4" x 11.75"

BupreLab-

(buprenorphine extended-release injection)

1mg/mL

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

NOT APPROVED BY FDA - Legally marketed as an FDA indexed Product under MIF 900-006.

Extra Label Use is Prohibited.

Note: In order to be legally marketed, an animal drug product intended for a minor species must be Approved, Conditionally Approved, or Indexed by the FDA. THIS PRODUCT IS INDEXED.

For Subcutaneous Use in Rats Only

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

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

BupreLab-Rat contains buprenorphine, a high concentration (1.0 mg/mL) opioid agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. The high concentration of BupreLab-Rat may be a particular target for human abuse. Buprenorphine has certain opioid properties that in humans may lead to dependence of the morphine type. Abuse of buprenorphine may lead to low or moderate physical dependence or high psychological dependence. The risk of abuse by humans should be considered when storing, administering, and disposing of BupreLab-Rat. 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).

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

Life-Threatening Respiratory Depression

The concentration of buprenorphine in BupreLab-Rat is 1.0 mg/mL. Respiratory depression, including fatal cases, may occur with abuse of BupreLab-Rat.

BupreLab-Rat has additive CNS depressant effects when used with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Because of the potential for adverse reactions associated with accidental injection, BupreLab-Rat should only be administered by a veterinarian or laboratory staff trained in the handling of potent opioids.

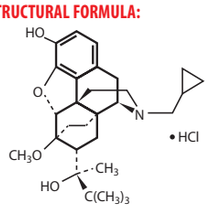
DESCRIPTION:

BupreLab-Rat (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-Rat 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 mu-opioid receptors and as a kappa antagonist.

Each mL contains 1 mg buprenorphine.

Buprenorphine is N-cyclopropylmethyl-7a-(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 $C_{29}H_{41}NO_4$.

STRUCTURAL FORMULA:



INDICATIONS:

BupreLab-Rat is indicated for the control of post-procedural pain in rats.

DOSAGE and ADMINISTRATION:

Rats should be dosed at a rate of 1 to 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 to 15 seconds, and slowly withdraw the needle while pinching the skin at the needle exit site. Continue to pinch the skin for 5 to 10 seconds after needle withdrawal.

CONTRAINDICATIONS:

Do not use in rats with pre-existing respiratory compromise, as administration of BupreLab-Rat may potentially further depress respiratory function and lead to critical hypoxemia. Do not use BupreLab-Rat 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.

Adult Human User Safety while handling* BupreLab-Rat *in the laboratory:

Two trained staff for administration: BupreLab-Rat should only be handled and administered to rats by 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-Rat.

Protective covering: To prevent direct contact of BupreLab-Rat 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-Rat 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-Rat, 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-Rat contains buprenorphine, a mu opioid partial agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. BupreLab-Rat can be abused and is subject to misuse, abuse, addiction, and criminal diversion. BupreLab-Rat 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-Rat 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-Rat 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-Rat injectable solution is a mu opioid partial agonist (1.0 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-Rat has not been evaluated in breeding, pregnant, or lactating rats.

Buprenorphine, like other opioids, may cause sedation, respiratory depression, decreased heart rate, decreased gastric motility, low body temperature, corneal drying, reduction in food consumption, and reduction in bodyweight gain. These effects may be dependent on a number of factors including dose, stock or strain of rat, individual variation in drug sensitivity, individual health status, and other drugs being given concurrently. Rats should be monitored for signs of decreased cardiovascular and respiratory function when receiving BupreLab-Rat.

Before administering BupreLab-Rat, 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.

NOTE: Studies have reported that both buprenorphine and norbuprenorphine are excreted in the feces of rodents due to enterohepatic circulation of the drug. Based on these findings, treated rats and cage mates could ingest some excreted drug or its metabolites through coprophagy.[2,3]

ADVERSE REACTIONS:

During a laboratory study in which rats received a single subcutaneous injection of BupreLab-Rat at a dose of 1.2 mg/kg bodyweight, the only adverse reaction noted was skin irritation, including erythema and scabbing around the site of injection[1]. The skin irritation occurred in rats that had leakage of BupreLab-Rat from the injection site immediately following removal of the needle. Skin irritation may be minimized by observing proper injection technique.

For technical assistance, or to report an adverse drug reaction, please call Wildlife Pharmaceuticals, Inc. at 970-795-0920.

Adverse drug reactions may also be reported to the FDA/CVM at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

CLINICAL PHARMACOLOGY:

Pharmacokinetic parameters of BupreLab-Rat were investigated in 6 female Sprague Dawley rats following a single subcutaneous injection of 1mg/kg bodyweight. Peak plasma concentrations of 3.18 ng/mL were reached at 4 hours, with linear decline thereafter to 1.0 ng/mL at 72 hours.

The $t_{1/2}$ of BupreLab-Rat was 14.8 hours.

STORAGE INFORMATION:

Store at controlled room temperature between 15° and 30°C (59°-86°F) in a facility consistent with appropriate Drug Enforcement Agency regulations regarding Schedule III Class drugs.

REFERENCES:

1. Foley PL, Liang H, Crichlow AR, Foley PL, Liang H, Crichlow AR. Evaluation of a sustained-release formulation of buprenorphine for analgesia in rats. *JAALAS* 2011;50:198–204.
2. Brewster D, Humphrey MJ, McLeavy A. Xenobiotica. 1981 Mar;11(3): 189-96.
3. Ohtani M, Kotaki H, Uchino K, Sawada Y, Iga T. Drug Metab Dispos. 1994 Jan-Feb;22(1):2-7

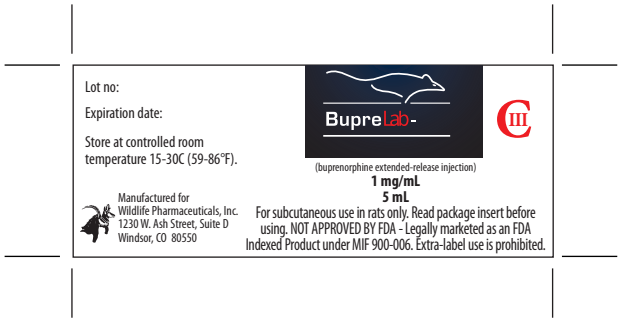
HOW SUPPLIED:

BupreLab-Rat is supplied in a 5 mL clear glass vial (1mg buprenorphine/mL).

Manufactured for

Wildlife Pharmaceuticals, Inc.
1230 W. Ash Street, Suite D, Windsor, CO 80550

Vial Label



Carton Label