Date of Index Listing: March 30, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL REQUEST FOR ADDITION TO THE INDEX OF LEGALLY MARKETED UNAPPROVED NEW ANIMAL DRUGS FOR MINOR SPECIES

MIF 900-020

BupreLab-Mouse™

(buprenorphine extended-release injection)

Mice

"For the control of post-procedural pain in mice"

Requested by:

Wildlife Pharmaceuticals, Inc.

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I. GENERAL INFORMATION:

File Number:

MIF 900-020

Requestor:

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

Proprietary Name:

BupreLab-Mouse™

Established Name:

Buprenorphine extended-release injection

Pharmacological Category:

Analgesic; Drug Enforcement Agency (DEA) Schedule III (CIII) controlled substance

Dosage Form:

Extended-release injectable

Amount of Active Ingredient:

0.5 mg buprenorphine/ml

How Supplied:

5 ml multi-dose glass vials

Dispensing Status:

by Prescription (Rx)

Dosage/Dosage Regimen:

1-1.5 mg/kg body weight, single subcutaneous injection

Routes of Administration:

Subcutaneous (SC) injection

Species/Class:

Mice

Indications:

For the control of post-procedural pain in mice

II. EFFECTIVENESS AND TARGET ANIMAL SAFETY:

In accordance with 21 CFR part 516, a qualified expert panel evaluated the target animal safety and effectiveness of BupreLab-Mouse™ for the control of post-procedural pain in mice to determine whether the benefits of using BupreLab-Mouse™ for the proposed use outweigh its risks to the target animals. The members of the qualified expert panel were:

Patricia L. Foley, DVM, DACLAM, CPIA - Panel Leader

Mark E. Epstein, DVM, DABVP, DAAPM, CVPP

John V. Roughan, PhD

A. Findings of the Qualified Expert Panel:

The qualified expert panel performed a comprehensive review of published literature on three related topics to evaluate the safety and effectiveness of BupreLab-Mouse™: the pharmacokinetics of buprenorphine in mice and other animal species, use of extended-release opioid formulations in laboratory animals, and current dosing recommendations for buprenorphine in mice. The qualified expert panel reviewed approximately 106 pieces of literature pertaining to these topics. The literature reviewed included use of buprenorphine, both immediate and extended-release formulations, in not only mice but also in rats, dogs, cats, rabbits, non-human primates, pigs, sheep, and elephant seals.

The qualified expert panel states in their report that buprenorphine is the most commonly used post-operative analgesic in rodent species. The literature includes doses for the control of post-procedural pain ranging from 0.01 to 0.5 mg/kg body weight administered subcutaneously every 6 to 12 hours. The report further states that there is a need for an extended-release analgesic for laboratory mice because repetitive daily dosing results in peaks and troughs in plasma levels rather than a steady state therapeutic level. Repeat dosing also requires the animal to be restrained multiple times a day. Repeated restraint of laboratory mice can result in a significant increase in post-procedural stress and increase the analgesic dose requirements.

While much of the literature on use of extended-release buprenorphine in mice reviewed by the qualified expert panel included formulations that are not identical to BupreLab-Mouse™, there were two pieces of literature that discussed this formulation. One article reviewed by the qualified expert panel examined the pharmacokinetics of BupreLab-Mouse™ (Kendall et al. 2014). Female CD1 mice were administered a subcutaneous injection of 0.6 mg/kg body weight. The mean time to peak drug concentration (Tmax) was 4 hours and the highest concentration of the drug in the blood (Cmax) was 14.5 ng/ml. At 24 hours post-dose, mean plasma concentration was 4.2 ng/ml and plasma concentrations of 0.03 - 0.45 ng/ml were detectable at 72 hours after dosing.

The second article described a study conducted to evaluate the use of BupreLab-Mouse™ for post-procedural analgesia in mice (Kendall et al. 2016). Adult female CD1 mice were administered a single subcutaneous injection 0.6 mg/kg body weight of BupreLab-Mouse™ prior to a laparotomy. Post-procedural pain was assessed using general activity of the mice, ability to construct a nest, and

orbital tightening. The study found that mice treated with BupreLab-Mouse™ had improved activity and nesting ability as compared to an untreated control group and a positive control group which received 0.1 mg/kg body weight of an immediate-release formulation of buprenorphine.

The qualified expert panel notes in their report that skin lesions at the injection site were the most common adverse effect reported in the literature. They recommend an adjustment in injection technique to minimize the occurrence of these lesions. Instructions on how to administer BupreLab-Mouse™ to help minimize skin lesions are included in the package insert of the labeling.

Based on a thorough review of the literature and anecdotal experience, the qualified expert panel came to a unanimous conclusion that the benefits of using BupreLab-Mouse™, for the control of post-procedural pain in mice, outweigh the risks to the target animals.

B. Literature Considered by the Qualified Expert Panel:

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III. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to BupreLab-Mouse™:

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.

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.

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.

IV. AGENCY CONCLUSIONS:

The information submitted in support of this request for BupreLab-Mouse™ for addition to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for the control of post-procedural pain in mice satisfies the requirements of section 572 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 516:

A. Determination of Eligibility for Indexing:

As part of the determination of eligibility for inclusion in the Index, FDA determined that the drug for this intended use was safe to the user, did not individually or cumulatively have a significant effect on the human environment, and that the description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packaging of the new animal drug was sufficient to demonstrate that the requestor has established appropriate specifications for the manufacture of the new animal drug. Additionally, the requestor has committed to manufacture the drug in accordance with current good manufacturing practices (CGMP).

The Index is only available for new animal drugs intended for use in minor species for which there is a reasonable certainty that the animal or edible products from the animal will not be consumed by humans or food-producing animals and for new animal drugs intended for use only in a hatchery, tank, pond, or other similar contained man-made structure in an early, non-food life stage of a food-producing minor species, where safety for humans is demonstrated in accordance with the standard of section 512(d) of the act. Because this new animal drug is not intended for use in food-producing animals, FDA did not require data pertaining to drug residues in food (i.e., human food safety) for granting this request for addition to the Index.

B. Qualified Expert Panel:

The qualified expert panel for BupreLab-Mouse™ met the selection criteria listed in 21 CFR 516.141(b). The panel satisfactorily completed its responsibilities in accordance with 21 CFR part 516 in determining the target animal safety and effectiveness of BupreLab-Mouse™ for the control of post-procedural pain in mice.

C. Marketing Status:

BupreLab-Mouse™ will be marketed by prescription.

D. Exclusivity:

Products listed in the Index do not qualify for exclusive marketing rights.