Date of Index Listing: November 1, 2024

FREEDOM OF INFORMATION SUMMARY

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

MIF 900-014

Ethiqa XR®

(buprenorphine extended-release injectable suspension)

Captive Rodents

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

Requested by:

Fidelis Animal Health, Inc.

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I. GENERAL INFORMATION:

A. File Number:	MIF 900-014
B. Requestor:	Fidelis Animal Health Inc. 685 US Highway One Suite 265 North Brunswick, NJ 08902
C. Proprietary Name(s):	Ethiqa XR®
D. Established Name(s):	Buprenorphine extended-release injectable suspension
E. Pharmacological Category:	Opioid analgesic; Drug Enforcement Agency (DEA) Schedule III (CIII) controlled substance
F. Dosage Form(s):	Injectable suspension
G. Amount of Ingredient(s):	1.3 mg buprenorphine/mL
H. How Supplied:	5 mL multi-dose glass vial containing 3 mL of injectable suspension
I. How Dispensed:	By prescription (Rx)
J. Dosage(s):	Dependent on rodent species
K. Route(s) of Administration:	Subcutaneous injection
L. Species/Class(es)	Captive rodents
M. Indication(s):	For the control of post-procedural pain in captive rodents.

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 Ethiqa XR® for subcutaneous injection for the control of post-procedural pain in captive rodents and determined whether the benefits of use outweigh the risks to the target animals. FDA found the below qualified expert panel members acceptable as per 21 CFR 516.141(b)**.** The members of the qualified expert panel were:

- Angela M. Lennox DVM, DABVP (Avian and Exotic Companion Mammal), DECZM (Exotic Small Mammal) - Panel Leader

- Stuart Levin DVM, PhD, DACVP
- Robert E. Meyer DVM, DACVAA

A. Findings of the Qualified Expert Panel:

The qualified expert panel performed a comprehensive review of published literature and unpublished study data on buprenorphine. Additionally, as experts in the field of veterinary medicine, they used anecdotal information and their own personal experience using buprenorphine to complete their assessment of the target animal safety and effectiveness of Ethiqa XR® in captive rodents. The literature reviewed included the use of buprenorphine, both short-acting and long-acting formulations, in several rodent species commonly used in research and laboratory settings.

The qualified expert panel focused on the use of buprenorphine for pain management in captive rodents following procedures such as surgery. Unlike short-acting acting formulations of buprenorphine (a single injection lasting between 4 hours and 8 hours), sustained- or extended-release formulations of buprenorphine, which are longer-acting, minimize repeated restraint and stress associated with multiple injections in the target animal as well as risk to handlers. Ethiqa XR® is an extended-release formulation of buprenorphine.

The qualified expert panel reviewed a total of thirty-three peer-reviewed published studies evaluating target animal safety and effectiveness of buprenorphine in captive rodents. Expert panel members conducted an in-depth review of each piece of literature and consulted their own expertise prior to conducting their risk-benefit analysis. FDA used the results of the panel's analysis to determine whether the benefit to the animal outweighs the risk, including the risk of not having access to Ethiqa XR® for the proposed intended use.

The same information used by the qualified expert panel to conduct their risk assessment was also used to support dosing recommendations. Establishing buprenorphine blood concentrations associated with analgesia can be difficult, even in humans, due to subjectivity of self-reporting. An article published in the Journal of Opioid Management (Guarnieri, 2021) confirmed buprenorphine blood concentrations can be an objective biomarker of analgesia for moderate to severe acute postoperative pain based on more than 30 years of data. The same article reports that mammalian species generally require a buprenorphine blood concentration of 0.5 - 2 ng/mL to provide acceptable analgesia. A therapeutic blood level for buprenorphine has not yet been established for all mammalian species. Studies reviewed by the panel that evaluated effectiveness of buprenorphine in some of the rodent species used plasma buprenorphine concentrations thought to be therapeutic in conjunction with

pharmacokinetic (PK) and pharmacodynamic (PD) studies to demonstrate analgesia. For example, PK and PD studies published in the Animal Models and Experimental Medicine journal (Navarro, 2021) showed analgesia in mice that received 3.25 mg/kg SQ of extended-release buprenorphine for up to 72 hours. A PK study in guinea pigs (Oliver, 2017) found therapeutic blood levels were maintained for up to 96 hours after receiving 0.48 mg/kg SQ of extended-release buprenorphine. The panel reviewed these and other PK/PD studies in rats, mice, guinea pigs, gerbils, and prairie dogs.

