

Zurnai™ (nalmefene injection)

1.5 mg/0.5 mL Auto-Injector

Discharge with the additional support they may need

**CHOOSE ZURNAI—
THE FIRST AND
ONLY NALMEFENE
AUTO-INJECTOR¹**



Actor portrayals.

INDICATIONS AND USAGE

ZURNAI is indicated for the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression.

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

ZURNAI is not a substitute for emergency medical care.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ZURNAI is contraindicated in patients known to be hypersensitive to nalmefene hydrochloride or to any other ingredients in the product.

Please see additional IMPORTANT SAFETY INFORMATION throughout and Full Prescribing Information.

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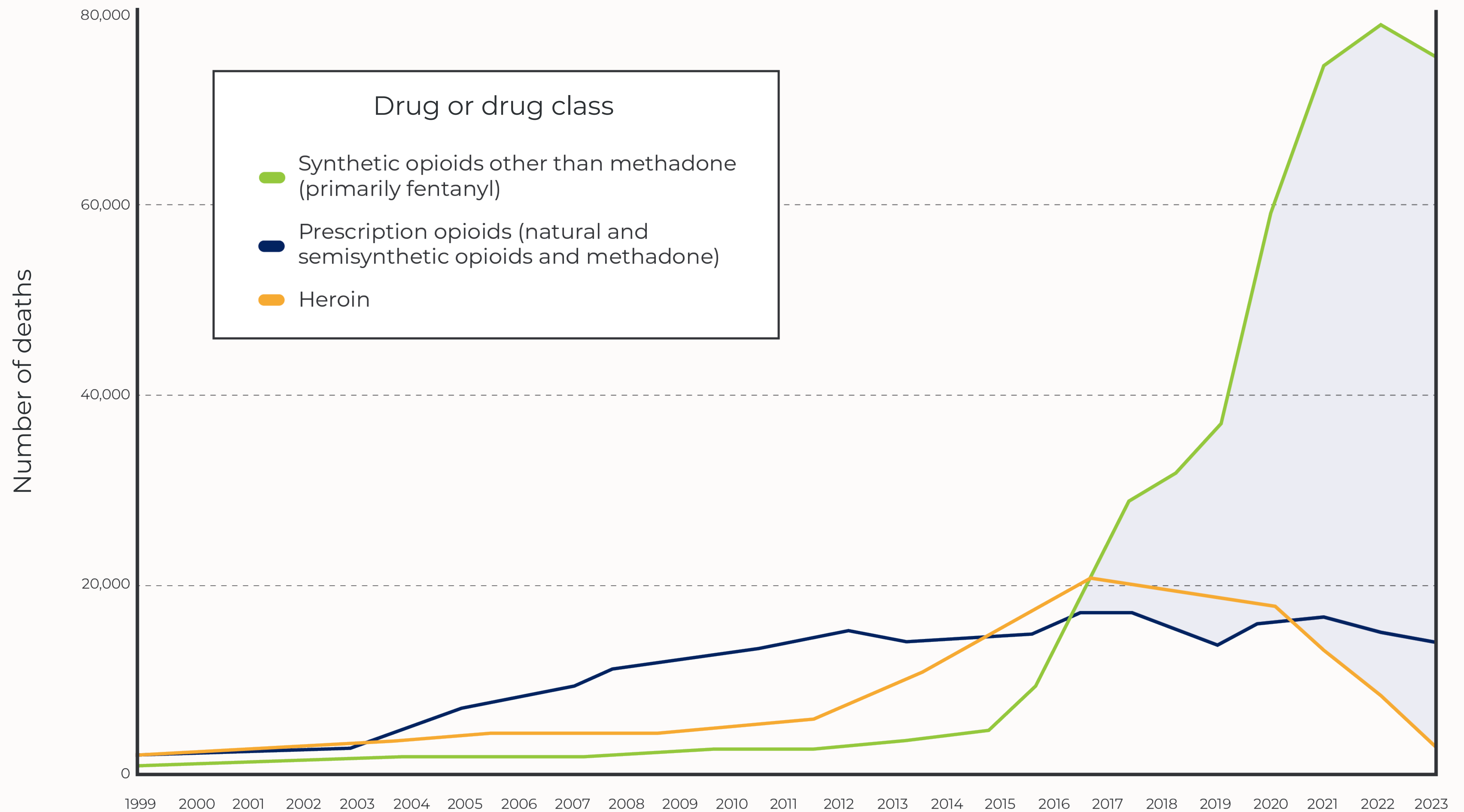
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National opioid-involved overdose deaths 1999–2023^{2,3*}



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision.

