BupreLab-Mouse
(buprenorphine extended-release injection)
0.5 mg/mL
Opioid Analgesic

CIII

For subcutaneous use in mice only.

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

LEGAL STATUS—In order to be legally marketed, a new animal drug intended for a minor species must be Approved, Conditionally Approved, or Indexed by the Food and Drug Administration. THIS PRODUCT IS INDEXED—MIF 900-020. Extra-label use is prohibited.

This product is not to be used in animals intended for use as food for humans or food-producing animals.

WARNING:

ABUSE POTENTIAL

BupreLab-Mouse contains a high concentration (0.5mg/ml) of buprenorphine, 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 BupreLab-Mouse.

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).

HUMAN SAFETY

Because of human safety risks, this drug should be used only with veterinary supervision. Do not dispense BupreLab-Mouse.

Life Threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur in people with the abuse of BupreLab-Mouse.

Additive CNS Depressant Effects

BupreLab-Mouse 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, BupreLab-Mouse should only be administered by veterinarians, veterinary technicians, or laboratory staff who are trained in the handling of potent opioids.

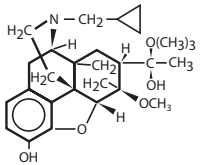
See Human Safety for detailed information.

DESCRIPTION: BupreLab-Mouse (buprenorphine extended-release injection) is a sterile injectable solution which contains buprenorphine as the active ingredient. It is formulated in a polymer that provides the sustained release characteristics, consisting of a biodegradable liquid polymer dissolved in a biocompatible solvent. The polymer used in the BupreLab-Mouse product is a copolymer of lactide and caprolactone. Buprenorphine is a semi-synthetic lipophilic derivative of oripavine that acts as a high affinity partial agonist at the mu-opioid receptors and as a kappa antagonist.

Each mL contains 0.5 mg/mL buprenorphine.

Inactive Ingredients:

Biodegradable liquid copolymer of lactide and caprolactone with biocompatible organic solvents (Triacetin, N-methyl-2-pyrrolidone (NMP)



Buprenorphine is N-cyclopropylmethyl-7α-(1-S-hydroxy, 1,2,2-trimethylpropyl)-6,14-endoethano-6, 7,8,14-tetrahydronororipavine. The molecular weight of buprenorphine is 467.6; the empirical formula is $C_{29}H_{41}NO_4$.

INDICATIONS: BupreLab-Mouse is indicated for the control of post-procedural pain in mice.

DOSAGE AND ADMINISTRATION: Wear protective clothing when administering BupreLab-Mouse **(see Human Safety Warnings)**.

Mice should be dosed at a rate of 1 -1.5 mg/kg body weight. The entire dose should be administered subcutaneously, generally in the dorsal mid-scapular region. To avoid any leakage of polymer contents out of the injection site, the injection should be given in the following manner. Remove a small amount of fur at the injection site. Prep the skin with 70% alcohol. Tent the skin and using a 25 gauge needle on the dosing syringe, insert the needle full length (5/8") under the skin. Inject the formulation slowly over 10-15 seconds, and slowly withdraw the needle while pinching the skin at the needle exit site. Continue to pinch the skin for 5-10 seconds after needle withdrawal.

CONTRAINDICATIONS: Do not use in mice with pre-existing respiratory compromise, as administration of BupreLab-Mouse may potentially further depress respiratory function and lead to critical hypoxemia. Do not use BupreLab-Mouse when general observation of the animal's clinical status is not possible.

HUMAN SAFETY WARNINGS: Not for use in humans. Keep out of the reach of children.

Human User Safety while handling BupreLab-Mouse in the laboratory:

Two trained staff for administration: BupreLab-Mouse should only be handled and administered to mice by veterinarians, veterinary technicians, or laboratory staff trained in the handling of potent opioids. To prevent human adverse reactions or abuse, at least 2 trained administrators should be present during injection of BupreLab-Mouse.

Protective covering: To prevent direct contact of BupreLab-Mouse with human skin or mucous membranes when handling the solution, protective clothing is recommended.

Mucous membrane or eye contact during administration: Direct contact of BupreLab-Mouse with the eyes, oral or other mucous membranes of humans 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.

Skin contact during administration: If human skin is accidentally exposed to BupreLab-Mouse, wash the exposed area with soap and water and contact a physician. Accidental exposure could result in absorption of buprenorphine and the potential for adverse reactions..

DRUG ABUSE, ADDICTION AND DIVERSION OF OPIOIDS: *Controlled Substance:* BupreLab-Mouse contains buprenorphine, a mu opioid partial agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. BupreLab-Mouse can be abused and is subject to misuse, abuse, addiction, and criminal diversion. BupreLab-Mouse 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 laboratory setting and as required by law.

