ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Outer carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCES

Methadone hydrochloride 5 mg
equivalent to methadone 4.47 mg

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

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

5. TARGET SPECIES

Cats and dogs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Dogs: SC, IM, IV
Cats: IM

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

Accidental self-injection is dangerous.

*****Only for those countries where expanded text is proposed:*****
Wear impermeable gloves.
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 symptoms is recommended

10. EXPIRY DATE

EXP {month/year}
Once broached use by…

11. SPECIAL STORAGE CONDITIONS

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

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

16. MARKETING AUTHORISATION NUMBER(S)

Vm 41821/4009

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

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

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Synthadon 5 mg/ml injection for cats and dogs
Methadone hydrochloride

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Methadone hydrochloride: 5 mg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

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

4. ROUTE(S) OF ADMINISTRATION

Dogs: SC, IM, IV
Cats: IM

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:
Synthadon 5 mg/ml solution for injection for cats and dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

Manufacturer responsible for batch release:
Produlab Pharma B.V.
Forellenweg 16
4941 SJ Raamsdonksveer
The Netherlands

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

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

A clear colourless to pale yellow solution.

4. INDICATION(S)

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. ADVERSE REACTIONS

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)

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.
Alternatively you can report via your national reporting system {national system details}.

7. TARGET SPECIES

Dogs and cats

8. DOSAGE FOR EACH SPECIES, ROUTE(S) 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 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 + 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 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.*, α_2-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.

9. ADVICE ON CORRECT ADMINISTRATION

See section 8.

10. WITHDRAWAL PERIOD(S)

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. The expiry date refers to the last day of that month.

Shelf-life after first opening the immediate packaging: 28 days
Shelf-life after dilution according to directions: 4 hours, protected from light

When the container is broached (opened) for the first time, using the in-use shelf-life which is specified on this package leaflet, the date on which any product remaining in the container should be discarded should be worked out. This discard date should be written in the space provided on the label.

12. SPECIAL WARNING(S)

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.
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.

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 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 installed. Administration of the opioid antagonist naloxone to reverse the symptoms is recommended.

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 has not been established during pregnancy or lactation.
The use is not recommended during pregnancy and lactation.

Interaction with other medicinal products and other forms of interaction
For concurrent use with neuroleptics refer to section 8.
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 (symptoms, emergency procedures, antidotes)
A 1.5-fold overdose resulted in the effects described in section 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.

Incompatibilities
Do not mix with any other veterinary medicinal product except the infusion solutions indicated in section 8.
The product is incompatible with injection fluids containing meloxicam or any other non-aqueous solution.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste. Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

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

Not all pack sizes may be marketed.

Approved 24 September 2019