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999–2023. CDC WONDER Online Database, 03/25.



90% of all opioid overdose deaths in 2023 involved synthetic opioids³

The most recent national data available show a significant decline in overdose deaths—the fewest overdose deaths in any 12-month period since June 2020.³

However, fentanyl and other synthetics, excluding methadone, continue to be the main driver of drug overdose deaths, with a more than 7.5-fold increase from 2015–2023.³

Actor portrayals.

Did you know?

Fentanyl was involved in at least **75% of adolescent** opioid overdose deaths in 2022.⁴





Actor portrayals.

Accidental
opioid exposure
is a substantial risk^{4,5}

5 out of every 10 counterfeit
prescription pills seized by the US
Drug Enforcement Administration (DEA)
contain a lethal dose of fentanyl⁶

Did you know?

In 2024, DEA seizures represented more than **380 million deadly doses** of fentanyl.⁷



After the overdose: Health risks continue post-discharge

The rate of fatal opioid overdoses, while alarming, is only part of the picture. By some estimates, for every fatal overdose, there are as many as **10 non-fatal overdoses treated in an emergency department (ED)**.⁸ These patients face significant health challenges after discharge.⁹

20% of patients experienced a **recurrent overdose** within 1 year¹⁰

24% of repeat overdoses occurred **within 30 days** of the initial event¹¹

4% of patients treated in an ED for opioid overdose **had a fatal overdose** within 1 year of the initial event¹⁰



Opioid reversal agents such as naloxone continue to make an impact. Still, more tools are needed¹²

Fentanyl-related non-fatal overdoses have declined from their peak, but are still more than twice as high as in the fourth quarter of 2020, based on ED visits.¹³

The National Institutes of Health (NIH) supports development of stronger, longer-acting formulations of opioid antagonists to counteract high-potency synthetic opioids.¹²

| Half-lives can vary across opioids* | | |
|-------------------------------------|------------------------------|--------------------------|
| Opioids | Drug | Plasma half-life (hours) |
| Natural | Morphine ¹⁴ | 3 to 4 |
| | Heroin ¹⁵ | 0.5 |
| Semisynthetic | Hydromorphone ¹⁴ | 2 to 3 |
| | Oxycodone ¹⁶ | 3 to 5 |
| | Fentanyl ^{14,17-19} | 2 to 8 |
| Synthetic | Carfentanil ²⁰ | 5.7 |
| | Tramadol ²¹ | 6.3 |
| | Methadone ¹⁴ | >12 |

*This is not an exhaustive list of all opioids. Half-lives reported are approximations. Patient- and drug-specific variables may impact the actual half-life of a drug. Pharmacokinetic data may not necessarily correlate with clinical effects.

Summary

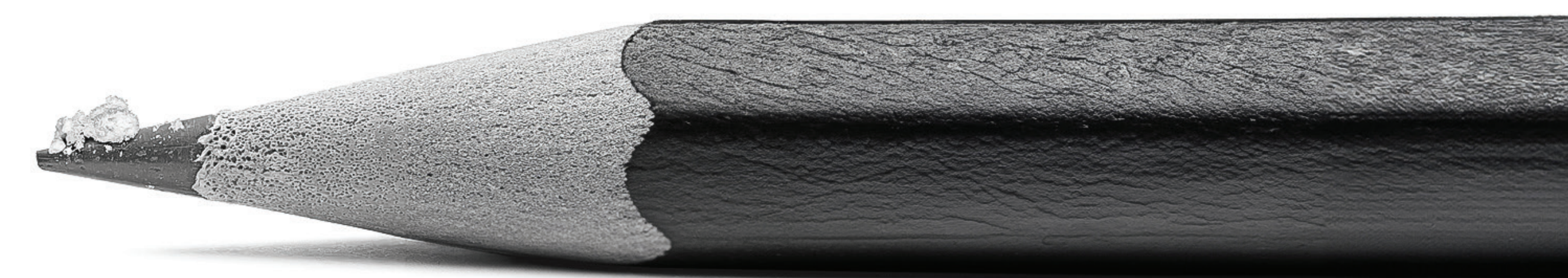
Synthetic opioids continue to drive overdose deaths³

