1. Name of the veterinary medicinal product

BUPAQ MULTIDOSE 0.3 MG/ML VETERINARY

2. Qualitative and Quantitative Composition

Each ml contains:

Active substances:
Buprenorphine (as hydrochloride) 0.3 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 monohydrate	
Hydrochloric acid conc. (for pH adjustment)	
Water for injections	

Solution for injection

Clear, colourless to almost colourless solution

3. CLINICAL INFORMATION

3.1 Target species

Dogs and cats

3.2 Indications for use, specifying the target species

DOGS:

Post-operative analgesia.

Potentiation of the sedative effect of centrally acting medicines.

CATS:

Post-operative analgesia.

3.3 Contraindications

Do not use in case of hypersensitivity to the active substance or to any of the excipients.

Do not administer by the intrathecal or peridural route.

Do not use pre-operatively for Caesarian section (see section 3.7).

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the veterinary medicinal product in the below circumstances should only be in accordance with the benefit/risk assessment by the responsible veterinarian.

Buprenorphine may lead to respiratory depression. As with other opioids, care should therefore be taken when treating animals with impaired respiratory function or animals receiving medicines that can cause respiratory depression.

In case of renal, cardiac or hepatic dysfunction, or shock, there may be a greater risk associated with the use of the veterinary medicinal product.

Safety has not been fully evaluated in clinically compromised cats. Buprenorphine should be used with caution in animals with impaired liver function, especially biliary tract diseases, as the substance is metabolised by the liver and its intensity and duration of action may be affected in such animals.

Safety of buprenorphine has not been demonstrated in animals less than 7 weeks of age.

Repeated administration at shorter intervals than suggested in the section 3.9 is not recommended.

Long-term safety of buprenorphine in cats has not been investigated beyond 5 consecutive days of administration.

The effect of an opioid on head injury is dependent on the type and severity of the injury and on the respiratory support supplied.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Wash hands/affected area thoroughly after any accidental spillage.

As buprenorphine has an opioid-like effect, care should be taken to avoid self-injection. 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 parenteral exposure.

In case of accidental eye contamination or spillage onto skin, wash thoroughly with cold running water. Seek medical advice if irritation persists.

3.6 Adverse reactions

Dogs:

Rare (1 to 10 animals / 10 000 animals treated):	Hypertension, Tachycardia; Sedation[1].
Very rare (<1 animal / 10 000 animals treated, including isolated reports):	Injection site reaction[2], Injection site pain[2]; Vocalisation[3].
Undetermined frequency (cannot be estimated from the available data):	Hypersalivation; Bradycardia; Hypothermia, Dehydration; Agitation; Miosis; Respiratory depression.

[1] When used to provide analgesia. May occur at dose levels higher than those recommended.
[2] With local discomfort. The effect is normally temporary.
[3] Caused by injection site pain.

Cats:

Common (1 to 10 animals / 100 animals treated):	Mydriasis[1]; Behavioural disorder[1,2].
Rare (1 to 10 animals / 10 000 animals treated):	Sedation[3].
Very rare (<1 animal / 10 000 animals treated, including isolated reports):	Injection site reaction[4], Injection site pain[4]; Vocalisation[5].
Undetermined frequency (cannot be estimated from the available data):	Respiratory depression.

[1] Will usually resolve within 24 hours.
[2] Signs of euphoria (excessive purring, pacing, rubbing).
[3] When used to provide analgesia. May occur at dose levels higher than those recommended.
[4] With local discomfort. The effect is normally temporary.
[5] Caused by injection site pain.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

3.7 Use during pregnancy, lactation or lay

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 mother.

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 in accordance with 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 tranquilisers, 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, dexmedetomidine, halothane, isoflurane, ketamine, medetomidine,

propofol, sevoflurane, thiopental 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: Intramuscular, subcutaneous or intravenous injection for post-operative analgesia and sedation enhancement
CATS: Intramuscular or intravenous injection for post-operative analgesia

10 – 20 µg/kg (0.3 – 0.6 ml per 10 kg).

To prolong the analgesic effect, the dose may be repeated:
DOGS: either a 10 µg/kg dose after 3 - 4 hours or a 20 µg/kg dose after 5 – 6 hours.
CATS: repeated once with a 10 – 20 µg/kg dose after 1 - 2 hours.

While sedative effects already occur 15 minutes following administration, analgesic effects occur only after approximately 30 minutes. To ensure that analgesia is present during surgery and immediately upon awakening, the medicinal product should be administered pre-operatively as part of premedication. When administered for potentiation of sedation or as part of premedication, the dose of other centrally acting medicines, such as acepromazine or medetomidine, should be reduced. This reduction depends on the degree of sedation required, on the individual animal, on the type of other medicines included in premedication, and on how anaesthesia is induced and maintained. It may also be possible to reduce the amount of inhalational anaesthetic.

Animals that are given opioids with sedative and analgesic properties may show variable responses. It is therefore important to monitor the responses of the individual animals and adjust subsequent doses accordingly. It may occasionally happen that repeat doses fail to provide additional analgesia. In such cases, consideration should be given to using an appropriate injectable non-steroidal analgesic (NSAID).

Prior to administration, the weight of the animal should be determined accurately.

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

The rubber stopper may only be pierced up to 25 times.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

In case 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. 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 for dogs.

Please also refer to sections 3.5 and 3.6 of this SPC.

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

Prescription Only Medicine

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QN02AE01

4.2 Pharmacodynamics

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 medicines, 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

This veterinary medicinal product may be administered to dogs via the intramuscular, subcutaneous or intravenous route and to cats by intramuscular or intravenous 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 (such as mydriasis) may occur within minutes of administration and signs of sedation normally appear within 15 minutes.
Analgesic effects appear after around 30 minutes, with peak effects usually being observed at about 1 to 1.5 hours.
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.

Combined pharmacodynamic and pharmacokinetic studies have demonstrated a marked hysteresis between plasma concentrations 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 the liver, lung and brain. Peak levels occurred rapidly and declined to low levels within 24 hours after dosing.
Protein binding studies in rats have shown that buprenorphine is highly bound to plasma proteins, particularly 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
The expiry date of the product is indicated on the packaging materials.
Expiration period after first opening the immediate packaging: 28 days

5.3 Special precautions for storage
Keep out of the reach of children.
Do not store above 25ºC.
Keep the vial in the outer carton to protect its contents from light. Do not refrigerate or freeze.

5.4 Nature and composition of immediate packaging
Amber glass vials type I, bromobutyl rubber stopper type I, coated, aluminium cap
Pack sizes: 10 ml, 5 x 10 ml, 10 x 10 ml
Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements

6.

License Holder:
VETMARKET LTD**,** 23 HACHORESH WAY, INDUSTRIAL PARK
MODI'IN REGION 7319900, ISRAEL

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Durisolstrasse 14, 4600 Wels, Austria

Registration number: 161-36-35190
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