Due to the vast number of rodent species, the panel extrapolated information across species based on allometric principles (i.e., animals among closely related species and of similar body size should have similar metabolic rates) to support their assessment of the effectiveness and target animal safety of Ethiqa XR®. Since Ethiqa XR® is already indexed for use in mice and rats, dosing recommendations in rodents other than mice and rats, such as guinea pigs, black-tailed prairie dogs (*Cynomys ludovicianus*), chinchilla (*Chinchilla lanigera*), and the naked mole-rat (*Heterocephalus glaber*) were based on published literature and allometric scaling from known mouse and rat doses of the immediate release and the sustained release (polymer) buprenorphine products. Allometric scaling uses published scaling factors (FDA, 2005 and Nair, 2016) to determine the dose for an unknown species, as follows:

$$Dose_{uknown} = Dose_{known} \times \frac{Scaling\ Factor_{unknown}}{Scaling\ Factor_{known}}$$

Since hamster doses were not available in the published literature, the panel used this approach to calculate a dose for hamsters. References on how to apply allometric scaling will be provided in the product labeling. Based on the studies that were evaluated and their own personal experience, the qualified expert panel advised that Ethiqa XR® can be administered 30 minutes prior to painful stimulus in mice (Chan, 2022) and gerbils (Bowie, 2023), and 8 - 12 hours prior in guinea pigs (Oliver, 2017). The qualified expert panel also determined that a repeat dose of Ethiqa XR® can be administered every 72 hours after the initial dose, if needed.

Members of the qualified expert panel have extensive experience with the use of buprenorphine formulations in a variety of rodent species and received testimonies from laboratory animal caretakers and investigators that support the need for the drug in rodents used in research and clinical settings. The qualified expert panel reviewed a total of eight articles involving safety and adverse events associated with the use of short-acting and sustained-release buprenorphine as well as Ethiqa XR® in captive rodents. Animals in these studies had cases of nausea, inflammation at the injection site, decreased body weight and fecal output. Given that these are known adverse drug events associated with opioids (which can be

prevented or treated) and a general absence of any other significant adverse events, the qualified expert panel agreed that this information supports the safety of buprenorphine in captive rodents.

Based on a thorough review of the literature, anecdotal information, and personal experience, the qualified expert panel came to a unanimous conclusion that the benefits of using Ethiqa XR®, for the control of post-procedural pain in captive rodents, outweigh the risks to the target animals.

B. Literature Considered by the Qualified Expert Panel:

1. Alamaw ED, Franco BD, Jampachaisri K, Huss MK, Pacharinsak C. Extended-release Buprenorphine, an FDA indexed Analgesic, Attenuates Mechanical Hypersensitivity in Rats (*Rattus norvegicus*). Journal of the American Association for Laboratory Animal Science. 2022 Jan 1;61(1):81-8.
2. Allen M, Nietlisbach N, Johnson RA. Evaluation of self-injurious behavior, food intake, fecal output, and thermal withdrawal latencies after injection of a high-concentration buprenorphine formulation in rats (*Rattus norvegicus*). American journal of veterinary research. 2018 Feb 1;79(2):154-62.
3. Bender, H.M. Pica behavior associated with buprenorphine administration in the rat. Letter to the Editor - not available.
4. Bowie AR, Gibson-Corley KN, Yu EN. Pharmacokinetics of Extended-release Buprenorphine in Mongolian Gerbils (*Meriones unguiculatus*). Journal of the American Association for Laboratory Animal Science. 2023 Nov 11;62(6):538-44.
5. Cary CD, Lukovsky-Akhsanov NL, Gallardo-Romero NF, Tansey CM, Ostergaard SD, Taylor Jr WD, Morgan CN, Powell N, Lathrop GW, Hutson CL. Pharmacokinetic profiles of meloxicam and sustained-release buprenorphine in prairie dogs (*Cynomys ludovicianus*). Journal of the American Association for Laboratory Animal Science. 2017 Mar 1;56(2):160-5.
6. Chan G, Si C, Nichols MR, Kennedy L. Assessment of the safety and efficacy of pre-emptive use of extended-release buprenorphine for mouse laparotomy. Journal of the American Association for Laboratory Animal Science. 2022 Jul 1;61(4):381-7.
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14. Guarnieri M, Brayton C, DeTolla L, Forbes-McBean N, Sarabia-Estrada R, Zadnik P. Safety and efficacy of buprenorphine for analgesia in laboratory mice and rats. Lab animal. 2012 Nov;41(11):337-43.

15. Guarnieri M, Brayton C, Sarabia-Estrada R, Tyler B, McKnight P, DeTolla L. Subcutaneous Implants of a Cholesterol-Triglyceride-Buprenorphine Suspension in Rats. Journal of veterinary medicine. 2017;2017(1):3102567.

16. Guarnieri M, Brayton C, Tyler BM. A Long-Term Study of a Lipid-Buprenorphine Implant in Rats. Journal of Veterinary Medicine. 2018;2018(1):2616152.