- Synthetic opioids such as fentanyl cause the majority of drug overdose deaths in the US³
- Accidental opioid exposure via counterfeit pills and adulterated street drugs is a serious threat^{4,5}
- After an opioid overdose, patients are at substantial risk for a recurrent overdose, often within one year of the initial event¹⁰
- The National Institutes of Health supports development of stronger and longer-lasting opioid antagonists¹²

Actor portrayals.

Did you know?

2 mg of fentanyl, a potentially lethal dose, can fit on the tip of a pencil.⁷



Artist rendering.



Duration of action as long as most opioids¹

A LONG-ACTING OPTION FOR OPIOID OVERDOSE REVERSAL¹

While the duration of action of nalmeferene is as long as most opioids, a recurrence of respiratory depression is possible, even after an apparently adequate initial response to ZURNAL treatment.

Therefore, it is necessary to seek emergency medical assistance immediately after administration of the first dose of ZURNAL and to keep the patient under continued surveillance. A second dose may be necessary if there is recurrence of symptoms of opioid overdose.

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



Actor portrayal.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Risk of Recurrent Respiratory and Central Nervous System Depression

A recurrence of respiratory depression is possible, therefore, keep the patient under continued surveillance and administer repeat doses of ZURNAL if necessary, using a new auto-injector with each dose while awaiting emergency medical assistance.

Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonists/antagonists such as buprenorphine and pentazocine, may be incomplete. Repeat doses of ZURNAL may be required.

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>80% OF OPIOID RECEPTORS BLOCKED WITHIN 5 MINUTES¹

Following a 1 mg parenteral dose, nalmefene was rapidly distributed. In a pharmacology study of brain receptor occupancy, a 1 mg dose of nalmefene blocked more than 80% of brain opioid receptors within 5 minutes after administration.¹

ZURNAL WORKS FAST¹

Following ZURNAL administration, the time to onset of effect, ie, the onset of reversal of respiratory depression, was observed between 2.5 to 5 minutes, based on a pharmacodynamic study.¹

9-HOUR MEAN TERMINAL ELIMINATION HALF-LIFE¹

ZURNAL mean terminal elimination half-life of 9.07 hours is based on a pharmacokinetic study of 24 healthy adult subjects given a single dose of intramuscular (IM) ZURNAL.¹

DESIGNED TO BE USED BY ANYONE IN THE COMMUNITY

Instruct patients and their family members or caregivers to become familiar with all the information contained in the carton as soon as they receive ZURNAL and to read the Instructions for Use that come with ZURNAL.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Precipitation of Severe Opioid Withdrawal

The use of ZURNAL in patients who are opioid dependent may precipitate opioid withdrawal.

Abrupt postoperative reversal of opioid depression may result in adverse cardiovascular (CV) effects. These events have primarily occurred in patients who had preexisting CV disorders or received other drugs that may have similar adverse CV effects. Monitor these patients closely in an appropriate healthcare setting after use of ZURNAL.

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Evaluated using an experimental model¹

PHARMACODYNAMIC STUDY ASSESSED THE ABILITY OF ZURNAI TO REVERSE RESPIRATORY DEPRESSION¹

An experimental clinical opioid-induced respiratory depression (OIRD) model assessed pharmacodynamic effects of Zurnai, specifically changes in minute ventilation (MV) during administration of a 3-step intravenous fentanyl infusion.

Participants: 24 healthy adult subjects who were opioid-experienced and non-opioid dependent.

Actor portrayals.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Precipitation of Severe Opioid Withdrawal (cont)

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. Monitor the patient for the development of the signs and symptoms of opioid withdrawal.

