

Ethiqa XR[™]

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

Opioid Analgesic

For subcutaneous use in mice and rats only.

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.

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*.

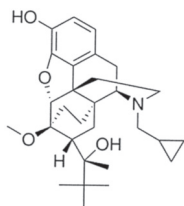
***Ethiqa XR* has additive CNS depressant effects when used with alcohol, other opioids, or illicit drugs that cause central nervous system depression.**

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.

DESCRIPTION

Ethiqa XR is an injectable suspension of extended-release buprenorphine. Buprenorphine hydrochloride, an opioid analgesic, is the active ingredient in *Ethiqa 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} *Ethiqa XR* has a slightly yellow to white opaque appearance. Each mL contains approximately 1.3 mg buprenorphine hydrochloride. The sterile product contains cholesterol, glyceryl tristearate, and buprenorphine hydrochloride suspended in MCT oil.

Buprenorphine Formula C₂₉H₄₁NO₄



INDICATIONS

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

MOUSE DOSAGE AND ADMINISTRATION

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

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.

The dosage of *Ethiqa XR* is a single subcutaneous injection of 0.05 mL per 20 gram mouse (3.25 mg/kg body weight). Therapeutic drug concentrations are maintained for 72 hours after the initial dose. If needed, a single repeat dose may be administered 72 hours after the initial dose.

Secure the mouse in a scruff-of-the-neck hold. Insert the needle into the dorsal subcutaneous space created by the scruff hold. Inject the entire dose into the dorsal subcutaneous space. An oily sheen may be observed in the dorsal fur of the mouse after injection due to leakage of the 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 mouse can be returned to its cage immediately after receiving *Ethiqa XR*.

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

Once the vial is broached, *Ethiqa XR* can be stored at 15° to 25°C (59° – 77°F) or refrigerated for 28 days. DO NOT FREEZE.

RAT DOSAGE AND ADMINISTRATION

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

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.

The dosage of *Ethiqa XR* is a single subcutaneous injection of 0.1 mL per 200 gram rat (0.65 mg/kg body weight). Therapeutic drug concentrations are maintained for 72 hours after the initial dose. If needed, a single repeat dose may be administered 72 hours after the initial dose.

Secure the rat in a passive restraint tube or by holding with a heavy glove with one person to secure the rat and a second person to administer the drug. Insert the needle in the dorsal subcutaneous space. Inject the entire dose into the dorsal subcutaneous space. An oily sheen may be observed in the dorsal fur after injection due to leakage of the 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 rat can be returned to its cage immediately after receiving *Ethiqa XR*. **See CONTRAINDICATIONS and Rat PRECAUTIONS for additional information on bedding.**

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

Once the vial is broached, *Ethiqa XR* can be stored at 15° to 25°C (59° – 77°F) or refrigerated for 28 days. DO NOT FREEZE.

CONTRAINDICATIONS

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

Do not use on mice or rats with pre-existing respiratory deficiencies.

Do not keep rats on wood chip-type bedding after administration of *Ethiqa XR*.

HUMAN SAFETY WARNINGS

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

Human User Safety while handling *Ethiqa XR*:

Two trained staff for administration: *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*.

Protective covering: To prevent direct contact of *Ethiqa XR* with human skin or mucous membranes when handling the suspension, protective clothing is recommended.

Mucous membrane or eye contact during administration: Direct contact of *Ethiqa XR* with the eyes, oral or other mucous membranes of humans 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.

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. *Ethiqa XR* can be abused and is subject to misuse, abuse, addiction, and criminal diversion. *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.

Abuse: Abuse of *Ethiqa XR* poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances including other opioids and benzodiazepines. Buprenorphine has been diverted for non-medical use into illicit channels of distribution. All people handling opioids require careful monitoring for signs of abuse. Drug abuse is the intentional non-therapeutic use of a prescription drug for its rewarding psychological or physiological effects. Abuse of opioids can occur in the absence of true addiction.

Storage and Discard: *Ethiqa XR* is a Class III opioid. Store in a locked, substantially constructed cabinet according to DEA and local controlled substance guidelines. Discard broached vials after 28 days. Any unused or expired vials must be destroyed by a DEA registered reverse distributor; for further information, call 1-833-384-4729.

