ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Outer carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bupredine Multidose 0.3 mg/ml solution for injection for dogs, cats and horses
Buprenorphine

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains:
Buprenorphine (as hydrochloride) 0.3 mg , equivalent to 0.324 mg buprenorphine hydrochloride

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

5 ml
10 ml
20 ml
50 ml
100 ml

5. TARGET SPECIES

Dogs, cats, horses.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use, intramuscular use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

The product is not authorised for use in horses intended for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Shelf life after first opening the container: 28 days
Once broached use by…

11. SPECIAL STORAGE CONDITIONS

-

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. To be supplied only on veterinary prescription.

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 41821/4027

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING UNITS (100 ML VIALS)

100 ml vial

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bupredine Multidose 0.3 mg/ml solution for injection for dogs, cats and horses
Buprenorphine

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains:
Buprenorphine (as hydrochloride) 0.3 mg, equivalent to 0.324 mg buprenorphine hydrochloride

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

100 ml

5. TARGET SPECIES

Dogs, cats, horses.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use, intramuscular use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

The product is not authorised for use in horses intended for human consumption.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Shelf life after first opening the container: 28 days
Once broached use by…

11. SPECIAL STORAGE CONDITIONS

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

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.

14. THE WORDS "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 41821/4027

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Glass vials of 5, 10, 20 or 50 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bupredine Multidose 0.3 mg/ml solution for injection
Buprenorphine

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

0.3 mg/ml

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

5 ml
10 ml
20 ml
50 ml

4. ROUTE(S) OF ADMINISTRATION

IV, IM

5. WITHDRAWAL PERIOD

The product is not authorised for use in horses intended for human consumption.

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Once broached use by …

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Bupredine Multidose 0.3 mg/ml solution for injection for dogs, cats and horses

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

Bupredine Multidose 0.3 mg/ml solution for injection for dogs, cats and horses
buprenorphine

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

1 ml contains:
Active substance:
Buprenorphine (as hydrochloride) 0.3 mg
equivalent to 0.324 mg buprenorphine hydrochloride

Excipients:
Chlorocresol 1.35 mg

Clear, colourless aqueous solution.

4. INDICATION(S)

Dog and cat: post-operative analgesia.
Horse: post-operative analgesia, in combination with sedation.
Dog and horse: potentiation of the sedative effects of centrally acting agents .

5. CONTRAINDICATIONS

Do not administer by the intrathecal or peridural route.
Do not use pre-operatively for Caesarean section (see section on special warnings).
Do not use in known cases of hypersensitivity to the active substance or any of the excipients.

6. ADVERSE REACTIONS

Salivation, bradycardia, hypothermia, agitation, dehydration and miosis can occur in the dog, and rarely hypertension and tachycardia.
Mydriasis and signs of euphoria (excessive purring, pacing, rubbing) commonly occur in cats and will usually resolve within 24 hours.
In horses, use of buprenorphine without the prior use of a sedative agent can cause excitement and spontaneous locomotor activity
Buprenorphine may occasionally cause respiratory depression (see section on special Warnings)
In horses, when used as directed in conjunction with sedatives or tranquillisers, excitation is minimal but ataxia may occasionally be marked. Buprenorphine may reduce gastrointestinal motility in horses but colic is rarely reported.

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.

Alternatively you can report via your national reporting system {national system details}.

7. TARGET SPECIES

Dogs, cats and horses.

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

Species and route	Post-Operative Analgesia	Potentiation of Sedative Effects
Dog: Intramuscular or intravenous injection	10 - 20 µg/kg* (0.3 - 0.6 ml product per 10 kg) repeated if necessary after 3 - 4 hours with 10 µg/kg or 5 - 6 hours with 20 µg/kg doses	10 - 20 µg/kg (0.3 - 0.6 ml product per 10 kg)
Cat: Intramuscular or intravenous injection	10 - 20 µg/kg (0.3 - 0.6 ml product per 10 kg) repeated once if necessary after 1 – 2 hours	--
Horse: Intravenous injection	10 µg/kg (3.3 ml product per 100 kg) 5 minutes after administration of an iv sedative. The dose may be repeated once, if necessary, after not less than	5 µg/kg (1.7 ml product per 100 kg) 5 minutes after administration of an iv sedative, repeated if necessary after 10

	1-2 hours, in combination with intravenous sedation.	minutes.

* The dosages expressed in µg/kg in the table above refer to buprenorphine (as hydrochloride). The kg in the table refers to body weight.

When used in horses, an intravenous sedative must be administered within five minutes prior to injection of buprenorphine.

In dogs, sedative effects are present by 15 minutes after administration. Analgesic activity may not develop fully until 30 minutes. To ensure that analgesia is present during surgery and immediately on recovery, the product should be administered preoperatively as part of premedication.
When administered for potentiation of sedation or as part of premedication, the dose of other centrally-acting agents, such as acepromazine or medetomidine, should be reduced. The reduction will depend on the degree of sedation required, the individual animal, the type of other agents included in premedication and how anaesthesia is to be induced and maintained. It may also be possible to reduce the amount of inhalational anaesthetic used.

