1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Active substances:

Buprenorphine	0.3 mg
equivalent to Buprenorphine hydrochloride	0.323 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Chlorocresol	1.35 mg
Glucose	
Hydrochloric acid dilute (for pH adjustment)	
Sodium hydroxide (for pH adjustment)	
Water for injections	

A clear, colourless to slightly yellowish solution..

3. CLINICAL INFORMATION

3.1 Target species

Dogs, cats, horses (non food-producing)

3.2 Indications for use for each target species

Dogs:
Post-operative analgesia.
Potentiation of the sedative effects of centrally-acting agents.

Cats:
Post-operative analgesia.

Horses:
Post-operative analgesia in combination with a sedative.
Potentiation of the sedative effects of centrally-acting agents.

3.3 Contraindications

Do not administer by the intrathecal or peridural route.
Do not use pre-operatively for Caesarean section (see Section 3.7).
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

Not applicable.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Buprenorphine should be used with caution in animals with impaired liver function, especially biliary tract disease, as the substance is metabolised by the liver and its intensity and duration of action may be affected in such animals.
Buprenorphine may 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.
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 benefit-risk assessment for using the veterinary medicinal product should be made by the responsible veterinarian. Safety has not been fully evaluated in clinically compromised cats.
The safety of buprenorphine has not been demonstrated in dogs and cats less than 7 weeks of age, and in horses younger than 10 months old and weighing less than 150kg; therefore, use in such animals should be based on the risk-benefit assessment of the veterinarian.
Repeat administration earlier than the recommended repeat interval suggested in section 3.9 is not recommended.
Long-term safety of buprenorphine has not been investigated beyond 5 consecutive days of administration in cats or 4 separate administrations on 3 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. The veterinary medicinal product should be used in accordance with the benefit-risk assessment of the attending veterinarian.
Safety has not been evaluated in clinically-compromised horses. 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. Buprenorphine may be absorbed systemically on accidental exposure to mucous membranes. The product, which is slightly acidic, may cause skin or eye irritation if contact occurs. Following eye, skin or mouth contact, wash the affected area thoroughly with water. Seek medical advice if irritation persists. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.Wash hands after use.
Buprenorphine and the excipient chlorocresol can cause hypersensitivity (allergic) reactions after skin contact. People with known hypersensitivity to buprenorphine or chlorocresol should avoid contact with the veterinary medicinal product. In case of accidental skin contact, wash off immediately with water.
To the physician: In case of accidental self-injection the opioid antagonist naloxone may be used as antidote.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Dogs:

Rare (1 to 10 animals / 10000 animals treated):	Hypertension, Tachycardia, Sedation[1].
Very rare (<1 animal / 10000 animals treated, including isolated reports):	Injection site pain, Discomfort[2], Vocalisation[3].
Undetermined frequency (cannot be estimated from available data)	Increased salivation, Bradycardia, Hypothermia, Dehydration, Agitation, Miosis, Respiratory depression.

[1] when used to provide analgesia.
[2] local
[3] resulting from injection site pain or local discomfort

Cats:

Common (1 to 10 animals / 100 animals treated):	Mydriasis[1], Euphoria (excessive purring, pacing, rubbing)[1].
Rare (1 to 10 animals / 10000 animals treated):	Sedation[2].
Very rare (<1 animal / 10000 animals treated, including isolated reports):	Injection site pain, Discomfort[3], Vocalisation[4].
Undetermined frequency (cannot be estimated from available data)	Respiratory depression.

[1] usually resolve within 24 hours.
[2] when used to provide analgesia.
[3] local
[4] resulting from injection site pain or local discomfort.

Horses:

Rare (1 to 10 animals / 10000 animals treated):	Sedation[1], Colic.
Undetermined frequency (cannot be estimated from available data)	Respiratory depression, Excitation[2], Ataxia[2].

[1] when used to provide analgesia.
[2] when used in conjunction with sedatives or tranquillisers, excitation is normally minimal, but ataxia may occasionally be marked.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during 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. These may have resulted from a reduction in parental body condition during gestation and in post-natal care owing to sedation of the mothers. 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 veterinary medicinal 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 according to the benefit-risk assessment by the responsible veterinarian.

3.8 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.

3.9 Administration routes and dosage

Dogs and cats: Intramuscular or intravenous use.
Horses: Intravenous use

Target species	Route of administration	Post-operative Analgesia	Potentiation of sedation
Dog	Intramuscular or intravenous injection	10-20 µg/kg*, equivalent to 0.3 to 0.6 ml per 10 kg. For further pain relief, repeat if necessary after: - 3-4 hours with 10 µg/kg or - 5-6 hours with 20 µg/kg.	10-20 µg/kg*, equivalent to 0.3 to 0.6 ml per 10 kg.

Cat	Intramuscular or intravenous injection	10-20 µg/kg*, equivalent to 0.03 to 0.06 ml per 1 kg. For further pain relief, repeat if necessary: - Once after 1-2 hours	-
Horse	Intravenous injection	10 µg/kg*, equivalent to 3.3 ml per 100 kg, 5 minutes after administration of an IV sedative. For further pain relief, repeat if necessary: once, after not less than 1 - 2 hours.	5 µg/kg*, equivalent to 1.7 ml per 100 kg, 5 minutes after administration of an IV sedative. The dose may be repeated if necessary after 10 minutes

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

In dogs, sedative effects are present by 15 minutes after administration. In dogs, cats and horses 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 used in horses, an intravenous sedative should be administered within five minutes prior to injection of buprenorphine.

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.

Due to the small volume to be administered, especially in small dogs and cats, extra care should be taken to use an appropriately graduated syringe to allow accurate dosing.
The stopper can be safely punctured up to 25 times.

3.10 Symptoms of overdose (and where applicable, emergency procedures and 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.
Naloxone may be of benefit in reversing reduced respiratory rate and respiratory stimulants such as doxapram are also effective in man. Because of the prolonged duration of effect of buprenorphine in comparison to such drugs, they may need to be administered repeatedly or by continuous infusion.
Volunteer studies in man have indicated that opiate antagonists may not fully reverse the effects of buprenorphine.
Studies in horses where buprenorphine has been administered with sedatives have shown very few effects at up to five times the recommended dosage, but when administered on its own it may cause excitement in pain-free-animals.
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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance.

For administration by a veterinarian or under their direct supervision.

3.12 Withdrawal periods

Not authorised for use in horses intended for human consumption.
Treated horses may never be slaughtered for human consumption.
The horse must have been declared as not intended for human consumption under national horse passport legislation.
Not authorised for use in animals producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QN02AE01

4.2 Pharmacodynamics

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.

4.3 Pharmacokinetics

Buprenorphine is rapidly absorbed after intramuscular injection in various animal species and man. 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 20μg/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 2.5L/kg and a clearance rate of 10L/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 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.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years
Shelf life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

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

5.4 Nature and composition of immediate packaging

Colourless type I glass vial of 10 ml, with a type I fluorinated bromobutyl rubber stopper and aluminium cap.
Pack size:
Cardboard box with 1 x 10 ml.

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

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 national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Alfasan Nederland B.V.

7. MARKETING AUTHORISATION NUMBER(S)

VPA10980/049/001

8. DATE OF FIRST AUTHORISATION

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).