Buprelieve®
Injection

Active Constituent

Buprenorphine 0.3 mg/mL

Description

A clear, colourless solution for injection containing 0.3 mg buprenorphine per mL and presented in a multi-use amber injection vial.

Pharmacology

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 to various subclasses of opiate receptors, particularly μ, in the central nervous system. At clinical dose levels for analgesia, it 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 gastrointestinal motility.

Pharmacokinetics

When given parenterally, the product may be administered by intramuscular (cats and dogs) or intravenous (cats, dogs and horses) injection. 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. miosis in dogs or mydriasis in cats) may occur within minutes of administration and signs of sedation normally appear by 15 minutes. Analgesic effects appear around 30 minutes with peak effects usually being observed at about 1 – 1.5 hours. In painfree horses, antinociceptive effects appear during the first 15 - 30 minutes. Duration of antinociception and clinical analgesic effects at the proposed dose have been demonstrated for approximately 6 hours.

Following intravenous administration to dogs at the 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 intravenous administration to cats at the 20 µg/kg dose and intramuscular administration to cats at the 10 µg/kg dose the mean terminal half-life was 6.1 and 6.3 hours respectively and the clearance was 23 mL/kg/min for the latter; however, there was considerable inter-cat variability in pharmacokinetic parameters.

Following intravenous administration in horses, buprenorphine has a mean residence time of approximately 145 minutes, a volume of distribution of approximately 2.8 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 (pain assessments post-operatively).

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.

Buprenorphine is highly bound to plasma proteins (78-81% in dogs), and in protein-binding studies in rats is has been shown to bind principally to alpha and beta globulins.

Buprenorphine undergoes N-dealkylation and glucuronide conjugation by the intestinal wall and the liver. Most of the buprenorphine dose is excreted unchanged via the bile into the gastrointestinal tract. Buprenorphine metabolites are also excreted in the urine. The major route of excretion in all species except the rabbit (where urinary excretion predominates) is the faeces.

Indications

An analgesic injection for dogs, cats and horses.

For the control of postoperative pain associated with surgical procedures in dogs and cats. It is intended that the first dose of buprenorphine is given as part of a premedication regimen prior to general anaesthesia and surgery.

For the relief of post-operative pain in the horse only in conjunction with a sedative agent.

Restraints

DO NOT USE in horses that may be used for human consumption.

Contraindications

This product should not be administered by the intrathecal or peridural route.
This product should not be used pre-operatively for caesarean section.

Directions For Use

Dosage and Administration

For intramuscular or intravenous use.

An appropriately graduated syringe must be used to allow accurate dosing.

Species	Route of Administration	Post-operative analgesia
Dog	IM or IV	20 micrograms per kilogram (0.67 mL per 10 kg) repeated if necessary after 5 to 6 hours*.
Cat	IM or IV	20 micrograms per kilogram (0.33 mL per 5 kg) repeated if necessary once as required.
Cat	IV	5 - 10 micrograms per kilogram (1.7 - 3.3 mL per 100 kg), 5 minutes after administration of an IV sedative. The dose may be repeated if necessary, once, after not less than 1 - 2 hours, and only after repeating the administration of an IV sedative.

* If possible, the repeat dose should not be administered earlier than the recommended repeat interval.

While sedative effects are present by 15 minutes after administration, analgesic activity becomes apparent after approximately 30 minutes. To ensure that analgesia is present during surgery and immediately on recovery, the product should be administered pre-operatively as part of premedication.

Animals administered opioids possessing sedative and analgesic properties may show variable responses. Therefore, the response of individual animals should be monitored and if additional analgesia is subsequently required, this may be achieved by administration of a further dose of buprenorphine* or concomitant use of a suitable injectable NSAID. In some cases, repeat doses may fail to provide additional analgesia. In these cases, consideration should be given to the use of an analgesic from an alternative class.

Use of buprenorphine in conjunction with other centrally acting agents such as acepromazine, medetomidine, or inhalation anaesthetics, may enable the dose of these agents to be reduced.

A proportion of animals may react to repeated IV administration at the same site by withdrawing and/or vocalising.

Precautions

Buprenorphine may cause respiratory depression, however this is generally not clinically significant. 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.

A margin of safety in dogs younger than 5 months and cats younger than 4 months has not been established.

