1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

8.9 mg Methadone equivalent to 10.0 mg Methadone hydrochloride

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Methyl parahydroxybenazoate (E218)	1.0 mg
Propyl parahydroxybenzoate	0.2 mg
Sodium chloride	
Sodium hydroxide	
Hydrochloric acid, concentrated	
Water for Injection	

The veterinary medicinal product is a clear, colourless solution for injection.

3. CLINICAL INFORMATION

3.1 Target species

Dogs and cats.

3.2 Indications for use for each target species

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

3.3 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.

3.4 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.

3.5 Special precautions for use

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 case 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. Pregnant women are advised not to handle the veterinary medicinal 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 initiated. Administration of the opioid antagonist naloxone to reverse the symptoms is recommended.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cats:

Very common (>1 animal / 10 animals treated):	Respiratory depression. Excitation[1] Vocalisation. Hyperthermia. Urination. Lip licking, involuntary defecation and diarrhoea. Hypersensitivity to pain, mydriasis.

All reactions were transient.
[1]: Mild
Methadone can be antagonised by naloxone (for further information see section 3.10)

Dogs:

Very common (>1 animal / 10 animals treated):	Respiratory depression, panting, irregular breathing; Bradycardia; Vocalisation; Lip licking, increased salivation, and involuntary defecation[2]; Urination[2]; Hypothermia; Fixed stare and tremor.

All reactions were transient.
[2:] Within first hour post dose
Methadone can be antagonised by naloxone (for further information see section 3.10)

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See also the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

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

3.8 Interaction with other medicinal products and other forms of interaction

For concurrent use with neuroleptics refer to section 3.9.

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.

3.9 Administration routes and dosage

Dogs – intravenous, intramuscular or subcutaneous use;
Cats – intramuscular use.

To ensure a correct dosage, body weight should be determined as accurately as possible. The cap may be safely punctured up to 34 times.

Analgesia

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

Cats: 0.3 to 0.6 mg Methadone HCl per kg bodyweight IM (corresponding to 0.03 to 0.06 ml/kg)

The use of suitably calibrated measuring equipment is recommended.

As the individual response to methadone is variable, 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, following intramuscular injection, onset of action is 15 minutes, 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 to1 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 with 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 with 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), + α2-agonist (e.g. xylazine or medetomidine)
  Induction with propofol, maintenance with isoflurane in oxygen, 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 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. α2-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 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.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

A 1.5 fold overdose resulted in the effects described in section 3.6.
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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

This veterinary medicinal product is for administration only by a veterinarian or under their supervision.

3.12 Withdrawal period

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QN02AC90

4.2 Pharmacodynamics

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 μ1 and μ2. The analgesic effects of methadone are believed to be mediated by both the μ1 and μ2 subtypes, whereas the μ2 subtype appears to mediate respiratory depression and inhibition of gastrointestinal motility. The μ1 subtype produces supraspinal analgesia and the μ2 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.

4.3 Pharmacokinetics

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 veterinary medicinal 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.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

The veterinary medicinal product is incompatible with injection fluids containing meloxicam, or any other non-aqueous solution.

In the absence of further compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products, with the exception of those stated in section 3.9.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 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.
Shelf-life of diluted solutions: use immediately.

5.3 Special precautions for storage

This medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

Presented in either a 5 ml, 10 ml or 20 ml amber, Type I glass vial, with Teflon-coated chlorobutyl rubber stopper type 1 secured with a 20 mm aluminium collar with a flip-off cap.
1 vial in a cardboard box.

Not all pack sizes may be marketed.

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

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 national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Zoetis Belgium S.A.

7. MARKETING AUTHORISATION NUMBER(S)

VPA 10387/106/001

8. DATE OF FIRST AUTHORISATION

08 September 2023

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

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