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NAL1004 study design¹

STEP 1

Fentanyl was infused until MV nadir* (functional OIRD) was achieved

STEP 2

Following attainment of MV nadir, fentanyl infusion rate was decreased to maintain the fentanyl concentrations

ZURNAI was administered at 10 minutes following MV nadir

STEP 3

10 minutes following ZURNAI administration, fentanyl infusion rate was further decreased to maintain constant fentanyl concentrations for remaining duration of reversal session

* MV nadir was defined as a 50% reduction in MV from baseline or the MV reduction achieved following the maximum permitted fentanyl titration.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Risk of Opioid Overdose from Attempts to Overcome the Blockade

Attempts to overcome opioid withdrawal symptoms caused by opioid antagonists with high or repeated doses of exogenous opioids may lead to opioid intoxication and death.

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Pharmacodynamic study key findings¹

ZURNAL WORKS FAST¹

This study was conducted in an experimental setting where fentanyl was infused over an extended period and titrated to maintain consistent plasma concentrations. As such, the clinical implications of these findings for real-world overdose situations are unknown.



Following ZURNAL administration, the time to **onset of reversal** of respiratory depression was observed between 2.5 to 5 minutes

At 5 minutes, mean change in minute ventilation (MV) from nadir* was 4.42 L/min



Full recovery of respiratory drive was noted between 5 and 15 minutes after ZURNAL administration

*MV nadir was defined as a 50% reduction in MV from baseline or the MV reduction achieved following the maximum permitted fentanyl titration.

IMPORTANT SAFETY INFORMATION (cont)

ADVERSE REACTIONS

Most common adverse reactions (> 5%) are feeling hot, nausea, headache, dizziness, chills, vomiting, allodynia, palpitations, tinnitus, ear discomfort, feeling abnormal, burning sensation, hot flush, and irritability.

