ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box (5 ml, 5 x 5 ml, 10 ml, 5 x 10 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

methadone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCES

Methadone hydrochloride 10 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

5 ml, 5 x 5 ml, 10 ml, 5 x 10 ml.

5. TARGET SPECIES

Dogs and cats

6. INDICATION(S)

-

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Dog: IV, IM, SC; Cat: IM

8. WITHDRAWAL PERIOD(S)

-

9. SPECIAL WARNING(S), IF NECESSARY

Accidental injection is dangerous.
Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once broached, use within 28 days by …..

11. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton 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.
Administration only by a veterinary surgeon.

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

VetViva Richter GmbH, 4600 Wels, Austria

16. MARKETING AUTHORISATION NUMBER(S)

Vm 57446/4011

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label: 5 ml, 10 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Insistor 10 mg/ml Injection for dogs and cats

methadone hydrochloride

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Methadone hydrochloride 10 mg/ml

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

5 ml, 10 ml

4. ROUTE(S) OF ADMINISTRATION

Dog: IV, IM, SC; Cat: IM

5. WITHDRAWAL PERIOD

-

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:
Insistor 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:
VetViva Richter GmbH, Durisolstrasse 14, 4600 Wels, Austria

Manufacturer responsible for batch release:
Richter Pharma AG, Durisolstrasse 14, 4600 Wels, Austria

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Insistor 10 mg/ml solution for injection for dogs and cats
methadone hydrochloride

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

1 ml contains:

Active substance:
Methadone hydrochloride 10 mg
(equivalent to 8.9 mg Methadone)

Excipients:
Methyl parahydroxybenzoate (E 218) 1.0 mg
Propyl parahydroxybenzoate 0.2 mg

Clear colourless to slightly yellow solution.

4. INDICATION(S)

- Analgesia
- Premedication for general anaesthesia or neuroleptanalgesia 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

In very common cases, 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.

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 side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs and cats.

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

Before administration the body weight should be accurately determined.

Analgesia
Dogs: 0.5 to 1 mg Methadone HCl per kg bodyweight, SC, IM or IV (corresponding to 0.05 to 0.1 ml/kg)
Cats: 0.3 to 0.6 mg Methadone HCl per kg bodyweight, IM (corresponding to 0.03 to 0.06 ml/kg)
To ensure accuracy of dosing in cats, an appropriately calibrated syringe should be used to administer the product.

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 administration, 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 0.5-1 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), + α_2-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 only been demonstrated for dilutions 1:5 with the following solutions for infusion: sodium chloride 0.9 %, Ringer's solution, Ringer's lactate solution and glucose 5 %.

Cats:

- Methadone HCl 0.3 to 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. α_2-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 products, lower dosages can be used.
For safe use with other veterinary medicinal products, reference must be made to the relevant product literature.

The stopper should not be punctured more than 20 times.

9. ADVICE ON CORRECT ADMINISTRATION

Refer to section 8.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special temperature storage conditions.
Keep the vial in the outer carton in order to protect from light.
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 immediate packaging: 28 days.
Shelf life after dilution according to directions: Chemical and physical stability of the dilutions has been demonstrated for 24 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
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 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.

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.
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 on the skin or accidental self-injection. Avoid skin, eyes 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 or the label 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.

Use during pregnancy or 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 section 8.
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.

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 products, except for 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

Any unused product or waste materials should be disposed of in accordance with local requirements.

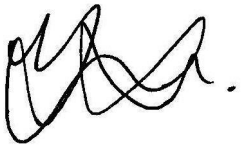
14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

January 2023

15. OTHER INFORMATION

Pack size: 1 x 5 ml, 5 x 5 ml, 1 x 10 ml, 5 x 10 ml.
Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.



Approved: 23 January 2023