10 mg methadone hydrochloride

3. TARGET SPECIES

Dogs and cats.

4. ROUTES OF ADMINISTRATION

Dog: SC, IM or IV use.
Cat: IM use.
Read the package leaflet before use.

5. WITHDRAWAL PERIODS

6. EXPIRY DATE

Exp. {mm/yyyy}
Once broached, use within 28 days. Use by:__/__/__

7. SPECIAL STORAGE PRECAUTIONS

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

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Eurovet Animal Health B.V.

9. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / 5 ML, 10 ML, 20 ML, 25 ML, 30 ML

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Comfortan

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Each ml contains:
10 mg methadone hydrochloride.

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp.: {mm/yyyy}
Once broached, use within 28 days. Use by: __/__/__

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

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

2. Composition

Each ml contains:

Active substance:
Methadone 8.9 mg
equivalent to methadone hydrochloride 10 mg

Methyl parahydroxybenzoate (E218) 1.0 mg
Propyl parahydroxybenzoate 0.2 mg

A clear colourless to pale yellow solution.

3. Target species

Dogs and cats.

4. Indications for use

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

5. Contraindications

Do not use in 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.

6. Special warnings

Special warnings:

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 veterinary medicinal 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.

Special precautions for safe use in the target species:

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 veterinary medicinal 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 cases of renal, cardiac or hepatic dysfunction, or shock, there may be greater risk associated with the use of the veterinary medicinal 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 veterinary medicinal 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 veterinary medicinal 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. The veterinary medicinal product should not be administered by pregnant women.

In 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.

To the physician: 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.

Pregnancy and lactation:

The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Methadone diffuses across the placenta. The use is not recommended during pregnancy or lactation.

Fertility:

Studies in laboratory animals have shown adverse effects on reproduction.

Interaction with other medicinal products and other forms of interaction:

For concurrent use with neuroleptics refer to section “Dosage for each species, routes and method of administration”.
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.

Overdose:

A 1.5 fold overdose resulted in the effects described in section “Adverse events”.
Cats: In cases of overdose (>2 mg/kg) the following signs can be observed: increased salivation, excitation, hind leg paralysis and loss of righting reflex.

Seizures, convulsions 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.

Special restrictions for use and special conditions for use:

Major incompatibilities:
Do not mix with any other veterinary medicinal products, except for the infusion solutions indicated in section “Dosage for each species, routes and method of administration”.
The veterinary medicinal product is incompatible with injection fluids containing meloxicam, or any other non-aqueous solution.

7. Adverse events

Cats[1]:

Very common (>1 animal / 10 animals treated):	Respiratory depression. Excitation [2]: lip licking, vocalisation, urination, involuntary defecation, mydriasis (dilated pupils), hyperthermia (elevated body temperature), diarrhoea. Hypersensitivity to pain.

[1] All reactions were transient.
[2] Mild

Dogs[1]:

Very common (>1 animal / 10 animals treated):	Respiratory depression. Bradycardia (slow heart rate). Excitation [2]: panting, lip licking, hypersalivation (increased salivation), vocalisation, irregular breathing, hypothermia (low body temperature), staring, tremor, urination [3] and involuntary defaecation [3].

[1] All reactions were transient.
[2] Mild.
[3] Occasional, within first hour post dose.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or the local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system {national system details}.

8. Dosage for each species, routes and method of administration

To ensure accuracy of dosing, bodyweight should be accurately measured and an appropriately calibrated syringe should be used to administer the veterinary medicinal product.

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).

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 (diseases etc.), 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 on isoflurane in oxygen, in combination with fentanyl or total intravenous anaesthesia (TIVA) protocol: maintenance on propofol in combination with fentanyl.

TIVA protocol: induction propofol, to effect. Maintenance on 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 on 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 veterinary medicinal products, lower dosages can be used.
For safe use with other veterinary medicinal products, reference must be made to the relevant product literature.

9. Advice on correct administration

Refer to section "Dosage for each species, routes and method of administration"

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.
Store in the original package in order to protect from light.

Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of the month.

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.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Vm 16849/3005

Pack sizes: 5 ml, 10 ml, 20 ml, 25 ml, 30 ml and 50 ml.
Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

August 2023

Detailed information on this veterinary medicinal product is available in the Union Product Database (*https://medicines.health.europa.eu/veterinary*).

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:

Manufacturer responsible for batch release:
Eurovet Animal Health BV
Handelsweg 25
5531 AE Bladel,
The Netherlands

Local representatives and contact details to report suspected adverse reactions:

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

Approved 03 November 2023