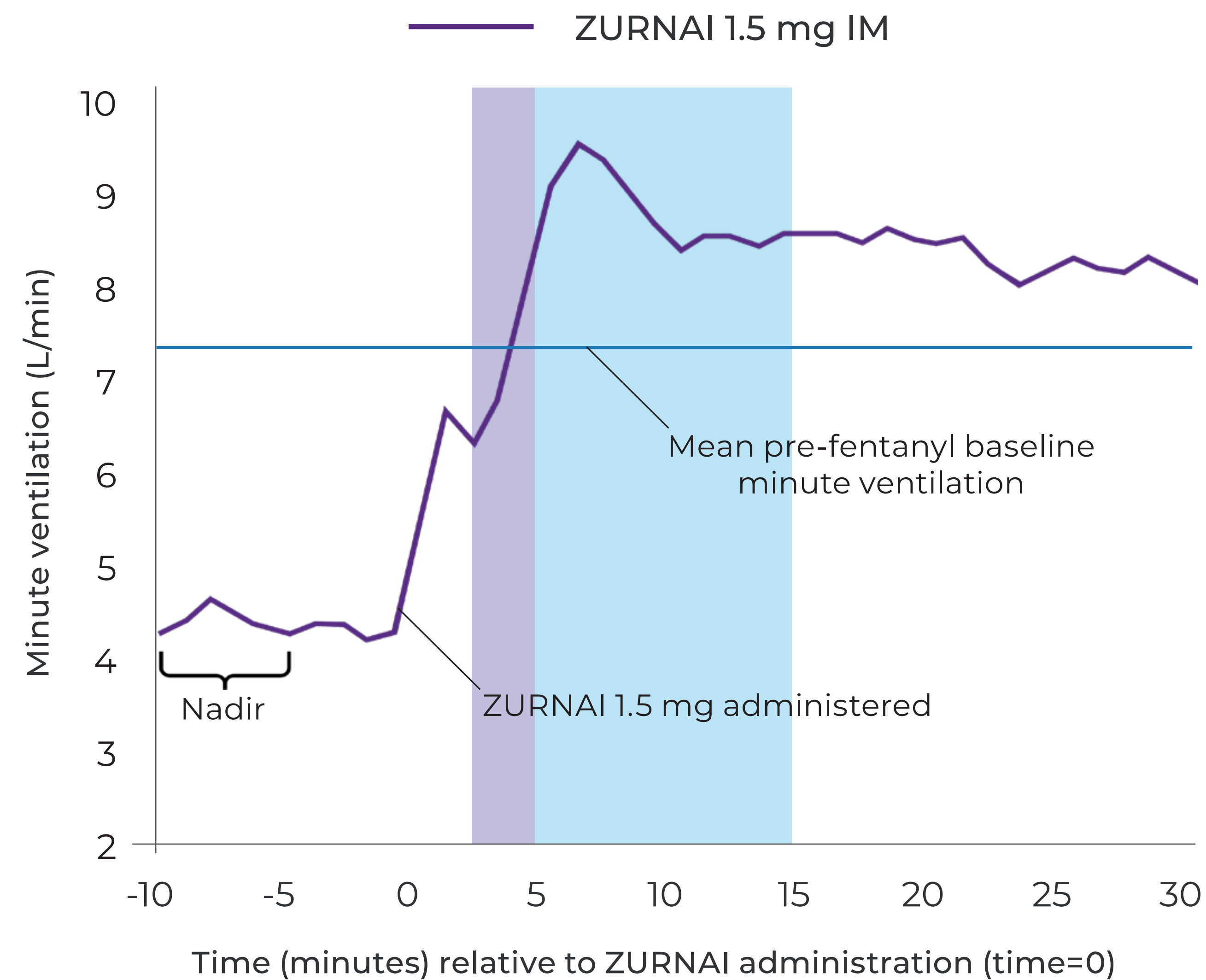
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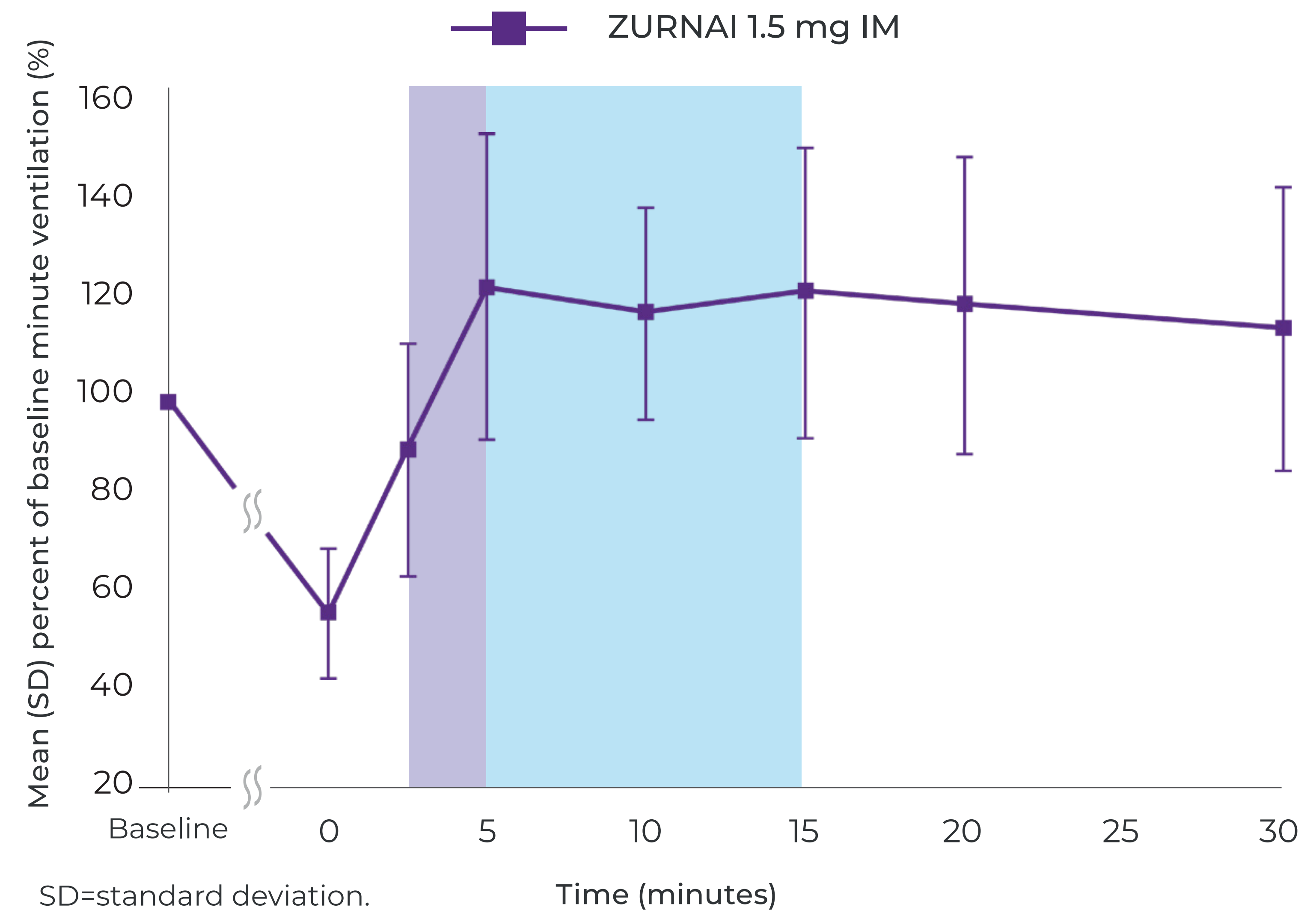


