HUMAN SAFETY WARNING

Abuse Potential
SIMBADOL contains buprenorphine (1.8 mg/mL), an opioid agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. Buprenorphine has certain opioid properties that in humans may lead to dependence of the morphine type. Abuse of buprenorphine may lead to physical dependence or psychological dependence. The risk of abuse by humans should be considered when storing, administering, and disposing of SIMBADOL. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (suicidal depression).

Life-Threatening Respiratory Depression
Respiratory depression, including fatal cases, may occur with abuse of SIMBADOL.

Additive CNS Depressant Effects
SIMBADOL has additive CNS depressant effects when used with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Accidental Exposure
Because of the potential for adverse reactions associated with accidental injection, SIMBADOL should only be administered by veterinarians or veterinary technicians who are trained in the handling of potent opioids. See Human Safety for detailed information.

DESCRIPTION:
SIMBADOL is a clear, colorless to slightly yellow, sterile, injectable solution intended for subcutaneous administration for use in cats. Each milliliter of SIMBADOL contains 1.8 mg buprenorphine (equivalent to 1.94 mg buprenorphine hydrochloride), 50 mg anhydrous dextrose, 1.8 mg methylparaben, 0.2 mg propylparaben, 0.3 mg sodium acetate trihydrate, 0.5 mg glacial acetic acid, 100.0 mg anhydrous ethanol, water for injection, and hydrochloric acid and/or sodium hydroxide to adjust pH.

Chemically, it is 17-(cyclopropylmethyl)-3α,4α-epoxy-18,19-dihydro-3α-methyl-6,14-ethenomorphinan-7-methanol hydrochloride. Buprenorphine hydrochloride has the molecular formula of C29H41NO4•HCl, the molecular weight of 504.09, and the following structural formula:

INDICATION:
SIMBADOL is indicated for the control of postoperative pain associated with surgical procedures in cats.

DOSAGE AND ADMINISTRATION:
The dosage of SIMBADOL is 0.24 mg/kg (0.11 mg/lb) administered subcutaneously once daily, for up to 3 days. Administer the first dose approximately 1 hour prior to surgery. Do not disperse SIMBADOL for administration at home by the pet owner (see Human Safety).

CONTRAINDICATIONS:
SIMBADOL is contraindicated in cats with known hypersensitivity to buprenorphine hydrochloride or any of the components of SIMBADOL, or known intolerance to opioids.

WARNINGS:
For subcutaneous (SQ) injectable use in cats.

Human Safety:

Adult Human Use Safety while handling SIMBADOL in the hospital:
Mucus membrane or eye contact during administration:
Direct contact of SIMBADOL with the eyes, oral or other mucous membranes could result in absorption of buprenorphine and the potential for adverse reactions. If accidental eye, oral or other mucous membrane contact is made during administration, flush the area with water and contact a physician.

Drug Abuse, Addiction, and Diversion of Opioids:
Controlled Substance:
SIMBADOL contains buprenorphine, a mu opioid partial agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. SIMBADOL can be abused and is subject to misuse, abuse, addiction, and criminal diversion. SIMBADOL should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods, as appropriate to the clinical setting and as required by law.
Buprenorphine is a potent, long-acting analgesic acting at opiate receptors in the central nervous system. Buprenorphine exerts its analgesic effect via high affinity binding to various subclasses of opiate receptors with high affinity and high receptor avidity, such that its disassociation from the receptor is slow, as demonstrated in in vitro studies. This unique property of buprenorphine could account for its duration of activity.1

Following subcutaneous injection in cats, there is considerable inter-cat variability in plasma concentration and pharmacokinetic parameters.4 Formulated as an immediate release product, buprenorphine is quickly absorbed from the subcutaneous site of injection. Pharmacological effects (e.g. mydriasis) may occur within minutes after injection. Buprenorphine plasma concentrations following subcutaneous injection did not appear to correlate to pharmacodynamics measurements (change in the thermal threshold data). In studies with SIMBADOL analgesic effects of subcutaneous dosing were demonstrated a marked time delay between plasma concentrations and the onset and offset of the analgesic effect which is due to the slow equilibration between drug concentrations in the biophase and the slow association and dissociation of drug binding to the receptor.5, 5

Buprenorphine is metabolized in the liver. The major route of excretion of buprenorphine is in the feces. Buprenorphine undergoes hepatic oxidative metabolism by N-dealkylation to form norbuprenorphine (an active metabolite) via CYP3A4. Buprenorphine and norbuprenorphine subsequently form inactive glucuronide conjugates in the intestinal wall and the liver and its metabolites are excreted via the bile into the gastrointestinal tract.6 The elimination half-life in cats is reported to be similar to that associated with human beings, slower than that observed in dogs.7 It is also noted that because the cat is devoid of uridine diphosphate glucuronosyltransferase enzymes, conjugated metabolites may be absent.8

EFFECTIVENESS:
The effectiveness of SIMBADOL was demonstrated in two randomized, masked, placebo-controlled, multi-site field studies involving client-owned cats of various breeds. In one study (soft tissue), 221 cats underwent a soft tissue surgical procedure. In the other study (orthopedic), 229 cats underwent a soft tissue surgical procedure. In both studies, the majority of the treatment failures required rescue within 4 hours after anesthetic recovery.

