Date of Index Listing: September 29, 2023

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)

Ferrets

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

Requested by:

Fidelis Animal Health, Inc.

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## I. GENERAL INFORMATION:

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|---|---|
| **A. File Number:** | MIF 900-014 |
| **B. Requestor:** | Fidelis Animal Health Inc.<br>675 US Highway One<br>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:** | 3 mL multi-dose glass vial |
| **I. How Dispensed:** | By prescription (Rx) |
| **J. Dosage(s):** | 0.6 mg buprenorphine/kg body weight |
| **K. Route(s) of Administration:** | Subcutaneous injection |
| **L. Species/Class(es)** | Ferrets |
| **M. Indication(s):** | For the control of post-procedural pain in ferrets |

## 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 ferrets. 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 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 ferrets. The literature reviewed included use of buprenorphine, both immediate and extended-release formulations, in ferrets as well as rodents and other mammal species.

The qualified expert panel focused on the use of buprenorphine for pain management in ferrets following procedures such as surgery. They state in their report that a single injection lasting 72 hours is beneficial to limit repeated restraint and stress associated with multiple injections. After the initial dose, it is important that investigators and veterinarians carefully assess pain in each individual animal or experimental group. The qualified expert panel determined that a single repeat dose of Ethiqa XR® can be administered 72 hours after the initial dose, if needed.

The qualified expert panel used available data and personal experience to support dosing recommendations. They state that published doses in ferrets range from 0.01-0.5 mg/kg body weight without specifying if the buprenorphine is an immediate or extended-release formulation. An article reviewed by the qualified expert panel (Guarnieri, 2021) reports that mammal species generally require a buprenorphine blood concentration of 0.5-2 ng/mL to provide acceptable analgesia.

Another article described the pharmacokinetics of immediate-release buprenorphine in ferrets (Katzenbach, et al, 2018). One-year old male ferrets were administered 0.04 mg buprenorphine/kg body weight intramuscularly every 4-6 hours. The peak drug concentration (Tmax) was reached at 9 minutes with a peak concentration in the blood of 6.96 ng/mL. The half-life was 3.6 hours making the blood concentration approximately 0.4 ng/mL after 5.5 hours, which is below the level needed for analgesia (Guarnieri, 2021). The qualified expert panel determined that this study demonstrated that providing analgesia with immediate-release buprenorphine requires repeated injections to maintain an effective blood concentration over time.

The qualified expert panel reviewed anecdotal information involving Ethiqa XR® administered subcutaneously to ferrets at 0.6 mg/kg body weight (Plunkard, 2022). Blood levels believed to be therapeutic in other species were reached in 30 minutes and lasted at least 72 hours in all animals. While effectiveness was not objectively measured, no animals required additional analgesics post spay surgery.

The qualified expert panel states in their written report that basic allometric principles based on scaling factors related to the influence of size on metabolism

has been commonly used to extrapolate pharmacokinetic parameters across a wide range of species. Using an allometric scaling factor method with the rat as comparator at a dose of 0.65 mg/kg Ethiqa XR® (Nair & Jacob, 2018), the qualified expert panel calculated that a 1 kg ferret would require an extrapolated buprenorphine extended-release dose of 0.56 mg/kg. This finding is in agreement with the anecdotal information reviewed for Ethiqa XR® (Plunkard, 2022) .

The qualified expert panel reviewed several articles which they determined support the safety of buprenorphine in ferrets. In one article (Katzenbach et al, 2018), ferrets were administered 4 different opioids and then blood was drawn to measure pharmacokinetic parameters. Groups of 6 male ferrets were administered the following doses, morphine (1 mg/kg SQ), hydromorphone (0.1 mg/kg SQ), butorphanol (0.03 mg/kg SQ) and buprenorphine (0.04 mg/kg IM). According to the authors, "there were no observable detrimental side effects following the administration of butorphanol, buprenorphine. . . or the other opioids."

In a second article (Mrotz, et al, 2022), ferrets were used to test whether treatment with buprenorphine would have an effect on the pathogenesis of disease in animals inoculated with influenza type A virus (IAV). Three groups of 4 male castrated ferrets were studied. Group 1 was treated with buprenorphine at 0.04 mg/kg subcutaneously twice daily for 5 days starting at the day of IAV inoculation. Group 2 was treated at the same dose and frequency of buprenorphine, but from Days 5 through 9 post-IAV inoculation. Group 3 was sham-treated with normal saline. The authors concluded that the buprenorphine-treated ferrets had some evidence of lethargy post-injection but did not demonstrate significant safety concerns associated with buprenorphine administration.

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 ferrets, outweigh the risks to the target animals.

**B. Literature Considered by the Qualified Expert Panel:**

1. Plunkard J. Unofficial communication of unpublished data with Fidelis, March 27-August 9, 2022. John Hopkins University School of Medicine.
2. Katzenbach JE, Wittenburg LA, Allweiler SI, Gustafson DL, Johnston MS. Pharmacokinetics of single-dose buprenorphine, butorphanol and hydromorphone in the domestic ferret (Mustela putorius furo). J Exotic Pet Med. 2018; 27: 95-102.
3. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm. 2016 Mar;7(2):27-31.

