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)

Laboratory Rabbits

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

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
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):	0.15 mg buprenorphine/kg body weight
K. Route(s) of Administration:	Subcutaneous injection
L. Species/Class(es)	Laboratory rabbits
M. Indication(s):	For the control of post-procedural pain in laboratory rabbits.

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 laboratory rabbits 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The qualified expert panel performed a comprehensive review of published literature and unpublished study data on buprenorphine.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, 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 laboratory rabbits. The literature reviewed included the use of buprenorphine, both short-acting and long-acting formulations, in laboratory rabbits.

The qualified expert panel focused on the use of buprenorphine for pain management in laboratory rabbits 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 twenty-one peer-reviewed published studies and one preliminary study (unpublished) evaluating target animal safety and effectiveness of buprenorphine in laboratory rabbits**.** Expert panel members conducted an in-depth review of each piece of literature, the information from the preliminary study, and consulted their own expertise prior to conducting their risk-benefit analysis. FDA used the results of their analysis to determine whether the benefit to the animal outweighs the risk, including the risk of not having access to the proposed drug for this intended use.

The same information used by the qualified expert panel to conduct their risk assessment was also used to support the current dosing recommendation. 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. However, a theoretical minimal concentration of buprenorphine in the blood for rabbits has been cited to be 0.1 ng/mL. A 2024 article published in the Journal of American

Association for Laboratory Animal Science (Farkas et. al., 2024) combined the use of therapeutic blood levels (0.1 ng/mL) and grimace pain scores to determine onset and sustained analgesia in rabbits that received either Ethiqa XR® at the recommended dosage (0.15 mg/kg SQ) or a fentanyl patch following a surgical procedure. Grimace pain scores revealed no significant difference in post-procedural pain between treatment groups. According to the unpublished preliminary study**,** a dose of 0.15 mg/kg SQ was used when administering Ethiqa XR® to male and female New Zealand White rabbits to evaluate the time to reach the blood level thought to be therapeutic (0.1 mg/mL). The results showed blood levels reached the therapeutic threshold in 30 minutes and 1 hour in female and male rabbits, respectively. In the 2024 study by Farkas et. al., the time to reach therapeutic blood levels was 60 minutes for both male and female rabbits in the study. Based on their evaluation of these studies and their own personal experience, the qualified expert panel advised that Ethiqa XR® can be administered 30 to 60 minutes prior to painful stimulus in laboratory rabbits. However, they stated that it remains important for investigators and veterinarians to assess pain in each individual animal or experimental group carefully when dosing patients for analgesia.

The qualified expert panel also reviewed the safety and any adverse drug events associated with use of Ethiqa XR®, short-acting, sustained-release, and high concentration buprenorphine in laboratory rabbits (mostly New Zealand White rabbits) found in the published literature. Animals in many of the studies showed decreased respiratory rates regardless of the route of administration of buprenorphine, decreased food/water consumption and fecal output, injection site erythema, and occasionally, rabbits who received high doses of buprenorphine developed neurological signs. While these are known effects of opioids, in general, in both humans and animals, the qualified expert panel believed buprenorphine is regarded to be safer than other opioid analgesics used in rabbits, especially when avoiding higher doses of buprenorphine. 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 laboratory rabbits.

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

B. Literature Considered by the Qualified Expert Panel:

1. Andrews DD, Fajt VR, Baker KC, Blair RV, Jones SH, Dobek GL. A Comparison of Buprenorphine, Sustained-release Buprenorphine, and High concentration Buprenorphine in Male New Zealand White Rabbits. J Am Assoc Lab Anim Sci 2020; 59(5): 546-556.
2. Askar R, Fredriksson E, Manell E, Hedeland M, Bondesson U, Bate S, et al. Bioavailability of subcutaneous and intramuscular administrated buprenorphine in New Zealand White rabbits. BMC Vet Res. 2020; 16(1): 1-10.
3. Cooper CS, Metcalf-Pate KA, Barat CE, Cook JA, Scorpio DG. Comparison of Side Effects between Buprenorphine and Meloxicam Used Postoperatively in Dutch Belted Rabbits (*Oryctolagus cuniculus*). J Am Assoc Lab Anim Sci. 2009; 48(3): 279-285.
4. Costa RS, Ciotti-McClallen M, Tilley R, Perry S, Maki L, Starks D, Stein AB. Intramuscular alfaxalone with or without buprenorphine or hydromorphone provides sedation with minimal adverse effects in healthy rabbits (*Oryctolagus cuniculus*) in a randomized blinded controlled trial. J Am Vet Med Assoc.2023; 261(2):223-8.
5. Defiers H, Gandar F, Bolen G, Farnir F, Marlier D. Influence of a single dose of buprenorphine on rabbit (*Oryctolagus cuniculus*) gastrointestinal motility. Vet Anaesth Analg. 2018; 45(4):510-519.
6. DiVincenti L, Meirelles LAD, Westcott RA. Safety and clinical effectiveness of a compounded sustained-release formulation of buprenorphine for postoperative analgesia in New Zealand White rabbits. J Am Vet Med Assoc. 2016; 248(7):795-801.
7. Farkas MR, Dorn S, Muller L, et al. Pharmacokinetics, Fecal Output, and Grimace Scores in Rabbits Given Long-Acting Buprenorphine or Fentanyl for Postsurgical Analgesia. J Am Assoc Lab Anim Sci. 2024; 99(99): 1-7.
8. Feldman ER, Singh B, Mishkin NG, Lachenauer ER, Martin-Flores M, Daugherity EK. Effects of Cisapride, Buprenorphine, and Their Combination on Gastrointestinal Transit in New Zealand White Rabbits. J Am Assoc Lab Anim Sci. 2021; 60(2):221-228.
9. Goldschlager GB, Gillespie VL, Palme R, Baxter MG. Effects of Multimodal Analgesia with Low-Dose Buprenorphine and Meloxicam on Fecal Glucocorticoid Metabolites after Surgery in New Zealand White Rabbits (*Oryctolagus cuniculus*). J Am Assoc Lab Anim Sci 2013; 52(5): 571-576.
10. Gronsky S, Di Girolamo N, Maranville R, Pathak D, Womble W, Hanziicek AS, et al. A single injection of high-concentration buprenorphine significantly reduces food