For both studies, combining both studies (450 cats), sedation was observed in 68 cats in the buprenorphine group and 62 cats in the placebo control group for up to 4 hours after anesthetic recovery. In both studies, during surgery, mean respiratory rates and mean blood pressures were lower in the buprenorphine group compared to the placebo control group. There were a higher number of cats with post-operative increases in temperature in the buprenorphine group (30 cats, 28 incidences) compared to the placebo control group (6 cats, 10 incidences). The results of two field studies demonstrate that SIMBADOL is effective and has an acceptable safety margin for the control of postoperative pain in cats.

ANIMAL SAFETY:
Nine-Day Target Animal Safety Study: In a 9 day safety study, 4 month old healthy cats (4/sex/group) were administered SIMBADOL subcutaneously at 0X (saline), 1X (0.24 mg/kg), 3X (0.72 mg/kg), or 5X (1.2 mg/kg) once daily. All 32 cats survived to study termination. Buprenorphine-related clinical observations included difficulty in handling, lower incidence of urination, abnormal oral dryness, dilated pupils, and decreased pupillary light reflex. The incidence of temperatures ≥103°F was higher in the buprenorphine-treated groups compared to the control group. The highest temperature observed in the buprenorphine-treated group was 103.8°F in a 5X cat. One 1X cat and one 3X cat experienced an episode of hyperactivity, difficulty in handling, slight disorientation, dilated pupils, and decreased pupil light reflex but no response to light, and respiratory sinus arrhythmia. One 1X cat (one episode) and one 3X cat (three episodes) were reported with nystagmus. One 1X and one 3X cat were reported with decreased blink response (one episode). Three cats in the 5X group lost body weight (79 g or less) during the study which correlated with decreased food consumption. All other cats gained weight during the study. The incidence of "moderate responses" (minimal vocalization or wincing and quick resolution) and "severe responses" (tried to bite or scratch or had marked vocalization or persistent attention to the injection site) to injection was higher in the buprenorphine-treated groups compared to the control group.

Respiratory rate, heart rate, and blood pressure were similar between all groups, including the control group.

Buprenorphine-related clinical pathology findings included an increase in creatine kinase values in the 5X and 3X groups and correlated with subcutaneous inflammation at the injection sites. Histologic lesions included minimal to moderate subcutaneous inflammation at the injection sites, which correlated with the administration of buprenorphine compared to the control group. The incidence of subcutaneous inflammation was higher in the buprenorphine-treated groups; however, most sites with mild and moderate inflammation were observed in the 5X group compared to the 1X and 3X groups, where more sites with minimal inflammation were observed. Mineralization at an injection site was seen in one 1X and one 3X cat. Chronic inflammation in the heart (valve or myocardium) was seen in two 5X cats. Subcutaneous inflammation was seen in one control cat; two 1X cats, three 3X cats and two 5X cats. Lymphoid hyperplasia of the mediastinal lymph node was seen in one 5X cat, and acute inflammation was seen in the mediastinal lymph node of one 3X cat. Lymphoid hyperplasia of the Peyer’s Patches was seen in two 1X cats and one 5X cat. Lymphoid hyperplasia, lymphocytic infiltrate, or subcutaneous inflammation of the stomach was seen in four 1X cats, four 3X cats, and three 5X cats. Subcutaneous plasmacytoid lymphocytic infiltrate of the thyroid glands was seen in two 1X cats, one 3X cat, and four 5X cats.

Arterial Blood Pressure Study in Cats: Healthy 8.5 to 21.9 month old cats (4/sex/group) were subcutaneously administered SIMBADOL at 0.24 mg/kg (1X) or meloxicam (control), 1 hour prior to anesthetic induction for a 1 hour exploratory laparotomy. Arterial blood pressure was monitored following anesthetic induction and through laparotomy, with indirect blood pressure monitoring prior to anesthesia and for 8 hours following anesthetic recovery. All 16 animals were clinically healthy for the duration of the study. There were no differences between treatment groups in mean blood pressure during the study. During surgery and postoperatively, heart rate was higher for the buprenorphine group. During surgery, the incidence of heart rates ≥180 beats/minute was higher in the buprenorphine-treated group compared to the control group. Post-operatively, the incidence of heart rates ≥200 beats/minute was higher in the buprenorphine-treated group compared to the control group. During surgery, respiration rate was lower for the buprenorphine group. Post-operatively, body temperature was higher for the buprenorphine group. Four cats in the buprenorphine group had temperatures ≥104°F post-operatively compared to none in the control group. The highest temperature observed in the buprenorphine group was 104.3°F. Electrocardiograms were qualitatively normal in all cats. During surgery, one cat in the buprenorphine group had hemoglobin saturation less than 90% (88% at one time point).

STORAGE INFORMATION:
Store at temperatures up to 25°C (77°F). Protect from light and excessive heat (above 40°C or 104°F). Use within 56 days of first puncture.

HOW SUPPLIED:
SIMBADOL (buprenorphine injection) is supplied in a carton containing one 1 mL amber glass vial with a needle and metal control 1.1 mg/mg of buprenorphine.

NADA 141-434, Approved by FDA

REFERENCES:

Distributed by: Zoetis Inc.

Kalama zao, MI 49007

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