Abuse: Abuse of BupreLab-Mouse poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances including other opioids and benzodiazepines. Buprenorphine has been diverted for non-medical use into illicit channels of distribution. All people handling opioids require careful monitoring for signs of abuse. Drug abuse is the intentional non-therapeutic use of a prescription drug for its rewarding psychological or physiological effects. Abuse of opioids can occur in the absence of true addiction.

STORAGE AND DISCARD: BupreLab-Mouse is a Class III opioid. Store in a locked, substantially constructed cabinet according to DEA and local controlled substance guidelines. Discard broached vials after 90 days. Any unused or expired vials must be destroyed by a DEA registered reverse distributor; for further information, call 1-970-795-0920.

PHYSICIAN INFORMATION: BupreLab-Mouse injectable solution is a mu opioid partial agonist (0.5 mg buprenorphine/mL). In the case of an emergency, provide the physician with the package insert. Naloxone may not be effective in reversing respiratory depression produced by buprenorphine. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride has also been used as a respiratory stimulant.

PRECAUTIONS: The safe use of BupreLab-Mouse has not been evaluated in breeding, pregnant, or lactating mice.

Care should be taken to avoid improper injection technique because skin irritation can occur (see Dosage and Administration and Adverse Reactions).

Opioids as a class of drugs may cause sedation, slow respiratory rate, slow heart rate, low body temperature, corneal drying, and decreased gastric motility. Mice should be monitored for signs of decreased cardiovascular and respiratory function, and ophthalmic ointment should always be applied for the duration of the surgical procedure and until the mouse is fully awake. Before using this product, an opiate antagonist such as naloxone should be available in case reversal is required. Naloxone's duration of action in most animals ranges from 45 minutes to 3 hours, so re-administration may be needed.

Mice that are moderately sedated and therefore not drinking and eating may require fluid supplementation.

ADVERSE REACTIONS: During laboratory studies in which mice received a single subcutaneous injection of BupreLab-Mouse at dosages ranging from 0.3 to 1.5 mg/kg bodyweight, the only adverse reaction noted was skin irritation, including mild ulcerative dermatitis. Skin irritation may be minimized by observing proper injection technique.

CONTACT INFORMATION: To report adverse reactions or to obtain a copy of the SDS for this product call Wildlife Pharmaceuticals, Inc. at 1-970-795-0920.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY: Pharmacokinetic parameter studies of BupreLab-Mouse were evaluated in adult female CD1 mice following a single subcutaneous injection of 0.6 mg/kg bodyweight. The T_{max} of BupreLab-Mouse was 4 hours (C_{max} 14.5 ng/ml); at 24 hours plasma levels were at 4.2 ng/ml and maintained above 1.0 ng/ml for up to 48 hours. The $T_{½}$ was 10.1 hours.

EFFECTIVENESS (sex and strain differences): While the differences in effectiveness of buprenorphine have not been studied in mice, there are a few studies that suggest differences in rats. A few studies have suggested that the effectiveness of buprenorphine for post-surgery analgesia can vary according to both the sex and strain of rat. Jablonski et al showed clear differences in effectiveness of buprenorphine between Sprague-Dawley (SD) and Dark Agouti (DA) rats, with DA rats requiring a repeated dose (pre-op & 9H post-op) to achieve the same post-surgical reduction in pain indicators.[1] Further strain and sex differences have been demonstrated for the effectiveness of buprenorphine, e.g. Terner et al. showed that 0.5 to 1mg/kg had a potentially more potent effect on male compared to female ACI rats.[2] However, the majority of these studies used analgesiometric tests to assess efficacy, which may not offer an accurate representation of efficacy for treating post-surgical pain.[3] Sex and strain differences in mice have not been studied.

HOW SUPPLIED: BupreLab-Mouse is supplied in a 5 mL clear glass vial containing 0.5 mg of buprenorphine per mL.

STORAGE AND DISPOSAL INFORMATION: Store at controlled room temperature (59-86°F) in a facility consistent with appropriate Drug Enforcement Agency regulations regarding Schedule III Class drugs. Protect from prolonged exposure to excessive heat.

Lot and Expiration Date:

Label Revision Date:

REFERENCES:

1. Jablonski P, Howden BO, Baxter K, Jablonski P, Howden BO, Baxter K. Influence of buprenorphine analgesia on post-operative recovery in two strains of rats. *Lab Anim* 2001;35:213–22.
2. Terner JM, Lomas LM, Smith ES, Barrett AC, Picker MJ. Pharmacogenetic analysis of sex differences in opioid antinociception in rats. *Pain* 2003;106:381–391.
3. Roughan JV, Flecknell PA. Buprenorphine: a reappraisal of its antinociceptive effects and therapeutic use in alleviating post-operative pain in animals. *Lab Anim* 2002;36:322–343.

Manufactured for:

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