Date of Index Listing: October 28, 2013

FREEDOM OF INFORMATION SUMMARY

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

MIF 900-006

BUPRELAB-RAT

(buprenorphine extended-release injection)

Rats

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

Requested by:

Wildlife Pharmaceuticals, Inc.

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I. GENERAL INFORMATION:

A. File Number:	MIF 900-006
B. Requestor:	Wildlife Pharmaceuticals, Inc. 1230 W. Ash Street Suite D Windsor, CO 80550
C. Proprietary Name(s):	BUPRELAB-RAT
D. Established Name(s):	Buprenorphine extended-release injection
E. Pharmacological Category:	Opioid analgesic
F. Dosage Form(s):	Injectable
G. Amount of Active Ingredient(s):	1 mg buprenorphine/mL
H. How Supplied:	5 mL multi-dose glass vial
I. How Dispensed:	By veterinary prescription (Rx)
J. Dosage(s):	1 to 1.5 mg buprenorphine/kg body weight
K. Route(s) of Administration:	Subcutaneous injection
L. Species/Class(es):	Rats
M. Indication(s):	For the control of post-procedural pain in rats

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-RAT for subcutaneous injection in rats, for the control of post-procedural pain, to determine whether the benefits of using BUPRELAB-RAT for the proposed use outweigh its risks to the target animal. The members of the qualified expert panel were:

Patricia L. Foley, DVM, DACLAM, CPIA, Charlottesville, VA;
Mark E. Epstein, DVM, DABVP, DAAPM, Gastonia, NC; and
Matthew C. Leach, PhD, Newcastle, UK.

A. FINDINGS OF THE QUALIFIED EXPERT PANEL:

Based on a review of the literature, data from laboratory studies, and their own personal experience, the qualified expert panel concluded that BUPRELAB-RAT is both effective and safe for subcutaneous injection in rats for the control of post-procedural pain.

Buprenorphine, a semi-synthetic lipophilic opioid derived from oripavine, is classified as a partial mu-opioid receptor agonist and kappa-opioid receptor antagonist. It is widely used in animals, and has advantages over other opioids, including pure mu-opioid agonists, because of its long lasting effect and relatively low risk of adverse side effects including respiratory depression.

In order to assess the safety and effectiveness of BUPRELAB-RAT, the qualified expert panel performed a comprehensive review of available information on three related topics: the pharmacokinetics of buprenorphine in rats and other animal species, use of extended-release opioid formulations in laboratory animals, and current dosing recommendations for buprenorphine in rats. After reviewing the available information, the qualified expert panel was able to collectively draw conclusions about the use of buprenorphine in rats, dosing recommendations to achieve analgesia, and the potential advantages of an extended-release formulation.

The qualified expert panel reviewed data from two laboratory studies conducted to evaluate the pharmacokinetic parameters and effectiveness of BUPRELAB-RAT. In the first study, 6 female Sprague Dawley rats received a single subcutaneous injection of 1mg BUPRELAB-RAT/kg bodyweight. A peak plasma concentration of 3.18 ng/ml was achieved at 4 hours post-injection, with a linear decline thereafter to 1.0 ng/ml at 72 hours. The $t_{½}$ was 14.8 hours and the K_{elim} was 0.047 h^{-1}. No adverse reactions were noted during the study.

The second study included a negative control group, a positive control group which received 0.2 mg buprenorphine HCl/kg bodyweight subcutaneously every 12 hours for 3 days, and a treated group which received a single subcutaneous injection of 1.2 mg BUPRELAB-RAT/kg bodyweight. The effectiveness of BUPRELAB-RAT was assessed using a thermal threshold model and a post-surgical pain model (unicortical tibial defect). Pain was assessed using an ethogram in the surgical model group; noting activity, vertical raises (standing on hind limbs), and guarding or vocalization upon handling and/or palpation of the surgical limb. Body weight and food and water consumption were also recorded for all study animals.

In the thermal threshold model, BUPRELAB-RAT increased latency 28.4% on Day 1 post-injection and 15.6% on Day 2; thermal latency returned to baseline by Day 3 post-injection. The latency on Day 2 was significantly prolonged in the rats treated with BUPRELAB-RAT when compared to the rats treated with buprenorphine HCl. In the surgical model, the rats treated with BUPRELAB-RAT showed similar willingness as the negative control rats (no surgery) to bear weight on the surgical limb for 2-3 days post-injection. When compared to the buprenorphine HCl-treated group, the rats treated with BUPRELAB-RAT had statistically fewer vertical raises.

There was no difference in body weight, food or water consumption, nor any adverse effect on normal behavior among any of the groups in the study. The only adverse reaction reported was erythema and crusting at the injection site in some of the rats treated with BUPRELAB-RAT. The injection site reaction appeared to be caused by leakage of BUPRELAB-RAT from the injection site and was minimized by modifying injection technique. The pharmacokinetics of BUPRELAB-RAT revealed plasma concentrations that remained over 1 ng/ml for 72 hours post-injection. Cmax were similar for buprenorphine HCl and BUPRELAB-RAT at 2.8 ng/ml and 2.7 ng/ml, respectively and Tmax was 4 hours for both.

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-RAT, and regarding abuse potential:

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.

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 28 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.

IV. AGENCY CONCLUSIONS:

The information submitted in support of this request for BUPRELAB-RAT for addition to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for subcutaneous injection in rats for the control of post-procedural pain 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 in rats 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 packing 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-RAT 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-RAT for the control of post-procedural pain in rats.

C. MARKETING STATUS:

BUPRELAB-RAT is restricted to use by or on the order of a licensed veterinarian because it is an extended-release formulation of a Schedule III opioid.

D. EXCLUSIVITY:

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

E. ATTACHMENTS:

Facsimile Labeling:

5 mL bottle; carton; and package insert