

Date of Index Listing: March 29, 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)

Non-human Primates

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

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):** Ethiq® 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):** 0.2 mg buprenorphine/kg body weight
- K. Route(s) of Administration:** Subcutaneous injection
- L. Species/Class(es)** Non-human primates
- M. Indication(s):** For the control of post-procedural pain in non-human primates

**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 Ethiq® XR for subcutaneous injection for the control of post-procedural pain in non-human primates (NHP) 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The qualified expert panel performed a comprehensive review of published literature and unpublished study data on buprenorphine.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 Ethiq<sup>a</sup> XR<sup>®</sup> in non-human primates. The literature reviewed included use of buprenorphine, both short-acting and long-acting formulations, in non-human primates as well as other mammalian species.

The qualified expert panel focused on the use of buprenorphine for pain management in non-human primates 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. Ethiq<sup>a</sup> XR<sup>®</sup> is an extended-release formulation of buprenorphine. Due to the diversity of non-human primate species, the panel extrapolated information across species to support their assessment of the effectiveness and target animal safety of Ethiq<sup>a</sup> XR<sup>®</sup>. As a result, the qualified expert panel advised that when dosing patients for analgesia, it is important for investigators and veterinarians carefully assess pain in each individual animal or experimental group. The qualified expert panel determined that a repeat dose of Ethiq<sup>a</sup> XR<sup>®</sup> can be administered every 72 hours after the initial dose, if needed.

The qualified expert panel used available information and personal experience to support dosing recommendations. They stated that published doses in non-human primates range from 0.01-0.72 mg/kg body weight buprenorphine. An article reviewed by the qualified expert panel (Guarnieri, 2021) reports that mammalian species generally require a buprenorphine blood concentration of 0.5-2 ng/mL to provide acceptable analgesia.

A second article described the pharmacokinetics (PK) of immediate-release (IR) buprenorphine compared to a sustained-release (SR) formulation of buprenorphine (Nunamaker, et al, 2013). Adult rhesus and cynomolgus monkeys were administered 0.01 mg/kg IR, 0.03 mg/kg IR, or 0.2 mg/kg SR. The monkeys maintained a plasma concentration of buprenorphine above 0.5 ng/mL for 4, 8, and 96 hours respectively. The qualified expert panel determined that this study demonstrated that providing analgesia with IR buprenorphine requires repeated

injections to maintain an effective blood concentration over time compared to SR formulations.

Two articles specifically looked at buprenorphine levels with Ethiq XR<sup>®</sup> administration. In adult common marmosets, Ethiq XR<sup>®</sup> was administered at 0.1, 0.15, or 0.2 mg/kg by subcutaneous injection and plasma concentrations were above 0.5 ng/mL for 72 hours for all animals (Fabian, et al, 2023.) In cynomolgus monkeys administered Ethiq XR<sup>®</sup> at 0.2 mg/kg, plasma levels were above 0.5 mg/mL for more than 96 hours (Klein, et al, 2023.)

The qualified expert panel reviewed a total of six articles and an American Association of Laboratory Animal Science (AALAS) conference report involving safety and adverse events associated with the use of IR and SR buprenorphine as well as Ethiq XR<sup>®</sup> in non-human primates. The authors of one article (Nunamaker, et al. study, 2013), stated that, “Buprenorphine is the cornerstone of pain management in non-human primates.” Animals in these studies had occasional cases of mild sedation, mild skin lesions/redness, and mild diarrhea, but no serious adverse events or deaths were noted. The qualified expert panel determined that this information along with their own personal experience using Ethiq XR<sup>®</sup> supports the safety of buprenorphine in non-human primates.

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 Ethiq XR<sup>®</sup>, for the control of post-procedural pain in non-human primates, outweigh the risks to the target animals.

