

ETHIQA XR- buprenorphine hydrochloride injection, suspension, extended release

Fidelis Animal Health, Inc.

Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click [here](#).



Ethiqa XR®
(buprenorphine extended-release injectable suspension) 1.3 mg/mL

Opioid Analgesic

For subcutaneous use in mice, rats, and ferrets.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

LEGAL STATUS--In order to be legally marketed, a new animal drug intended for a minor species must be Approved, Conditionally Approved, or Indexed by the Food and Drug Administration. THIS PRODUCT IS INDEXED--MIF 900-014. Extra-label use is prohibited.

This product is not to be used in animals intended for use as food for humans or food-producing animals.

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.

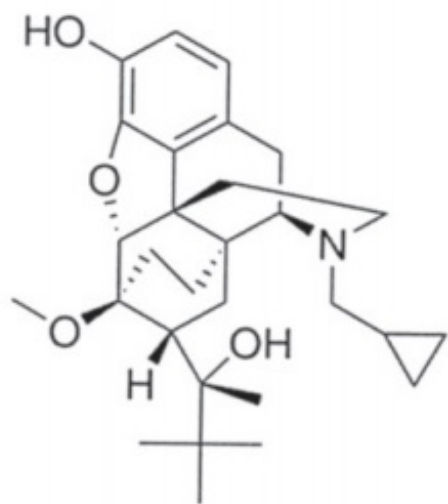
See HUMAN SAFETY WARNINGS for detailed information.

DESCRIPTION

Ethiq^a XR is an injectable suspension of extended-release buprenorphine. Buprenorphine hydrochloride, an opioid analgesic, is the active ingredient in Ethiq^a XR. Lipid-bound buprenorphine hydrochloride is suspended in medium chain fatty acid triglyceride (MCT) oil. Lipids encapsulate the buprenorphine limiting diffusion which provides for larger doses and prolonged action.^{1,2} Ethiq^a XR has a slightly yellow to white opaque appearance. Each mL contains approximately 1.3 mg buprenorphine hydrochloride. The sterile product contains cholesterol, benzyl alcohol, glyceryl tristearate, and buprenorphine hydrochloride suspended in MCT oil. Buprenorphine belongs to the opioid class of drugs and is a narcotic under the Controlled Substances Act due to its chemical derivation from thebaine.

Buprenorphine

Formula C₂₉H₄₁NO₄



INDICATIONS

Ethiqa XR is indicated for the control of post-procedural pain in mice, rats, and ferrets.

DOSAGE AND ADMINISTRATION

Wear protective clothing when administering Ethiqa XR. Do not dispense Ethiqa XR for administration at home by the pet owner (see **HUMAN SAFETY WARNINGS**).

It is important to carefully assess pain in each individual animal or experimental group and adjust the timing of Ethiqa XR administration accordingly. For mice, therapeutic blood levels are achieved within 30 minutes of administration⁷, for rats within 6 hours⁴, and for ferrets within 30 minutes.⁶

Dosing

The dosage of Ethiqa XR is a single subcutaneous injection. At the recommended doses, therapeutic blood levels are maintained for 72 hours after the initial dose. If needed, a single repeat dose may be administered 72 hours after the initial dose.

TABLE: DOSING FOR ETHIQA XR

Species	Dose mg/Kg Body Weight
Mouse	3.25 mg/Kg
Rat	0.65 mg/Kg
Ferret	0.6 mg/Kg

For example, the dose for a 20-gram mouse would be a single subcutaneous injection of 0.05 mL (3.25 mg/Kg body weight).

Administration

Shake the vial briefly before each use to ensure uniform suspension. If stored refrigerated, bring to room temperature before use.

Use aseptic techniques to withdraw the dose into a disposable 0.5- or 1-mL syringe. A 20-to-23-gauge needle should be used for injections due to the viscosity of the drug suspension.

Administer Ethiqa XR using minimally stressful restraint techniques, or in sedated animals.

Inject the entire dose into the dorsal subcutaneous space.

An oily sheen may be observed in the dorsal fur after injection. This is due to leakage of Ethiqa XR, which is an oil-based drug suspension, from the injection site. The oily sheen may last for 4 to 5 days post-injection. Leakage from the injection site can be minimized by slowly injecting Ethiqa XR into the subcutaneous space.

The animal can be returned to its cage immediately after receiving Ethiqa XR. (See **CONTRADICTIONS**, **PRECAUTIONS**, and **ADVERSE REACTIONS** for additional information on bedding).

Do not return any unused drug suspension from the syringe back into the vial.

CONTRAINDICATIONS

Only administer Ethiq XR by subcutaneous injection. Ethiq XR is not intended for intravenous, intra-arterial, intrathecal, intramuscular, or intra-peritoneal injection.

Do not use in animals with pre-existing respiratory compromise.

