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

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:

Methadone hydrochloride	5 mg
equivalent to methadone	4.47 mg

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

Dogs: subcutaneous, intramuscular or intravenous use.
Cats: intramuscular 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

Le Vet Beheer B.V.

14. MARKETING AUTHORISATION NUMBERS

Vm 41821/3007

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

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

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Synthadon

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

5 mg/ml

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

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

2. 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

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 regularly monitored to ensure sufficient efficacy for the desired effect duration. Use of the veterinary medicinal 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 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. 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 personal protective equipment consisting of impermeable gloves should be worn when handling the veterinary medicinal 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 veterinary medicinal 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:
A 1.5-fold overdose resulted in the effects described in section 7.

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.

<Special restrictions for use and special conditions for use:>

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

7. Adverse events

Cats:

Very common (>1 animal / 10 animals treated):	Lip licking[1,2], diarrhoea[1,2], involuntary defecation[1,2] Respiratory depression[2] Vocalisation[1,2] Urination[1,2] Mydriasis (dilated pupils)[1,2] Hyperthermia (elevated body temperature)[1,2] Hypersensitivity to pain[2]

[1]Mild
[2]Transient

Dogs:

Very common (>1 animal / 10 animals treated):	Respiratory depression[2], panting[1,2], irregular breathing[1,2] Bradycardia (slow heart rate)[2] Lip licking[1,2], hypersalivation (increased salivation)[1,2] Vocalisation[1,2] Hypothermia (low body temperature)[1,2] Staring[1,2], Tremor[1,2]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Urination[2,3] Involuntary defecation[2,3]

[1]Mild
[2]Transient
[3]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

Dogs:
Subcutaneous, intramuscular or intravenous use.

Cats:
Intramuscular use.

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 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.

9. Advice on correct administration

The stopper should not be punctured more than 20 times.

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 carton and the label after Exp. 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 veterinary medicinal 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 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

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

Not all pack sizes may be marketed.

15. PID LINK (Do not print heading)

[The following statement must be included where reference to the European Union Product Database is included on the product information. This statement is relevant to both UK(GB) and UK(NI) products:]

Find more product information by searching for the 'Product Information Database' on www.gov.uk.

16. Contact details

Marketing authorisation holder <and contact details to report suspected adverse reactions>:
Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands
Tel.: +31 348 563434

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

Local representatives and contact details to report suspected adverse reactions:

Animalcare Ltd
Moorside
Monks Cross
York,
YO32 9LB
United Kingdom
+44 (0)330 8189 717

17. Other information

Gavin Hall

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