

Date of Index Listing: October 31, 2013

FREEDOM OF INFORMATION SUMMARY

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

MIF 900-014

ANIMALGESICS FOR MICE

(buprenorphine extended-release injectable suspension)

Mice

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

Requested by:

Animalgesic Laboratories, Inc

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I. GENERAL INFORMATION:

- A. File Number:** MIF 900-014
- B. Requestor:** Animalgesic Laboratories, Inc
1121 Benfield Blvd.
Suite Q
Millersville, MD 21108
- C. Proprietary Name(s):** ANIMALGESICS FOR MICE
- D. Established Name(s):** Buprenorphine extended-release injectable suspension
- E. Pharmacological Category:** Opioid analgesic
- F. Dosage Form(s):** Injectable
- G. Amount of Active Ingredient(s):** 1.3 mg buprenorphine/mL
- H. How Supplied:** 3 mL multi-dose glass vial
- I. How Dispensed:** By veterinary prescription (Rx)
- J. Dosage(s):** 3.25 mg buprenorphine/kg body weight
- K. Route(s) of Administration:** Subcutaneous injection
- L. Species/Class(es):** Mice
- M. Indication(s):** 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 ANIMALGESICS FOR MICE for subcutaneous injection in mice for the control of post-procedural pain to determine whether the benefits of using ANIMALGESICS FOR MICE for the proposed use outweigh its risks to the target animal. The members of the qualified expert panel were:

Ward R. Richter, DVM, MS, DACVP, Leeds, AL;
Scott E. Boley, PhD, DABT, Mattawan, MI; and
Ira W. Daly, PhD, DABT, RAC, CBiol FSB, ERT, Lebanon, NJ.

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 ANIMALGESICS FOR MICE is both effective and safe for subcutaneous injection in mice for the control of post-procedural pain.

There is extensive published literature available for buprenorphine. However, the literature the qualified expert panel reviewed is limited to the references they determined to be supportive of the safety and effectiveness of an extended-release formulation of buprenorphine. The literature was used in conjunction with data from studies conducted with ANIMALGESICS FOR MICE to support the safety and effectiveness of the drug.

The LD50 of buprenorphine in mice following intravenous and intraperitoneal injection is 27 mg/kg and 94 mg/kg, respectively.² A common adverse effect associated with the opioid class of drugs is respiratory depression. In one study reported in the literature, respiratory rate decreased, in relation to dose, in mice injected with 1, 5, or 10 mg/kg buprenorphine subcutaneously. The maximum effect was achieved at a dose of 0.1 mg/kg when tested over a dose range of 0.01-10 mg/kg, indicating a ceiling effect for respiratory depression caused by buprenorphine.²

The qualified expert panel reviewed data from two studies conducted to evaluate the safety of ANIMALGESICS FOR MICE. Laboratory parameters evaluated in the studies included hematology, clinical chemistry, and coagulation profiles. Body weights, clinical observations, histopathology, and organ weights were also performed. In the first study, adult male and female mice underwent a surgical procedure and then received a single subcutaneous injection of ANIMALGESICS FOR MICE at 5 times (5X) the indicated dose. The mice were observed for 4 days post-injection. On Day 4 of the study, the mice were euthanized and necropsies were performed. No adverse reactions were reported during the study and there were no significant differences on gross necropsy or histopathology between treated mice and untreated controls. In the second study, adult male and female mice received a 5X dose of ANIMALGESICS FOR MICE for 3 doses at 4 day intervals. A surgical procedure was performed on the study mice prior to each dose. Two male mice died on Day 12 of the study, 3 days after receiving the third 5X dose of the drug. The expert panel could not attribute the deaths directly to the drug, and concluded that the mice may have died due to multiple exposures to anesthesia and surgery. Reduced motor activity was observed in both male and female mice after a 5X dose of the drug, but no significant differences were noted on gross necropsy or histopathology between treated mice and untreated controls.

Evaluating the effectiveness of antinociceptive drugs in mice can be difficult because there are limited ways to test for analgesia in mice. Thermal sensitivity is the most common type of test conducted, and the hot plate (Hargreaves) and tail-flick test appear to be the most reliable¹². Buprenorphine has been reported to be an effective antinociceptive in the literature, with the results of some tests showing it to be slightly more effective than morphine in mice.^{13,14}

The qualified expert panel reviewed data from Hargreaves and tail-flick tests conducted with ANIMALGESICS FOR MICE. For the Hargreaves test, female mice were placed on an acrylic platform and a focused thermal heat stimulus was delivered from a fixed distance to the plantar surface of the right hind paw. The intensity of the heat stimulus was fixed at 40% and a full leg raise was considered a response to the stimulus. After receiving a single dose of ANIMALGESICS FOR MICE, the test mice had on average a 1 second delay in thermal response time compared to untreated controls up to 3 days after injection.

For the tail-flick test, male and female mice were placed in a limited movement environment, and their tails were immersed in water at 48 °C. The thermal response time in both male and female mice treated with ANIMALGESICS FOR MICE was delayed compared to untreated control mice. A statistically significant difference in response time was noted in female mice up to 2 days after injection and up to 1 day after injection in male mice. The average delay in response in treated male mice was more than double that of the untreated controls for up to 2 days after injection, but the large individual variation in response time prevented statistical significance.