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

1. Poliwoda S, Noor N, Jenkins JS, Stark CW, Steib M, Hasoon J, Varrassi G, Urits I, Viswanath O, Kaye AM, Kaye AD. Buprenorphine and its formulations: a comprehensive review. *Health Psychol Res.* 2022 Aug 20;10(3):37517
2. Guarnieri M. Buprenorphine blood concentrations: A biomarker for analgesia. *J Opioid Manag.* 2021 Jan 1;17(7):15-20.
3. 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.
4. Escher M, Daali Y, Chabert J, Hopfgartner G, Dayer P, Desmeules J. Pharmacokinetic and pharmacodynamic properties of buprenorphine after a

- single intravenous administration in healthy volunteers: a randomized, double-blind, placebo-controlled, crossover study. *Clin Ther.* 2007 Aug;29(8):1620-31.
5. Evans HC, Easthope SE. 2003. Transdermal buprenorphine. *Drugs.* 2003;63(19):1999-2010; discussion 2011-2.
  6. Sittl R, Griessinger N, Likar R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. *Clin Ther.* 2003 Jan;25(1):150-68.
  7. Ko JC, Freeman LJ, Barletta M, Weil AB, Payton ME, Johnson BM, Inoue T. Efficacy of oral transmucosal and intravenous administration of buprenorphine before surgery for postoperative analgesia in dogs undergoing ovariohysterectomy. *J Am Vet Med Assoc.* 2011 Feb 1;238(3):318-28.
  8. Nolan A, Livingston A, Waterman AE. Investigation of the antinociceptive activity of buprenorphine in sheep. *Br J Pharmacol.* 1987 Nov;92(3):527-33.
  9. Robertson SA, Lascelles BD, Taylor PM, Sear JW. PK-PD modeling of buprenorphine in cats: intravenous and oral transmucosal administration. *J Vet Pharmacol Ther.* 2005 Oct;28(5):453-60.
  10. Fabian NJ, Mannion AJ, Jamiel M, Anderson DJ, Rower JE, Reilly CA, Menegas W, Muthupalani S, Ta C, Fox JG, Kramer R, Haupt JL. Evaluation and comparison of pharmacokinetic profiles and safety of two extended-release buprenorphine formulations in common marmosets (*Callithrix jacchus*). *Sci Rep.* 2023 Jul 22;13:11864).
  11. Klein H, Levinson BL, Leary SL, Dobson G. A pharmacokinetic study of extended-release buprenorphine in Cynomolgus monkeys (*Macaca fascicularis*). *J Med Primatol.* 2023 Dec;52(6):369-373.
  12. Nunamaker EA, Halliday LC, Moody DE, Fang WB, Lindeblad M, Fortman JD. Pharmacokinetics of 2 formulations of buprenorphine in macaques (*Macaca mulatta* and *Macaca fascicularis*). *J Am Assoc Lab Anim Sci.* 2013 Jan;52(1):48-56.
  13. Fabian NJ, Moody DE, Averin O, Fang WB, Jamiel M, Fox JG, Burns MA, Haupt JL. Pharmacokinetics of single-dose intramuscular and subcutaneous injections of buprenorphine in common marmosets (*Callithrix jacchus*). *J Am Assoc Lab Anim Sci.* 2021 Sep 1;60(5):568-575.
  14. Kelly KR, Pypendop BH, Christe KL. Pharmacokinetics of buprenorphine following intravenous and intramuscular administration in male rhesus macaques (*Macaca mulatta*). *J Vet Pharmacol Ther.* 2014 Oct;37(5):480-5.

15. Mackiewicz AL, Salyards GW, Knych HK, Hill AE, Christe KL. Pharmacokinetics of a long- lasting, highly concentrated buprenorphine solution after subcutaneous administration in rhesus macaques (*Macaca mulatta*). J Am Assoc Lab Anim Sci. 2019 Jul 1;58(4):501-509.
16. Williams W, Norris A, Ding X. Pharmacokinetics of sustained-release buprenorphine in adult baboons (*Papio anubis*). Abstracts of Scientific Presentations: 2021 AALAS National Meeting, Kansas City, Missouri. J Am Assoc Lab Anim Sci. 2021 Sep 1;60(5):597-670.
17. Fitz CB, Goodroe AE, Moody DE, Fang WB, Capuano SV III. Pharmacokinetics of buprenorphine and sustained-release buprenorphine in common marmosets (*Callithrix jacchus*). J Am Assoc Lab Anim Sci. 2021 Mar 1;60(2):188-194.

### III. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Ethiqra 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 Ethiq XR® in the hospital:**

Ethiq 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 Ethiq XR®.**

Wear protective clothing when administering Ethiq XR®.

### **Mucous membrane or eye contact during administration:**

Direct contact of Ethiq 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 Ethiq 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:*

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

### *Abuse:*

**Ethiq 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.**

**Ethiq 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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 non-human primates 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 Ethiq® 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 Ethiq® XR for the control of post-procedural pain in non-human primates.

**C. Marketing Status:**

Ethiq® 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.