9. ADVICE ON CORRECT ADMINISTRATION

Animals administered opioids possessing sedative and analgesic properties may show variable responses. Therefore, the response of individual animals should be monitored and subsequent doses should be adjusted accordingly. In some cases, repeat doses may fail to provide additional analgesia. In these cases, consideration should be given to using a suitable injectable NSAID.
An appropriately graduated syringe must be used to allow accurate dosing.
The closure must not be punctured more than 100 times (with a 21G or 23G needle).

10. WITHDRAWAL PERIOD

The product is not authorised for use in horses intended for human consumption.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
This veterinary medicinal product does not require any special storage conditions.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
Shelf life after first opening the container: 28 days

12. SPECIAL WARNING(S)

Special warnings for each target species
As buprenorphine is metabolised by the liver, its intensity and duration of action may be affected in animals with impaired liver function.

Special precautions for use in animals:
The safety of buprenorphine has not been demonstrated in kittens or puppies less than 7 weeks of age, nor in horses younger than 10 months old and weighing less than 150 kg: therefore use in such animals should be based on the benefit/risk assessment of the veterinarian.
Safety has not been fully evaluated in clinically compromised cats or horses.
Long-term safety of buprenorphine has not been investigated beyond 5 consecutive days of administration in cats or 4 separate administrations on three consecutive days in horses.
The effect of an opioid on head injury is dependent on the type and severity of the injury and the respiratory support supplied. In case of renal, cardiac or hepatic dysfunction, or shock, there may be greater risk associated with the use of the product. In all of these cases the product should be used in accordance with the benefit risk assessment of the attending veterinarian.

Buprenorphine 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.

Repeat administration earlier than the recommended repeat interval suggested in the section on dosage for each species is not recommended.

In horses, use of opioids has been associated with excitation, but effects with buprenorphine are minimal when administered in conjunction with sedatives and tranquilisers such as detomidine, romifidine, xylazine and acepromazine.
Ataxia is a known effect of detomidine and similar agents; consequently it may be seen after administration of buprenorphine with such substances. Occasionally, ataxia may be marked. To ensure ataxic horses sedated with detomidine/buprenorphine do not lose their balance, they should not be moved or otherwise handled in any way that would compromise their stability.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
As buprenorphine has opioid-like activity, care should be taken to avoid self-injection or ingestion.
In case of accidental self-injection or ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
The product may cause skin or eye irritation or hypersensitivity reactions if contact occurs. Following eye, skin or mouth contact, wash the affected area thoroughly with water. Seek medical advice in case of hypersensitivity reactions or if irritation persists. Wash hands after use.

To the physician:
Naloxone should be available in case of accidental self-injection.

Pregnancy and Lactation:
Pregnancy: Laboratory studies in rats have not produced any evidence of a teratogenic effect. However, these studies have shown post-implantation losses and early foetal deaths.
As reproductive toxicity studies have not been conducted in the target species, use only according to the benefit/risk assessment by the responsible veterinarian.

The product should not be used pre-operatively in cases of Caesarean section, due to the risk of respiratory depression in the offspring periparturiently, and should only be used post-operatively with special care (see below).

Lactation: Studies in lactating rats have shown that, after intramuscular administration of buprenorphine, concentrations of unchanged buprenorphine in the milk equalled or exceeded that in the plasma. As it is likely that buprenorphine will be excreted in the milk of other species, use is not recommended during lactation. Use only accordingly to benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:
Buprenorphine may cause some drowsiness, which may be potentiated by other centrally-acting agents, including tranquillisers, sedatives and hypnotics.
There is evidence in humans to indicate that therapeutic doses of buprenorphine do not reduce the analgesic efficacy of standard doses of an opioid agonist, and that when buprenorphine is employed within the normal therapeutic range, standard doses of opioid agonist may be administered before the effects of the former have ended without compromising analgesia. However, it is recommended that buprenorphine is not used in conjunction with morphine or other opioid-type analgesics, e.g. etorphine, fentanyl, pethidine, methadone, papaveretum or butorphanol.

Buprenorphine has been used with acepromazine, alphaxalone/alphadalone, atropine, detomidine, dexmedetomidine, halothane, isoflurane, ketamine, medetomidine, propofol, romifidine, sevoflurane, thiopentone and xylazine.
When used in combination with sedatives, depressive effects on heart rate and respiration may be augmented.

Overdose (symptoms, emergency procedures, antidotes):
In cases of overdosage, supportive measures should be instituted, and, if appropriate, naloxone or respiratory stimulants may be used.
When administered at overdose to dogs, buprenorphine may cause lethargy. At very high doses, bradycardia and miosis may be observed.
Studies in horses where buprenorphine has been administered with sedatives have shown very few side effects at up to five times the recommended dosage, but when administered on its own it can cause excitement.
When used to provide analgesia in horses, sedation is rarely seen, but may occur at dose levels higher than those recommended.
Naloxone may be of benefit in reversing reduced respiratory rate.
In toxicological studies of buprenorphine hydrochloride in dogs, biliary hyperplasia was observed after oral administration for one year at dose levels of 3.5 mg/kg/day and above. Biliary hyperplasia was not observed following daily intramuscular injection of dose levels up to 2.5 mg/kg/day for 3 months. This is well in excess of any clinical dose regimen in the dog.
Please also see the section on special precautions for use in animals and the section on adverse reactions of this insert.

Incompatibilities:
In the absence of 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.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

February 2022

15. OTHER INFORMATION

Pack sizes: 5 ml, 10 ml, 20 ml, 50 ml and 100 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 14 February 2022