

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVZIO safely and effectively. See full prescribing information for EVZIO.

EVZIO (naloxone hydrochloride injection) Auto-Injector for intramuscular or subcutaneous use

Initial U.S. Approval: 1971

INDICATIONS AND USAGE

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. (1)
EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present. (1)
EVZIO is not a substitute for emergency medical care. (1)

DOSAGE AND ADMINISTRATION

- EVZIO is for intramuscular or subcutaneous use only. (2.1)
- Seek emergency medical care immediately after use. (2.1)
- Administer EVZIO to adult or pediatric patients into the anterolateral aspect of the thigh, through clothing if necessary. (2.2)
- Additional doses may be administered every 2 to 3 minutes until emergency medical assistance arrives. (2.2)
- In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering the dose. (2.2)
- **If the electronic voice instruction system does not operate properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on the flat surface of its label. (2.1)**

DOSAGE FORMS AND STRENGTHS

Injection: 0.4 mg/0.4 mL naloxone hydrochloride solution in a pre-filled auto-injector. (3)

CONTRAINDICATIONS

Patients known to be hypersensitive to naloxone hydrochloride (4)

WARNINGS AND PRECAUTIONS

- Due to the duration of action, keep the patient under continued surveillance and repeated doses of naloxone should be administered, as necessary, while awaiting emergency medical assistance. (5.1)
- Other supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance. (5.1)
- Reversal of respiratory depression by partial agonists or mixed agonists/antagonists such as buprenorphine and pentazocine, may be incomplete. (5.2)
- Use in patients who are opioid dependent may precipitate acute abstinence syndrome. (5.3)
- Patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects should be monitored in an appropriate healthcare setting (5.3)
- In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated. (5.3)

ADVERSE REACTIONS

The following adverse reactions have been identified during use of naloxone hydrochloride in the post-operative setting: Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia and have caused agitation. (6)

Abrupt reversal of opioid effects in persons who were physically dependent on opioids has precipitated signs and symptoms of opioid withdrawal including: body aches, fever, sweating, runny nose, sneezing, piloerection, yawning, weakness, shivering or trembling, nervousness, restlessness or irritability, diarrhea, nausea or vomiting, abdominal cramps, increased blood pressure, tachycardia. In the neonate, opioid withdrawal signs and symptoms also included: convulsions, excessive crying, hyperactive reflexes. (6)

To report SUSPECTED ADVERSE REACTIONS, contact kaleo, Inc. at 1-855-773-8946 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 4/2014

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EVZIO is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present.

EVZIO is not a substitute for emergency medical care.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- EVZIO is for intramuscular and subcutaneous use only.
- Because treatment of suspected opioid overdose must be performed by someone other than the patient, instruct the prescription recipient to inform those around them about the presence of EVZIO and the *Instructions for Use*.
- Seek emergency medical care immediately after use. Since the duration of action of most opioids exceeds that of naloxone hydrochloride, and the suspected opioid overdose may occur outside of supervised medical settings, seek immediate emergency medical assistance, keep the patient under continued surveillance, and administer repeated doses of EVZIO as necessary. Always seek emergency medical assistance in the event of a suspected, potentially life-threatening opioid emergency after administration of the first dose of EVZIO.
- Additional doses of EVZIO may be required until emergency medical assistance becomes available.
- Do not attempt to reuse EVZIO. Each EVZIO contains a single dose of naloxone.
- Visually inspect EVZIO through the viewing window for particulate matter and discoloration prior to administration. Do not administer unless the solution is clear and the glass container is undamaged.

The *Instructions for Use* should be read by the patient or caregiver at the time they receive a prescription for EVZIO. Provide the following instructions to the patient or caregiver:

- EVZIO must be administered according to the printed instructions on the device label or the electronic voice instructions (EVZIO contains a speaker that provides voice instructions to guide the user through each step of the injection). **If the EVZIO electronic voice instruction system does not operate properly, EVZIO will still deliver the intended dose of naloxone hydrochloride when used according to the printed instructions on its label.**
- Once the red safety guard is removed, EVZIO must be used immediately or disposed of properly. Do not attempt to replace the red safety guard once it is removed.

