Date of Modification to the Index Listing: September 3, 2014

FREEDOM OF INFORMATION SUMMARY

MODIFICATION OF A LISTING IN THE INDEX OF LEGALLY MARKETED UNAPPROVED NEW ANIMAL DRUGS FOR MINOR SPECIES

MIF 900-014

ANIMALGESICS FOR MICE & RATS

(buprenorphine extended-release injectable suspension)

Rats

This modification provides for the addition of a new indication for the control of post-procedural pain in rats.

Requested by:

Animalgesic Laboratories, Inc

TABLE OF CONTENTS

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 & RATS
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:	1.6 mL and 3 mL multi-dose glass vial
I. How Dispensed:	By veterinary prescription (Rx)
J. Dosage(s):	0.65 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 ANIMALGESICS FOR MICE & RATS for subcutaneous injection in rats for the control of post-procedural pain to determine whether the benefits of using ANIMALGESICS FOR MICE & RATS 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 & RATS is both effective and safe for subcutaneous injection in rats for the control of post-procedural pain.

The literature reviewed by the qualified expert panel is the same literature used to support the original addition to the Index for this product in mice. The extensive amount of literature published on buprenorphine was limited to the references the expert panel determined to be pertinent to the safety and effectiveness of an extended-release formulation. The literature was used in conjunction with data from studies conducted with ANIMALGESICS FOR MICE & RATS to support the safety and effectiveness of the drug.

The qualified expert panel reviewed data from two laboratory studies conducted to evaluate the safety of ANIMALGEISICS FOR MICE & RATS. Parameters evaluated in the studies included hematology, clinical chemistry, body weights, clinical observations, histopathology, and organ weights. In the first study, adult male and female rats underwent a surgical procedure and then received a single subcutaneous injection of ANIMALGESICS FOR MICE & RATS at 0, 2, 6, or 10 times the indicated dose of 0.65 mg/kg buprenorphine. In the second study, adult male and female rats received a 0, 2, 6, or 10 times the indicated dose of ANIMALGESICS FOR MICE & RATS for 3 doses at 4 day intervals. A surgical procedure was performed on the study rats prior to each dose. Signs of nausea, including self-licking, self-gnawing, and consumption of wood bedding were noted in treated animals, regardless of dose, within 24 hours of injection. Mortality was seen in 1 of 36 rats. Necropsy revealed the stomach and esophagus were impacted with wood bedding. A mild reduction in body weight gain was also noted in treated animals, but no significant findings were noted on gross necropsy or histopathology.

The qualified expert panel reviewed data from tail-flick tests conducted with ANIMALGESICS FOR MICE & RATS to assess analgesia. For the tail-flick test, male and female rats were placed in a limited movement environment, and their tails were immersed in heated water. The thermal response time in rats treated with ANIMALGESICS FOR MICE & RATS was delayed for up to 3 days following injection.

The qualified expert panel also reviewed pharmacokinetic data to support the effectiveness of ANIMALGESICS FOR MICE & RATS. Plasma levels of buprenorphine were measured at multiple time points in rats after receiving 0.65 mg/kg ANIMALGESICS FOR MICE & RATS subcutaneously. Plasma levels of $\geq$ 0.5 ng/mL were present up to 3 days after injection.

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 & RATS, and regarding abuse potential:

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

Abuse Potential

***Animalgesics for Mice & Rats* 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 & Rats* 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 & Rats*. 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 & Rats*.

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

***Animalgesics for Mice & Rats* 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 & Rats* 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 & Rats* in the laboratory:

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

Protective covering: To prevent direct contact of *Animalgesics for Mice & Rats* 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 & Rats* 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 & Rats*, 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 & Rats* 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 & Rats* can be abused and is subject to misuse, abuse, addiction, and criminal diversion. *Animalgesics for Mice & Rats* 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 & Rats* 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 & Rats* 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 & Rats* 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 to modify the listing in the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) for ANIMALGESICS FOR MICE & RATS to add an indication for the control of post-procedural pain in rats 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 ANIMALGESICS FOR MICE & RATS 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 & RATS for subcutaneous injection in rats.

C. MARKETING STATUS:

ANIMALGESICS FOR MICE & RATS 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:

1.6 mL bottle and carton; 3 mL bottle and carton; and package insert