1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bupredor Multidose 0.3 mg/ml solution for injection for dogs, cats and horses (NL)

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

Active substance:
Buprenorphine (as hydrochloride) 0.3 mg
Equivalent to 0.324 mg buprenorphine hydrochloride

Excipients:
Chlorocresol 1.35 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless aqueous solution

4. CLINICAL PARTICULARS

4.1 Target species

Dogs, cats and horses.

4.2 Indications for use, specifying the target species

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.

4.3 Contraindications

Do not administer by the intrathecal or peridural route.
Do not use pre-operatively for Caesarean section (see section 4.7).
Do not use in known cases of hypersensitivity to the active substance or any of the excipients.

4.4 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.

4.5 Special precautions for use

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 Section 4.9 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. Naloxone should be available in case of accidental self-injection.
The product may cause skin or eye irritation or hypersensitivity reactions if contact occurs. Following eye contamination or skin contact, wash the affected area thoroughly with water. Seek medical advice in case of hypersensitivity reactions or if irritation persists. Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

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; refer to section 4.5.
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).

4.7 Use during pregnancy and lactation

Pregnancy:
Laboratory studies in rats have not produced any evidence of a teratogenic effects. 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.

4.8 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.

4.9 Amounts to be administered and administration route

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 1-2 hours, in combination with intravenous sedation.	5 µg/kg (1.7 ml product per 100 kg) 5 minutes after administration of an iv sedative, repeated if necessary after 10 minutes.

* The dosages in the following table refer to buprenorphine (as hydrochloride)

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.
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).

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

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 refer to Sections 4.5 and 4.6 of this SPC.

4.11 Withdrawal period

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Opioids, oripavine derivatives, buprenorphine.
ATC Vet Code: QN02AE01.

5.1 Pharmacodynamic properties

In summary buprenorphine is a potent, long-acting analgesic acting at opiate receptors in the central nervous system.
Buprenorphine can potentiate the effects of other centrally-acting agents, but unlike most opiates, buprenorphine has, at clinical doses, only a limited sedative effect of its own.
Buprenorphine exerts its analgesic effect via high affinity binding to various subclasses of opiate receptors, particularly μ, in the central nervous system. At clinical dose levels for analgesia, buprenorphine binds to opiate receptors with high affinity and high receptor avidity, such that its dissociation from the receptor site is slow, as demonstrated in in vitro studies.
This unique property of buprenorphine could account for its longer duration of activity when compared to morphine. In circumstances where excessive opiate agonist is already bound to opiate receptors, buprenorphine can exert a narcotic antagonistic activity as a consequence of its high-affinity opiate receptor binding, such that an antagonistic effect on morphine equivalent to naloxone has been demonstrated.
Buprenorphine has little effect on gastro-intestinal motility.

5.2 Pharmacokinetic particulars

Buprenorphine is rapidly absorbed after intramuscular injection in various animal species. The substance is highly lipophilic and the volume of distribution in body compartments is large.
Pharmacological effects (e.g. mydriasis) may occur within minutes of administration and signs of sedation normally appear by 15 minutes. Analgesic effects in dogs and cats appear around 30 minutes with peak effects usually being observed at about 1 – 1.5 hours. In pain-free horses, antinociceptive effects appear during the first 15 - 30 minutes; peak antinociceptive effects occur between ¾ and 6 hours after administration
Following intravenous administration to dogs at a 20 µg/kg dose, the mean terminal half-life was 9 hours and the mean clearance was 24 ml/kg/min, however, there is considerable inter-dog variability in pharmacokinetic parameters.
Following intramuscular administration to cats, the mean terminal half-life was 6.3 hours and the clearance was 23 ml/kg/min; however, there was considerable inter-cat variability in pharmacokinetic parameters.
Following intravenous administration in horses, buprenorphine has a mean residence time of approximately 150 minutes, a volume of distribution of approximately 2.5 l/kg and a clearance rate of 10 l/minute.
Combined pharmacokinetic and pharmacodynamic studies have demonstrated a marked hysteresis between plasma concentration and analgesic effect. Plasma concentrations of buprenorphine should not be used to formulate individual animal dosage regimens, which should be determined by monitoring the patient's response.
The major route of excretion in all species except the rabbit (where urinary excretion predominates) is the faeces. Buprenorphine undergoes N-dealkylation and glucuronide conjugation by the intestinal wall and the liver and its metabolites are excreted via the bile into the gastro-intestinal tract.
In tissue distribution studies carried out in rats and rhesus monkeys the highest concentrations of drug-related material were observed in liver, lung and brain. Peak levels (C_{max}) occurred rapidly and declined to low levels by 24 hours after dosing.
Protein binding studies in rats have shown that buprenorphine is highly bound to plasma proteins, principally to alpha and beta globulins.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorocresol
Glucose monohydrate
Hydrochloric acid, dilute (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injection

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 5, 10, 20, 50 and 100 ml vials: 2 years.
Shelf life after first opening the immediate packaging: 28 days.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Clear type I glass vials closed with a coated bromobutyl rubber stopper and aluminium cap in a carton box.
Pack sizes: 5 ml, 10 ml, 20 ml, 50 ml and 100 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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

DE:
Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

8. MARKETING AUTHORISATION NUMBER

Xxxxxxx

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

xxxxxxx

10. DATE OF REVISION OF THE TEXT

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