The effects of an opioid on head injury are dependent on the type and severity of the injury and the respiratory support supplied. Opioids generally should be used with considerable caution in patients with head injuries and instances of intra-cranial pressure. The product should be used in accordance with the risk-benefit assessment of the attending veterinarian.

Buprenorphine should be used with caution in animals with impaired liver function or bile tract disease, as the substance is metabolised by the liver and its intensity and duration of action may be affected in such animals.

In case of renal, cardiac or hepatic dysfunction or shock, there may be greater risk associated with the use of the product. The risk-benefit assessment for using the product should be made by the attending vet.

Repeat administration earlier than the recommended repeat interval suggested is not recommended. Long-term safety of buprenorphine in cats has not been investigated beyond 5 consecutive days of administration or in horses 4 separate administrations on three consecutive days.

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.

The safety of buprenorphine has not been demonstrated in horses younger than 10 months old and weighing less than 150 kg; therefore, use in such animals should be based on the risk-benefit assessment of the veterinarian.

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.

Use during 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.

Reproductive toxicity studies have not been conducted in the target species. Therefore use of Buprelieve Injection in such cases should be based on the risk-benefit assessment of the veterinarian.

Buprelieve Injection 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.

Use during 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 risk-benefit assessment by the responsible veterinarian.

Side effects

In dogs, clinical side effects that have been demonstrated to occur at > 1% incidence rate when buprenorphine is administered to dogs repeated at the recommended dose rate include: Emesis, diarrhoea, mild to moderate sedation, anorexia, hypersalivation, ataxia, bradycardia, reduced body temperature (without loss of thermoregulation unless other sedatives, tranquilisers or anaesthetics are administered), tachycardia, shy behaviour or agitation and miosis.

Dogs generally recover from these side effects without intervention as the pharmacological effect of buprenorphine wears off, returning to normal within 24 hours.

In cats, mydriasis, signs of euphoria (excessive purring, pacing or rubbing) or agitation commonly occur and will usually resolve in 24 hours.

In case of physiological changes such as rectal temperature, heart rate and respiratory rate and oxygenation, it is recommended to monitor high-risk patients and treat them symptomatically if necessary.

When used to provide analgesia in horses, sedation is rarely seen, but may occur at dose levels higher than those recommended. When used in conjunction with sedatives or tranquilisers, excitation is normally minimal, but ataxia may occasionally be marked. Colic is rarely reported.

Overdose

Moderate sedation and respiratory depression may occur at doses higher than the indicated dose. In the case of overdose, supportive measures should be instituted, and if appropriate, naloxone or respiratory stimulants may be used.

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.

Naloxone may be of benefit in reversing reduced respiratory rate, and respiratory stimulants such as doxapram are also effective in man. Volunteer studies in man have indicated that opiate antagonists may not fully reverse the effects of buprenorphine. 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.

General directions

Interactions

In dogs buprenorphine has been administered safely in conjunction with acepromazine, atropine, dexmedetomidine, medetomidine, glycopyrrolate, midazolam, diazepam, ketamine, tiletamine/zolazepam, alfaxalone, propofol, thiopentone, halothane, isoflurane and sevoflurane, nitrous oxide and carprofen.

In cats buprenorphine has been administered safely in conjunction with acepromazine, atropine, medetomidine, dexmedetomidine, atipamezole, ketamine, etomidate, propofol, thiopentone, alfaxalone/alfadalone, halothane, isoflurane, nitrous oxide, and carprofen.

When used in combination with sedatives, depressive effects on heart rate and respiration may be augmented.

Buprenorphine may cause some drowsiness, which may be potentiated by other centrally acting agents, including tranquillisers, sedatives and hypnotics.

Safety Directions

Avoid contact with eyes and skin. Wash hands after use.

First Aid

If poisoning occurs, contact a doctor or Poisons Information Centre, and get to a doctor or hospital quickly. Phone Australia 13 11 26. If in eyes, hold the eyes open, flood with water for at least 15 minutes and see a doctor.

Additional User Safety

Buprenorphine is listed as a TGA Pregnancy Category C chemical (Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformation. These effects may be reversible). Appropriate precautions to minimise exposure to buprenorphine during use are recommended. For animal treatment only.

Disposal

Dispose of empty container by wrapping with paper and putting in garbage.

Storage

Store below 25°C (air conditioning). Protect from light. Discard unused portion 28 days after first opening.

Poisons Schedule

S8.

Registration Number

APVMA No. 69057