Do not house rats on wood chip-type bedding after administration of Ethiq XR. Signs of nausea, including pica, have been observed in rats for up to 3 days post-treatment with Ethiq XR. **Pica involving wood chip type bedding can be lethal** (see **ADVERSE REACTIONS**).

HUMAN SAFETY WARNINGS

Not for use in humans. Keep this and all medications out of 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 Application:

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 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 Ethiq 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:

Ethiq XR contains buprenorphine, a 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 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:

Ethiq XR is a Schedule III opioid. Store in a locked cabinet according to federal and state controlled substance 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 field office or call Fidelis Animal Health at 1-833-384-4729.

Information for Physician:

Ethiq XR contains a mu opioid partial agonist (1.3 mg buprenorphine/mL). In the case of an emergency, provide the physician with this 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.

PRECAUTIONS

The use of paper or soft bedding for up to 3 days following administration of Ethiq XR should be considered (see **CONTRADICTIONS** and **ADVERSE REACTIONS**).

Animals may exhibit an obtunded response to stimuli up to 4 hours after receiving Ethiq XR.

Ethiq XR may cause sedation, decreased blood pressure, decreased heart rate, decreased gastrointestinal mobility, and respiratory depression. Use caution with concomitant administration of Ethiq XR with drugs that cause respiratory depression.

Animals should be monitored for signs of decreased cardiovascular and respiratory function when receiving Ethiq XR. Buprenorphine is excreted in the feces (see **CLINICAL PHARMACOLOGY**). Coprophagy may lead to ingestion of buprenorphine or its metabolites by animals treated with Ethiq XR and untreated cage mates.

When using an opioid such as Ethiq XR, an opiate antagonist should be available in case reversal is required.

Ethiq XR forms a depot near the injection site. Granulomatous inflammation nodules have been observed in naked-skinned mice and rats administered Ethiq XR ^{4,5}.

The safety of Ethiq XR has not been evaluated in pregnant, lactating, neonatal, or immune-compromised animals.

Adverse effects, including death, have been reported when NSAIDs and Ethiq XR have been administered concomitantly in mice.

ADVERSE REACTIONS

Two Laboratory Studies in Mice

No adverse reactions were observed in sixteen 20-25-gram young adult mice (8 males,

8 females) after a single subcutaneous injection of 16.25 mg/kg Ethiq XR (5X). Laboratory parameters evaluated in the study included hematology and clinical chemistry; histopathology was also performed.

In a second study, 16 adult mice (8 males, 8 females) received 16.25 mg/kg (5X) Ethiq XR subcutaneously for three doses at four-day intervals. A surgical procedure was performed on the mice prior to receiving each of the three doses of Ethiq XR. Mortality was seen in two male mice after the third surgical procedure and third dose of Ethiq XR (total dose of 49 mg buprenorphine/kg body weight in 8 days). Weight loss was observed postprocedurally in mice administered Ethiq XR.

Two Laboratory Studies in Rats

Adverse reactions were evaluated in twenty-four 180-to-200-gram young adult rats (12 males, 12 females) after a single subcutaneous injection of Ethiq XR. A surgical procedure was performed on the rats prior to receiving a single dose of Ethiq XR of 0.65 (1X), 1.3 (2X), 3.9 (6X), or 6.5 mg/kg (10X); Six in each group (3 male and 3 female).

Adverse reactions also were evaluated in 24 young adult rats (8 weeks at start). There were 12 males and 12 females. The female rats weighed between 128-164 grams and males weighed between 169-219 grams. Each rat received a subcutaneous injection of 1.3 (2X), 3.9 (6X), or 6.5 mg/kg (10X) Ethiq XR for three doses at four-day intervals (8 rats per group; 4 males, 4 females). A surgical procedure was performed on the rats prior to receiving each of the three doses of Ethiq XR. Laboratory parameters evaluated in the study included hematology, clinical chemistry, urinalysis, histopathology, and bodyweight.

Signs of nausea were observed at all dose levels (1 rat at 1.3 mg/kg, 3 rats at 3.9 mg/kg, 2 rats at 6.5 mg/kg) within 24 hours of the dose. Signs included self-licking, self-gnawing, and efforts to eat wood-chip bedding. Mortality was seen in 1 of 36 rats exposed to wood chip bedding. Necropsy revealed the stomach and esophagus were compacted with bedding, the bladder was abnormally distended, and the urine contained blood.

3 out of 222 rats (the 222 rats are from five (5) pharmacokinetic and safety studies) were observed to bleed profusely from the jugular vein, which was used for obtaining blood samples, and subsequently died.

Two Laboratory Studies in Ferrets

No studies have been published administering Ethiq XR to ferrets. One unpublished study reports that no adverse reactions were observed after 4 adult female ferrets received a single subcutaneous injection of 0.6 mg/kg of Ethiq XR.

