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.\(^1\) Ethiqa 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

Formula C\(_{29}\)H\(_{41}\)NO\(_4\)

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 clothing: 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

Adverse reactions were evaluated in male and female rats exposed to 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 PHARMACOLOGY

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.\(^2\)

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.

<table>
<thead>
<tr>
<th>Ethiqa XR</th>
<th>3 mL vial</th>
<th>NDC 86084-100-30</th>
</tr>
</thead>
</table>

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


Manufactured for:

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www.EthiqaXR.com

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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.