ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON <THE OUTER PACKAGE

5 mL printed carton, 10ml printed carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Methadyne 10 mg/ml solution for injection for dogs and cats.
Methadone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCES

Methadone hydrochloride 10.0 mg/ml (equivalent to 8.9 mg/ml Methadone)
Preservative: Methyl paraben, propyl paraben

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

5 ml
10 ml

5. TARGET SPECIES

Dogs and cats

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Administration:
Read the package leaflet before use.
Dog – intravenous, intramuscular or subcutaneous injection
Cat – intramuscular injection

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

10. EXPIRY DATE

EXP (month/year)
Shelf life after first broaching vial: 28 days.

11. SPECIAL STORAGE CONDITIONS

Store below 30°C.
For further instructions on use after dilution, refer to package leaflet.

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

Dispose of waste material in accordance with local requirements. Any unused product must be disposed of in accordance with the Misuse of Drugs Regulations (2001).

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

For animal treatment only. To be supplied only on veterinary prescription. **POM-V**

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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

Zoetis UK Limited
1st Floor, Birchwood Building
Springfield Drive
Leatherhead
Surrey
KT22 7LP

16. MARKETING AUTHORISATION NUMBER(S)

Vm 42058/4220

17. MANUFACTURER'S BATCH NUMBER

Batch:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

5 mL vial label, 10mL vial label

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Methadyne 10 mg/ml solution for injection for dogs and cats.
Methadone hydrochloride

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

10 mg/ml

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

5 ml
10 ml

4. ROUTE(S) OF ADMINISTRATION

Administration:
Read the package leaflet before use.
Dog – IV, IM, SC injection
Cat – IM injection

5. WITHDRAWAL PERIOD(S)

6. BATCH NUMBER

Batch:

7. EXPIRY DATE

EXP: month/year
Once broached, use by 28 days.
Once broached, use by _____.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only. **POM-V**

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B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Methadyne 10 mg/ml solution for injection for dogs and cats.

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

Marketing authorisation holder
Zoetis UK Limited
1st Floor, Birchwood Building
Springfield Drive
Leatherhead
Surrey
KT22 7LP

Manufacturer responsible for batch release:
Zoetis Manufacturing & Research Spain, S.L.
Ctra. de Camprodón, s/n°
Finca La Riba
Vall de Bianya
17813 Gerona
Spain

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Methadyne 10 mg/ml solution for injection for dogs and cats.
Methadone hydrochloride

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

A clear colourless solution for injection containing methadone hydrochloride 10 mg/ml as the active substance, and methyl parahydroxybenazoate (E218) 1.0 mg/ml and propyl parahydroxybenzoate 0.2 mg/ml as preservatives.

4. INDICATION(S)

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

5. CONTRAINDICATIONS

Do not use in known 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

In very common cases (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment), the following 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. Occasional urination and defaecation can be seen within the first hour post dose. All reactions were transient.

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 inform the manufacturer or the national reporting system.

7. TARGET SPECIES

Dog and cats

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Administration: Dog –intravenous, intramuscular or subcutaneous injection
Cat – intramuscular injection

Species	Route of Administration	Analgesia	Premedication
Dog	Intravenous, intramuscular or subcutaneous injection	0.5 to 1 mg Methadone HCl per kg, (0.05 to 0.1 ml/kg)[B]	0.5 to 1 mg Methadone HCl per kg, (0.05 to 0.1 ml/kg)[B]
Cat	Intramuscular injection	0.3 to 0.6 mg Methadone HCl per kg, (0.03 to 0.06 ml/kg)[A].	0.3 to 0.6 mg Methadone HCl per kg, (0.03 to 0.06 ml/kg)[A].

[A] For cats use an appropriately calibrated syringe.
[B] Greyhounds may require higher doses than other breeds to achieve efficacious plasma levels.

Neuroleptanalgesia and use in combinations:
Dogs[B] (refer to dose table):

- 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 protocol, to effect. Maintenance with propofol and remifentanil

Cats:

- Methadone HCl 0.3-0.6 mg/kg bodyweight, IM (corresponding to 0.03 to 0.06 ml/kg) may be used in the following combinations:
  - 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.

9. ADVICE ON CORRECT ADMINISTRATION

Before administration the body weight should be accurately determined.
An appropriately graduated syringe must be used to allow for accurate dosing, particularly in cats.

For analgesia:
The individual patient's response to methadone varies depending on the dosage, the age of the patient, individual differences in pain sensitivity and general condition. The optimal dosing regimen should be based on the individual patient. 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 individual patient should be examined thoroughly and regularly to assess if additional analgesia is subsequently required and to ensure sufficient efficacy for the desired duration of effect. In cats, pupil dilation is observed long after the analgesic effect has disappeared. Therefore this sign should not be used to assess clinical efficacy of the administered dose.

For use as neuroleptanalgesia and in combinations:
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 products, lower dosages can be used. For safe use

with other veterinary medicinal products see dosage recommendations for each species on this package leaflet and make reference to the relevant product literature.

For use in TIVA protocol:
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%.

10. WITHDRAWAL PERIOD(S)

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Store below 30°C.
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 that month.
Shelf life after first opening the container: 28 days.
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 carton should be discarded should be worked out. This discard date should be written in the space provided.
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 WARNING(S)

Special warnings for each 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 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.
The benefit/risk ratio for using the 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 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 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 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 product during pregnancy and lactation has not been assessed in the target species. The use of the product is not recommended during pregnancy or lactation.

Interaction with other medicinal products and other forms of interaction:
For concurrent use with neuroleptics refer to the Dosage and Advice of Correct Administration sections of this package leaflet.

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 the Adverse Reactions section of this package leaflet.
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.

Incompatibilities:
The product is incompatible with injection fluids containing meloxicam, or any other non-aqueous solution.
This veterinary medicinal product can be mixed in the same syringe with aqueous solutions for injection containing acepromazine as maleate and medetomidine and dexmedetomidine as hydrochlorides. Syringes with these mixtures should be used as soon as practicable. Any unused mixed solution remaining in the syringe should be disposed appropriately. This veterinary medicinal product may also be mixed with the

infusion solutions indicated in Dosage and Advice on Correct Administration sections of this package leaflet. In the absence of further compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements. Any unused product must be disposed of in accordance with the Misuse of Drugs Regulation (2001).

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

August 2023

15. OTHER INFORMATION

5 mL vial.
10ml vial.

For any information about this veterinary medicinal product, please contact Zoetis UK Limited

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To be supplied only on veterinary prescription.

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Approved 21 September 2023