In a pharmacokinetic single-dose study, no adverse reactions were observed in 6 male, approximately 1-year old, ferrets after receiving 0.04 mg/kg buprenorphine immediate-release.⁶

CONTACT INFORMATION

Contact Fidelis Animal Health at 1-833-384-4729 or www.ethiqaxr.com. To report suspected adverse drug experiences, contact Fidelis Animal Health at 1-833-384-4729.

For additional information about reporting adverse drug experiences for animal drugs,

contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/reportanimalae>.

CLINICAL PHARMACOLOGY³

Mechanism of Action: Buprenorphine exerts its analgesic effect via high affinity binding to various subclasses of opiate receptors particularly mu, in the central nervous system. Buprenorphine analgesic and adverse reactions are mediated by mu opioid receptor agonism. Due to its partial agonist activity, buprenorphine exhibits a ceiling effect to its actions and thus has a greater therapeutic index compared to full mu opioid receptor agonists such as morphine. Buprenorphine binds tightly to and dissociates slowly from the opioid receptor. Therefore, the pharmacological effects of buprenorphine are not directly related to plasma concentrations.

Buprenorphine can act as an agonist and antagonist at different classes of opioid receptors. Agonism at the mu opioid receptor and, in some cases, antagonism at the kappa or delta opioid receptors are possible underlying mechanisms for the ceiling effect and bell-shaped dose-response curve of buprenorphine. Studies with knockout mice have shown that the antinociceptive effect of buprenorphine, which is mediated primarily by the mu opioid receptor, is attenuated by the ability of the drug to activate the opioid receptor like (ORL-1) receptor. The drug can be described as a 'full' and a 'partial' agonist at the same receptor depending on the specific assay. There appears to be no ceiling effect for analgesia, but there is a ceiling effect for respiratory depression.

Pharmacokinetic studies with bolus injections of buprenorphine in mice and rats provide similar models. After bolus intravenous administration, plasma levels decline tri-exponentially. The drug is n-dealkylated in the liver to norbuprenorphine (NBN), an active metabolite. Studies have shown that glucuronide metabolites of buprenorphine and NBN are also metabolically active, and can approximate or exceed the concentration of the parent drug. Un-metabolized drug excreted in the urine and feces one week after injection was 1.9 and 22.4% of the dose, respectively, and 92% of the dose was accounted for in one week.³

Mice

Pharmacokinetic parameters of Ethiq^a XR were studied in 6-8 week old male and female Balb/c mice following a single subcutaneous injection of 3.25 mg/kg bodyweight. Clinically significant blood levels were observed up to 72 hours after subcutaneous injection.

Rats

Pharmacokinetic parameters of Ethiq^a XR were studied in 8 week old male and female Fischer rats following a single subcutaneous injection of 0.65 mg/kg bodyweight. Clinically significant blood levels were observed up to 72 hours after subcutaneous injection.

Ferrets

Pharmacokinetic parameters of Ethiq^a XR were studied in 4 adult female ferrets following a single subcutaneous injection of 0.6 mg/Kg body weight. Clinically significant blood levels were observed within 30 minutes up to 72 hours after administration.

HOW SUPPLIED

Ethiq^a XR is supplied in a 5 mL glass vial containing 3 mL of injectable drug suspension.

STORAGE INFORMATION

Store between 15° and 25°C +/- 2°C (59° and 77°F) or refrigerated. DO NOT FREEZE. If stored refrigerated, bring to room temperature before use. Once broached, the multi-dose vial should be discarded after 90 days.

Product could change its physical properties if not stored within the specified storage conditions and original vial container.

REFERENCES

1. Mishra et al. Engineering solid lipid nanoparticles for improved drug delivery: promises and challenges of translational research. *Drug Delivery and Transl. Res*, 2: 238-253; 2012.
2. Bethune et al., The role of drug-lipid interactions on the disposition of liposome-formulated opioid analgesics in vitro and in vivo. *Anesth Analg*. 93(4):928-33; 2001.
3. Guarnieri et al. Safety and efficacy of buprenorphine for analgesia in laboratory mice and rats. *Lab Animal*, 41(11): 337-343; 2012.
4. Levinson BL, Leary SL, Bassett BJ, Cook CJ, Gorman GS, Coward LU. Pharmacokinetic and Histopathologic Study of an Extended-Release, Injectable formulation of Buprenorphine in Sprague-Dawley Rats. *J AM Assoc Lab Anim Sci*. Jan 1, 61(1): 81-8; 2022.
5. Fidelis' database.
6. Katzenbach JE, Wittenburg LA, Allweiler SI, Gustafson DL, Johnson MS. Pharmacokinetics of single-dose buprenorphine, butorphanol, and hydromorphone in the domestic ferret (*Mustela putorius furo*). *J Exotic Pet Med* 27:95-102; 2018.
7. Chan G, S C. Nichols MR Kennedy L. Assessment of the safety and efficacy of pre-emptive use of extended-release buprenorphine for mouse laparotomy. *J Am Assoc Lab Anim Sci*. 2022: Jul: 61(4):381-387.