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

5. Applegate JR, Harms CA. Ferrets. In: Carpenter's Exotic Animal Formulary. Carpenter JW, Harms CA (eds). Elsevier, 2023: 634.

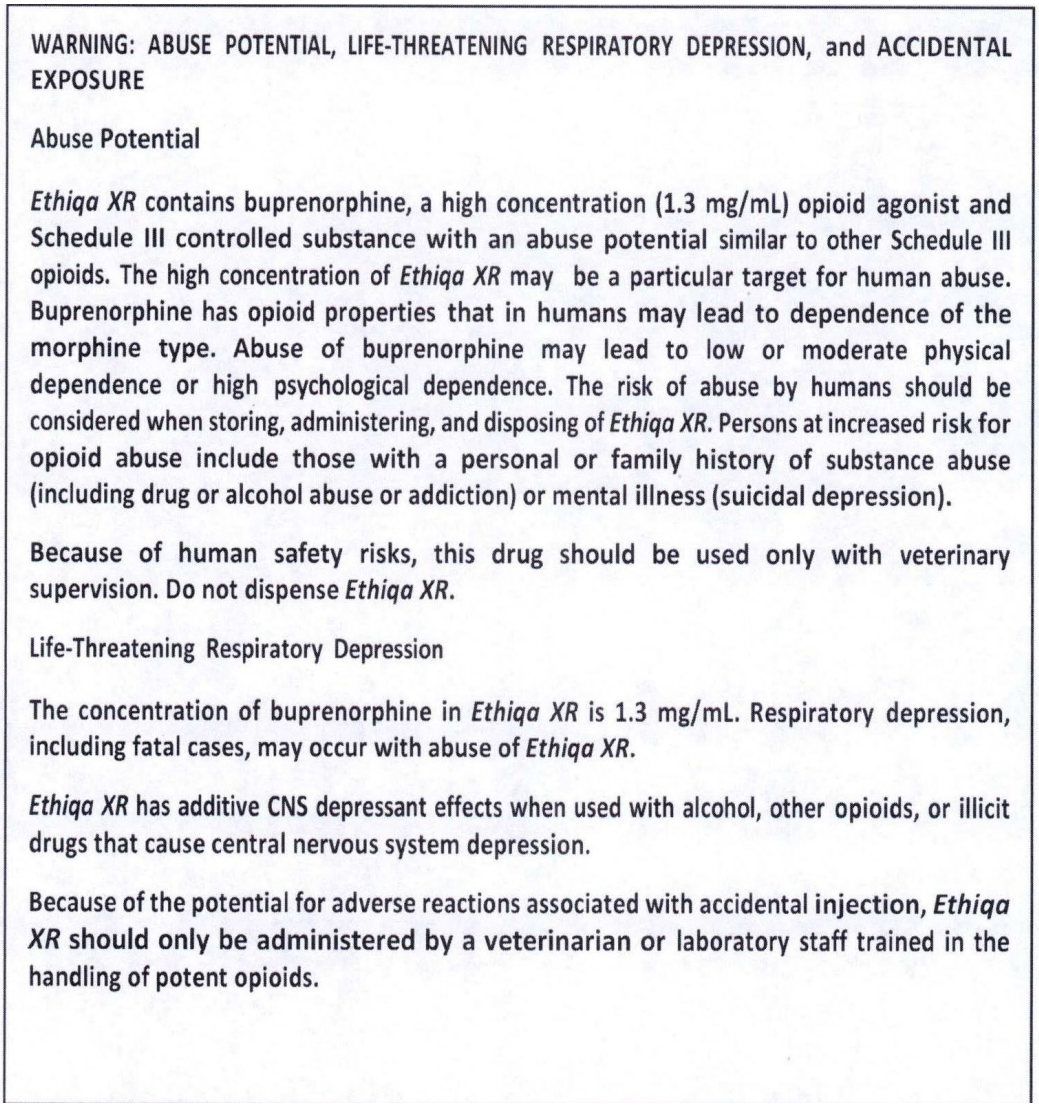
6. U Mass Boston Animal Care and Use, 2021 https://www.bu.edu/researchsupport/compliance/animal-care/working-with-animals/anesthesia/anesthesia-and-analgesia-iacuc/: accessed 11/28/22

7. Hawkins MG, Pascoe PJ. Anesthesia and sedation of small mammals. In: Ferrets, Rabbits and Rodents. Clinical Medicine and Surgery. Elsevier, 2012: 552.

8. Mrotz VJ, Nestor KM, Maines TR, Powell N, Belser, JA. Effects of buprenorphine treatment on influenza pathogenesis in the ferret (*Mustela putorius furo*). Comp Med, 72(8); 2022: 22-29.

## III. USER SAFETY:

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



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

Abuse Potential

*Ethiqa XR* 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 *Ethiqa XR* 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 *Ethiqa XR*. 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 *Ethiqa XR*.

Life-Threatening Respiratory Depression

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

*Ethiqa XR* 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, *Ethiqa XR* should only be administered by a veterinarian or laboratory staff trained in the handling of potent opioids.

Wear protective clothing when administering Ethiqa XR® (see **Human Safety Warnings**).

**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 Discard:*

Ethiqa XR® is a Class III opioid. Store in a locked, substantially constructed cabinet according to federal and state requirements/guidelines. 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 ferrets 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. 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 ferrets.

**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.