and water intake as well as fecal and urine production in New Zealand White rabbits (*Oryctolagus cuniculus*). 2024:1-8.

11. Guarnieri M. Buprenorphine blood concentrations: A biomarker for analgesia. J Opioid Manag. 2021 Jan l;17(7):15-20.
12. Hedenqvist P, Trbakovic A, Thor A, Ley C, Ekman S, Jensen-Waern M. Carprofen neither reduces postoperative facial expression scores in rabbits treated with buprenorphine nor alters long term bone formation after maxillary sinus grafting. Res Vet Sci 2016; 107:123-131.
13. Hsi ZY, Theil JH, Ma BW, Oates RS. Effects of Buprenorphine and Carprofen on Appetite in New Zealand White Rabbits (*Oryctolagus cuniculus*). J Am Assoc Lab Anim Sci 2022; 99(99): l-6.
14. Martin-Flores M, Singh B, Walsh CA, Brooks EP, Taylor LC, Mitchell LM. Effects of Buprenorphine, Methyinaltrexone, and Their Combination on Gastrointestinal Transit in Healthy New Zealand White Rabbits. J Am Assoc Lab Anim Sci. 2017; 56(2):155-159.
15. Murphy KL, Roughan JV, Baxter MG, Flecknell PA. Anaesthesia with a combination of ketamine and medetomidine in the rabbit: effect of premedication with buprenorphine Vet Anaesth Analg. 2010; 37(3):222-229.
16. Poliwoda S, Noor N, Jenkins JS, Start CW, Steib M, et al. Buprenorphine and its formulations: a comprehensive review. Health Psychol Res. 2022; 10(3): 1-10.
17. Personal Communication with Belvins C, Bristol Myer Squibb, AML January 2024.
18. Schnellbacher RW, Divers SJ, Comolli JR, Beaufrere H, Maglaras CH, Andrade N, et al. Effects of intravenous administration of lidocaine and buprenorphine on gastrointestinal tract motility and signs of pain in New Zealand White rabbits after ovariohysterectomy Am J Vet Res. 2017; 78(12): 1359-1371.
19. Schroeder CA, Smith U. Respiratory Rates and Arterial Blood-Gas Tensions in Healthy Rabbits Given Buprenorphine, Butorphanol, Midazolam, or Their Combinations. J Am Assoc Lab Anim Sci. 2011; 50(2):205-211.
20. Shafford HL, Schadt JC. Respiratory and cardiovascular effects of buprenorphine in conscious rabbits. Vet Anaesth Analg. 2008; 35(4):326-332.
21. Shafford HL, Schadt JC. Effect of buprenorphine on the cardiovascular and respiratory response to visceral pain in conscious rabbits. Vet Anaesth Analg. 2008; 35(4):333-340.
22. Sypniewski LA, Knych H, Breshears M, Fang WB, Moody DE, Rudra P, et al. Pharmacokinetics, blood and urine profile effects, and injection site histopathology following three daily injections of subcutaneous high concentration buprenorphine

in New Zealand white rabbits {Oryctolagus cuniculus). 1 Exot Pet Med. 2022; 43:51-56.

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 include 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 From Concurrent Misuse or Abuse with Benzodiazepines or Other CNS Depressants

Concurrent misuse or abuse of opioids with benzodiazepines or other central nervous system (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 this and all medications 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 application:

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 application, flush the area with water and contact a physician immediately. If wearing contact lenses, flush the eye first and then remove the contact lens.

Skin contact during application:

If human skin is accidentally exposed to Ethiqa XR®, wash the exposed area immediately 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 clinical 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 controlled substance requirements and 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 laboratory rabbits 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. Some rabbits are raised to be food for humans, so the use of Ethiqa XR® for the control of post-procedural pain is limited to laboratory rabbits because FDA has a reasonable certainty that this population of rabbits will not be consumed by humans or food-producing animals. Due to the reasonable certainty that laboratory rabbits will not be consumed, 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 laboratory rabbits.

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.