Physician information: *Ethiqa XR* injectable suspension is 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.

PRECAUTIONS

Mice

The safety of *Ethiqa XR* has not been evaluated in pregnant, lactating, neonatal, or immune-compromised mice. As with other opioids, buprenorphine may cause sedation, decreased blood pressure, decreased heart rate, decreased gastrointestinal mobility, and respiratory depression. Use caution with concomitant administration of *Ethiqa XR* with drugs that cause respiratory depression. The use of paper or soft bedding for up to 3 days following administration of *Ethiqa XR* should be considered.

Normal mice may exhibit an obtunded response to stimuli up to 4 hours after receiving *Ethiqa XR*.

Buprenorphine is excreted in the feces (see Clinical Pharmacology section below). Coprophagy may lead to ingestion of buprenorphine or its metabolites by mice treated with *Ethiqa XR* and untreated cage mates.

Rats

The safety of *Ethiqa XR* has not been evaluated in pregnant, lactating, neonatal, or immune-compromised rats. As with other opioids, buprenorphine may cause sedation, decreased blood pressure, decreased heart rate, decreased gastrointestinal mobility, and respiratory depression. Use caution with concomitant administration of *Ethiqa XR* with drugs that cause respiratory depression.

Rats may exhibit signs of nausea including pica up to 3 days post-treatment. Rats should be maintained on paper or soft bedding to avoid ingestion of wood chip-type bedding after administration of *Ethiqa XR*. **Pica involving wood chip-type bedding can be lethal in rats.**

Buprenorphine is excreted in the feces (see Clinical Pharmacology section below). Coprophagy may lead to ingestion of buprenorphine or its metabolites by rats treated with *Ethiqa XR* and untreated cage mates.

ADVERSE REACTIONS

Mice

No adverse reactions were observed in 20 to 25 gram young adult male and female mice after a single subcutaneous injection of *Ethiqa XR* at a dose 5 times the indicated dose. Laboratory parameters evaluated in the study included hematology and clinical chemistry; histopathology was also performed. In a second study, adult male and female mice received *Ethiqa XR* subcutaneously at 5 times the indicated dose for three doses at four day intervals. A surgical procedure was performed on the study mice prior to receiving each of the three doses of *Ethiqa XR*.

Mortality was seen in two male mice after the third surgical procedure and dose of *Ethiqa XR* (total dose of 49 mg buprenorphine/kg body weight in 8 days).

Weight loss has been observed in mice treated post-procedurally with *Ethiqa XR*.

Rats

Adverse reactions were evaluated in 180 to 200 gram young adult male and female rats after a single injection of *Ethiqa XR*. A surgical procedure was performed on the rats prior to administration of a single dose at the intended dose of 0.65 mg/kg or a single dose of 2, 6 or 10-fold excess dose. Adverse reactions also were evaluated in male and female rats administered 2, 6 and 10 times the intended dose for three doses at four day intervals. A surgical procedure was performed on the rats prior to administration of the first of three doses. Laboratory parameters evaluated in the study included hematology, clinical chemistry, urinalysis, histopathology, and bodyweight.

Signs of nausea were observed at all dose levels 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.

Mortality was seen in 3 of 222 rats treated with *Ethiqa XR* due to technical complications with serial bleeding of the jugular vein.

For technical assistance, or to report an adverse drug reaction, please call Fidelis Pharmaceuticals LLC at 1-833-384-4729.

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

CLINICAL PHARMACOLOGY³

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 *Ethiqa 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 *Ethiqa 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.

HOW SUPPLIED

Ethiqa XR is supplied in a multi-use glass vial containing 3.0 mL of injectable drug suspension.

<i>Ethiqa XR</i>	3 mL vial	NDC 86084-100-30
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U.S. Patent No. 8,461,173

STORAGE INFORMATION

Store between 15° and 25°C (59° – 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 28 days.

REFERENCES

1. Mishra et al., 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., Lab Animal, 41(11): 337-343; 2012.

Manufactured for:

Fidelis Pharmaceuticals LLC
CCIT Incubator
675 US Highway One, Suite B113
North Brunswick, NJ 08902

833-384-4729

www.EthiqaXR.com

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