Upon actuation, EVZIO automatically inserts the needle intramuscularly or subcutaneously, delivers 0.4 mg naloxone hydrochloride injection, and retracts the needle fully into its housing. Post injection,

the black base locks in place, a red indicator appears in the viewing window, and electronic visual and audible instructions signal that EVZIO has delivered the intended dose of naloxone hydrochloride and instructs the user to seek emergency medical attention.

2.2 Dosing Information

Administer the initial dose of EVZIO to adult or pediatric patients intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary, and seek emergency medical assistance. Administer EVZIO as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death. The requirement for repeat doses of EVZIO depends upon the amount, type, and route of administration of the opioid being antagonized.

If the desired response is not obtained after 2 or 3 minutes, another EVZIO dose may be administered. If there is still no response and additional doses are available, additional EVZIO doses may be administered every 2 to 3 minutes until emergency medical assistance arrives. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete or require higher doses of naloxone.

Dosing in Adults and Pediatric Patients over Age One

Instruct patients or their caregivers to administer EVZIO according to the *Instructions for Use*, intramuscularly or subcutaneously.

Dosing in Pediatric Patients under Age One

In pediatric patients under the age of one, the caregiver should pinch the thigh muscle while administering EVZIO.

3 DOSAGE FORMS AND STRENGTHS

Injection: 0.4 mg/0.4 mL naloxone hydrochloride solution in a pre-filled auto-injector. Each EVZIO delivers 0.4 mg naloxone hydrochloride injection (0.4 mL).

4 CONTRAINDICATIONS

EVZIO is contraindicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the other ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Duration of Effect

The duration of action of most opioids is likely to exceed that of EVZIO resulting in a return of respiratory and/or central nervous system depression after an initial improvement in symptoms. Therefore, it is necessary to seek immediate emergency medical assistance after delivering the first dose of EVZIO, keep the patient under continued surveillance, and repeat doses of EVZIO as

necessary. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.

5.2 Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonist/antagonists such as buprenorphine and pentazocine, may be incomplete. Large doses of naloxone hydrochloride are required to antagonize buprenorphine because the latter has a long duration of action due to its slow rate of binding and subsequent slow dissociation from the opioid receptor. Buprenorphine antagonism is characterized by a gradual onset of the reversal effects and a decreased duration of action of the normally prolonged respiratory depression.

5.3 Precipitation of Severe Opioid Withdrawal

The use of EVZIO in patients who are opioid dependent may precipitate an acute abstinence syndrome characterized by the following signs and symptoms: body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure. In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated and may include the following signs and symptoms: convulsions, excessive crying, and hyperactive reflexes.

Abrupt postoperative reversal of opioid depression after using naloxone hydrochloride may result in nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have occurred in patients most of whom had pre-existing cardiovascular disorders or received other drugs which may have similar adverse cardiovascular effects. Although a direct cause and effect relationship has not been established, after use of naloxone hydrochloride, patients with pre-existing cardiac disease or patients who have received medications with potential adverse cardiovascular effects should be monitored for hypotension, ventricular tachycardia or fibrillation, and pulmonary edema in an appropriate healthcare setting. It has been suggested that the pathogenesis of pulmonary edema associated with the use of naloxone hydrochloride is similar to neurogenic pulmonary edema, i.e., a centrally mediated massive catecholamine response leading to a dramatic shift of blood volume into the pulmonary vascular bed resulting in increased hydrostatic pressures.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Duration of effect [*see Warnings and Precautions (5.1)*]
- Precipitation of Severe Opioid Withdrawal [*see Warnings and Precautions (5.3)*]

The following adverse reactions have been identified during post-approval use of naloxone hydrochloride in the post-operative setting. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a

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