The qualified expert panel also reviewed pharmacokinetic data to support the effectiveness of ANIMALGESICS FOR MICE. Plasma levels of buprenorphine were measured at multiple time points in mice after receiving 3.25 mg ANIMALGESICS FOR MICE subcutaneously. Plasma levels of ≥ 0.5 ng/mL were present up to 3 days after injection. In a second group of mice, plasma levels of ≥ 1 ng/mL were reported up to 3 days after injection. Based on the data, the qualified expert panel concluded that clinically significant plasma levels of buprenorphine were present up to 3 days after injection with ANIMALGESICS FOR MICE.

B. LITERATURE CONSIDERED BY THE QUALIFIED EXPERT PANEL:

1. Stokes, E., Flecknell, P. and Richardson, C. (2009) Reported analgesic and anesthetic administration to rodents undergoing experimental surgical procedures. *Lab Anim.* 43(2): 149-154.
2. Cowan, A., Doxey, J. and Harry, E. (1977) The animal pharmacology of buprenorphine, an oripavine analgesic agent. *Brit J. Pharmacol.* 60: 547-554.
3. Guarnieri, M. (2011) Animalgesics[®] for post-surgical analgesia in mice: drug safety information reviewed. Unpublished report.
4. Guarnieri, M. (2011) Ethnographic study of Animalgesics[®] sustained release injection formula in mice. Bamvet report for study no. 6. Unpublished study report.
5. Guarnieri, M. (2011) Weight changes in Animalgesics[®] sustained release injection formula in mice. Bamvet report for study no. 4. Unpublished study report.

6. Guarnieri, M. (2011) Hematology and clinical chemistry studies in Animalgesics[®] sustained release injection formula–treated mice. Bamvet report for study no. 5. Unpublished study report.
7. Bannerjee, D. and Sarkar, N. (1997) Hematological changes in buprenorphine-treated mice. *Folia Biologica (Krakow)*. 45(3-4): 157-162.
8. Brayton, C. (2012) Pathology report: Buprenorphine sustained release injection formula: A target animal safety study in BALB/c Mice. Bamvet Pathology Report for Study Animalgesics-2. Unpublished study report.
9. Van Vleet, J. and Ferrans, V. (1986) Myocardial diseases of animals. *Am. J. Pathol.* 124(1): 98-178
10. Yu, S., Zhang, X., Sun, Y., Peng, Y., Johnson, J., Mandrell, T., Shukla, A. and Laizure, S. (2006) Pharmacokinetics of buprenorphine after intravenous administration in the mouse. *J. Amer. Assoc. Lab. Animal Science* 45(3): 12-16.
11. Guarnieri, M. (2011) Pharmacokinetic data for Animalgesics[®] sustained release injection formula in mice. Bamvet report for study no. 3. Unpublished study report.
12. Karas, A. (2002) Postoperative analgesia in the laboratory mouse, *Mus musculus*. *Lab Animal* 31(7) 1-4.
13. Cowan, A., Lewis, J. and MacFarlane, I. (1977) Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. *Brit. J. Pharmacol.* 60: 537-545.
14. Raffa, R. and Ding, Z. (2007) Examination of the preclinical antinociceptive efficacy of buprenorphine and its designation as full- or partial-agonist. *Acute Pain* 9: 145-152.
15. Guarnieri, M. (2011) Efficacy of Animalgesics[®] sustained release injection formula in mice. Bamvet report for study no. 2. Unpublished study report.
16. Foley, P., Liang, H. and Crichlow, A. (2011) Evaluation of a sustained-release formulation of buprenorphine for analgesia in rats. *J. Amer. Assoc. Lab. Animal Science.* 50(2): 198-204.

III. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ANIMALGESICS FOR MICE, and regarding abuse potential:

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

Abuse Potential

Animalgesics for Mice contains buprenorphine, a high concentration (1.3 mg/mL) opioid agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. The high concentration of *Animalgesics for Mice* may be a particular target for human abuse. Buprenorphine has 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 *Animalgesics for Mice*. 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 *Animalgesics for Mice*.

Life-Threatening Respiratory Depression

The concentration of buprenorphine in *Animalgesics for Mice* is 1.3 mg/mL. Respiratory depression, including fatal cases, may occur with abuse of *Animalgesics for Mice*.

Animalgesics for Mice 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, *Animalgesics for Mice* 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 *Animalgesics for Mice* in the laboratory:

Two trained staff for administration: *Animalgesics for Mice* should only be handled and administered to mice 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 *Animalgesics for Mice*.

Protective covering: To prevent direct contact of *Animalgesics for Mice* with human skin or mucous membranes when handling the solution, protective clothing is recommended.

Mucous membrane or eye contact during administration: Direct contact of *Animalgesics for Mice* 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 *Animalgesics for Mice*, 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: *Animalgesics for Mice* contains buprenorphine, a mu opioid partial agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. *Animalgesics for Mice* can be abused and is subject to misuse, abuse, addiction, and criminal diversion. *Animalgesics for Mice* 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 *Animalgesics for Mice* 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: *Animalgesics for Mice* 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 1-855-406-7660.

Physician information: *Animalgesics for Mice* injectable solution is a mu opioid partial agonist (1.3 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 ANIMALGESICS FOR MICE for addition to the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for subcutaneous injection in mice 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 mice 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 ANIMALGESICS FOR MICE 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 ANIMALGESICS FOR MICE for subcutaneous injection in mice.

C. MARKETING STATUS:

ANIMALGESICS FOR MICE 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:

3 mL bottle; carton; and package insert