17. Guarnieri M. Buprenorphine blood concentrations: A biomarker for analgesia. J Opioid Manag. 2021 Jan l;17(7):15-20.

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23. Masuda Y, Utsui Y, Shiraishi Y, Karasawa T, Yoshida K, Shimizu M. Relationships between plasma concentrations of diphenylhydantoin, phenobarbital, carbamazepine, and 3-sulfamoylmethyl-1, 2-benzisoxazole (AD-810), a new anticonvulsant agent, and their anticonvulsant or neurotoxic effects in experimental animals. Epilepsia. 1979 Dec;20(6):623-33.

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32. Sarabia-Estrada R, Cowan A, Tyler BM, Guarnieri M. Association of nausea with buprenorphine analgesia for rats. Lab animal. 2017 Jun;46(6):242-4.

33. Smith BJ, Wegenast DJ, Hansen RJ, Hess AM, Kendall LV. Pharmacokinetics and paw withdrawal pressure in female guinea pigs (*Cavia porcellus*) treated with sustained-release buprenorphine and buprenorphine hydrochloride. Journal of the American Association for Laboratory Animal Science. 2016 Nov 1;55(6):789-93.

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III. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Ethiqa XR®**.**

HUMAN SAFETY WARNING

Abuse Potential

ETHIQA XR contains buprenorphine, an opioid that exposes humans to risks of misuse, abuse, and addiction, which can lead to overdose and death. Use of buprenorphine may lead to physical dependence. The risk of abuse by humans should be considered when storing, administering, and disposing of ETHIQA XR. Persons at increased risk for opioid abuse including those with a personal or family history of substance abuse (including drugs or alcohol) or mental illness (e.g., depression).

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with accidental exposure to or with misuse or abuse of ETHIQA XR. Monitor for respiratory depression if human exposure to buprenorphine occurs. Misuse or abuse of buprenorphine by swallowing, snorting, or injecting poses a significant risk of overdose and death.

Accidental Exposure

Because of the potential for adverse reactions associated with accidental exposure, ETHIQA XR should only be administered by veterinarians, veterinary technicians, or laboratory staff who are trained in the handling of potent opioids. Accidental exposure to ETHIQA XR, especially in children, can result in a fatal overdose of buprenorphine.

Risks Form Concurrent Misuse or Abuse with Benzodiazepines or Other CNS Depressants

Concurrent misuse or abuse of opioids with benzodiazepines or other central nervous systems (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

See HUMAN SAFETY WARNINGS for detailed information.

HUMAN SAFETY WARNINGS

Not for use in humans. Keep out of the reach of children and pets.

Human User Safety while handling Ethiqa XR® in the hospital:

Ethiqa XR® should only be handled and administered by a veterinarian, veterinary technician, 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 Ethiqa XR®.

Wear protective clothing when administering Ethiqa XR®.

Mucous membrane or eye contact during administration:

Direct contact of Ethiqa XR® with the eyes, oral or other mucous membranes 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 immediately. If wearing contact lenses, flush the eye first and then remove contact lens.

Skin contact during administration:

If human skin is accidentally exposed to Ethiqa XR®, 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:

Ethiqa XR® contains buprenorphine, a mu opioid partial agonist and Schedule III controlled substance with an abuse potential similar to other Schedule III opioids.

Abuse:

Ethiqa XR® contains buprenorphine, an opioid substance, that can be abused and is subject to misuse, abuse, and addiction, which may lead to overdose and death. This risk is increased with concurrent use of alcohol and other central nervous system depressants, including other opioids and benzodiazepines.

Ethiqa XR® 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.

Prescription drug abuse is the intentional, non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Buprenorphine has been diverted for non-medical use into illicit channels of distribution. All people handling opioids require careful monitoring for signs of abuse.

Storage and Disposal:

Ethiqa XR® is a Schedule III opioid. Store in a locked, substantially constructed cabinet according to federal and state requirements/guidelines. Discard any broached vials after 90 days. Any unused or expired vials must be destroyed by a reverse distributor; for further information, contact your local DEA office or call Fidelis Animal Health at 1-833-384-4729.

Information for Physician:

Ethiqa XR® contains 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 for Ethiqa XR® on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species (Index) to add an indication for the control of post-procedural pain in captive rodents 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. The use of Ethiqa XR® for the control of post-procedural pain is limited to captive rodents because FDA has a reasonable certainty that these animals will not enter the human food supply. The term “captive rodents” refers to animals belonging to the order Rodentia that are held in captivity and subsequently, will not be released into the wild after receiving the indexed drug. This is because some free-ranging rodents in the wild may be trapped or hunted for food. Some examples of captive rodent species include mice, rats, hamsters, prairie dogs, and guinea pigs. 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 to modify the index listing.

B. Qualified Expert Panel:

The qualified expert panel for Ethiqa XR® 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 Ethiqa XR® for the control of post-procedural pain in captive rodents.

C. Marketing Status:

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

D. Exclusivity:

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