MANUFACTURED FOR

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NDC 86084-100-30. U.S. Patent Nos. 10,555,899; 11,058,629

October 2023

FID-ETH-PI012

WARNING: Due to serious human safety and abuse concerns, read the entire product insert before using this drug, including the complete Boxed Warning.

Packaging

VIAL LABEL



1-833-384-4729
CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
FID-ETH-VR008

Ethiqua XR[®]
(buprenorphine extended-release injectable suspension)
1.3 mg/mL
Opioid Analgesic

For subcutaneous use in mice, rats, and ferrets only.

WARNING: Due to serious human safety and abuse concerns read the entire product insert before using this drug, including the complete Boxed Warning.
Legally Marketed—MIF 900-014.
Extra-label use is prohibited.

SHAKE WELL BEFORE USE.
Once broached, discard vial after 90 days.
Date to be discarded:
Storage: 15°-25°C +/- 2°C
(59°-77°F)

RL-LA000779

CARTON LABEL

DOSAGE AND ADMINISTRATION

For subcutaneous use only. Due to serious human safety concerns, read the entire package insert before using this drug.

Shake vial well prior to use.

Use a 0.5 or 1 mL syringe fitted with a 20- or 23-gauge needle for injections.

TABLE: DOSING FOR ETHIQA XR

Species	Dose mg/Kg Body Weight
Mouse	3.25 mg/Kg
Rat	0.65 mg/Kg
Ferret	0.6 mg/Kg

For example, the dose for a 20-gram mouse would be a single subcutaneous injection of 0.05 mL (3.25 mg/Kg body weight).

Therapeutic drug concentrations are maintained for 72 hours after injection. If needed, a single repeat dose may be administered 72 hours after the initial dose.

Each mL contains approximately 1.3 mg buprenorphine hydrochloride, cholesterol, benzyl alcohol, and glyceryl tristearate suspended in MCT oil.

Before using this drug, read package insert for full prescribing information.

INDICATIONS

For the control of post-procedural pain in mice, rats, and ferrets.

HUMAN SAFETY WARNINGS

Not for use in humans. Keep this and all medications out of reach of children and pets.

Human User Safety While Handling

Ethiqua XR in the Hospital:

Ethiqua 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 Ethiqua XR.

Wear protective clothing when administering Ethiqua XR.

STORAGE

Store vial at temperatures between 15° and 25°C +/- 2°C (59° and 77°F). Once broached, the multi-dose vial should be discarded after 90 days. Do not store outside original vial or storage conditions.



Ethiqua XR[®]
(buprenorphine extended-release injectable suspension)
1.3 mg/mL
Opioid Analgesic

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WARNING: Due to serious human safety and abuse concerns, read the entire product insert before using this drug, including the complete Boxed Warning.

NDC 86084-100-30

Vial contains 3 mL

CONTACT INFORMATION

Contact Fidelis Animal Health at 833-384-4729 or www.ethiquaxr.com. To report suspected adverse drug experiences; contact Fidelis Animal Health at 833-384-4729.

For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/reportanimalae>.

MANUFACTURED FOR

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September 2023
FID-ETH-CR011

Fidelis
ANIMAL HEALTH

Vial contains 3 mL

RL-CT001000

FID-ETH-CR011

ETHIQA XR

buprenorphine hydrochloride injection, suspension, extended release

Product Information

Product Type	PRESCRIPTION ANIMAL DRUG	Item Code (Source)	NDC:86084-100
Route of Administration	SUBCUTANEOUS	DEA Schedule	CIII

Active Ingredient/Active Moiety

Ingredient Name		Basis of Strength	Strength	
BUPRENORPHINE HYDROCHLORIDE (UNII: 56W8MW3EN1) (BUPRENORPHINE - UNII:40D3SCR4GZ)		BUPRENORPHINE	1.3 mg in 1 mL	
Inactive Ingredients				
Ingredient Name		Strength		
CHOLESTEROL (UNII: 97C5T2UQ7J)				
BENZYL ALCOHOL (UNII: LKG8494WBH)				
GLYCERYL TRISTEARATE (UNII: P6OCJ2551R)				
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:86084-100-30	1 in 1 CARTON		
1		3 mL in 1 VIAL, MULTI-DOSE		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
legally marketed unapproved new animal drugs for minor species		MIF900014	01/01/2020	

Labeler - Fidelis Animal Health, Inc. (080839562)

Revised: 10/2023

Fidelis Animal Health, Inc.