SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Synthadon 5 mg/ml solution for injection for cats and dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:	Methadone hydrochloride	5 mg
	equivalent to methadone	4.47 mg
Excipients:	Methyl parahydroxybenzoate (E218)	1.0 mg
	Propyl parahydroxybenzoate (E216)	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 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 regularly monitored to ensure sufficient efficacy for the desired effect duration. Use of the product must be preceded by a thorough clinical examination. In cats pupil dilatation 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. Use in the above mentioned cases should be in accordance with a benefit/risk assessment by the responsible veterinarian.

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

Methadone can cause respiratory depression following spillage on the skin or accidental self injection. Avoid skin, eyes and mouth contact and wear impermeable gloves when handling the product. In case of spilling on the skin or splashing in 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 case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label 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 initiated. Administration of the opioid antagonist naloxone to reverse the symptoms is recommended.

4.6 Adverse reactions (frequency and seriousness)

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

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))

- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

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 veterinary medicinal product has not been established during pregnancy or lactation.
The use is not recommended during pregnancy and 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 inhibiters 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

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

Analgesia
Dogs: 0.5 to 1 mg methadone hydrochloride per kg bodyweight, subcutaneously, intramuscularly or intravenously (corresponding to 0.1 to 0.2 ml/kg)
Cats: 0.3 to 0.6 mg methadone hydrochloride per kg bodyweight, intramuscularly (corresponding to 0.06 to 0.12 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 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 in 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, IV, SC or IM

Combinations e.g.:
- Methadone HCl 0.5 mg/kg, IV + e.g. midazolam or diazepam

Induction with propofol, maintenance on isoflurane in oxygen.

- Methadone HCl 0.5 mg/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, IV or IM + α2-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 solution, and glucose 5%.

Cats:

- Methadone HCl 0.3 to 0.6 mg/kg, IM
  - Induction with Benzodiazepine (e.g. midazolam) and dissociative (e.g. ketamine);
  - With a tranquilizer (e.g. acepromazine) and NSAID (meloxicam) or sedative (e.g. α2-agonist);
  - Induction with propofol, maintenance with isoflurane in oxygen.

Doses depend 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 pharmaceuticals, reference must be made to the relevant product literature.

The stopper should not be punctured more than 20 times.

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 antagonized by naloxone. Naloxone should be given to effect. A starting dose of 0.1 mg/kg intravenously is recommended.

4.11 Withdrawal period(s)

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

noncompetitively antagonizes 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 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.

5.2 Pharmacokinetic particulars

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 mean estimate 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 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 min), 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%). 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Major incompatibilities

Do not mix with any other veterinary medicinal product except the infusion solutions indicated in section 4.9.
The product is incompatible with injection fluids containing meloxicam or any other nonaqueous 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
Shelf-life after dilution according to directions: 4 hours, protected from light

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

Nature of container:
Clear colourless type I glass bottle
Teflon coated bromobutyl rubber 20 mm stopper
Aluminium 20 mm cap

Pack size:
Cardboard box containing 1 vial of 5, 10, 20, 25, 30 or 50 mL

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

8. MARKETING AUTHORISATION NUMBER

Vm 41821/4009

9. DATE OF FIRST AUTHORISATION

07 October 2014

10. DATE OF REVISION OF THE TEXT

24 September 2019

Approved 24 September 2019