This study was conducted in an experimental setting where fentanyl was infused over an extended period and titrated to maintain consistent plasma concentrations. As such, the clinical implications of these findings for real-world overdose situations are unknown.¹

Reversal of fentanyl-induced respiratory depression in adult healthy volunteers treated with ZURNAI¹



Percent recovery of respiratory drive after fentanyl infusion in minute ventilation (mean SD) in adult healthy volunteers with ZURNAI 1.5 mg¹



IMPORTANT SAFETY INFORMATION (cont)

USE IN SPECIFIC POPULATIONS

Pregnancy

An opioid overdose is a medical emergency and can be fatal for the pregnant woman and fetus if left untreated. Treatment with ZURNAI for opioid overdose should not be withheld because of potential concerns regarding the effects of ZURNAI in the fetus.

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Pharmacokinetic study key findings¹

ZURNAI HAS A LONG HALF-LIFE¹

PK Study NAL1005¹

To determine the relative bioavailability of ZURNAI, one dose was administered intramuscularly in 24 healthy adult subjects. A 1.0 mg dose of nalmeferene administered as an IM injection was used as a comparator.

While the duration of action of nalmeferene is as long as most opioids,* a recurrence of respiratory depression is possible, even after an apparently adequate initial response to ZURNAI treatment.

Therefore, it is necessary to seek emergency medical assistance immediately after administration of the first dose of ZURNAI and to keep the patient under continued surveillance. A second dose may be necessary if there is recurrence of symptoms of opioid overdose.

*The half-life of fentanyl used as anesthesia is approximately 7.5 hours; the half-life of illicit fentanyl has not been characterized.¹⁹

Actor portrayals.

IMPORTANT SAFETY INFORMATION (cont)

USE IN SPECIFIC POPULATIONS (cont)

Pediatric Use

The safety and effectiveness of ZURNAI for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, have not been established in pediatric patients younger than 12 years of age.

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IN THE PK STUDY NAL1005, THE MEAN HALF-LIFE OF ZURNAI WAS 9.07 HOURS¹

Pharmacokinetic studies are conducted in healthy subjects; as such, the clinical implications of these findings for real-world overdose situations are unknown.

Key pharmacokinetic (PK) parameters in healthy volunteers (n=24)¹

| Drug | C _{max} (ng/mL)* | T _{max} (hours) [†] | Half-life (hours) [‡] |
|---------------------|---------------------------|---------------------------------------|--------------------------------|
| ZURNAI IM 1.5 mg | 7.37 (47.5) | 0.25 (0.083-1.00) | 9.07 (26.6) |
| Nalmefene IM 1.0 mg | 2.39 (32.6) | 0.50 (0.083-2.00) | 7.74 (24.3) |
| Nalmefene IV 1.0 mg | 6.94 (55.7) | 0.083 (0.083-0.25) | 9.12 (16.5) |

C_{max} = maximum concentration; IV=intravenous; T_{max} = time to maximum concentration.

*Presented as geometric mean (coefficient of variation percentage).

[†]Presented as median (range).

[‡]Presented as arithmetic mean (coefficient of variation percentage).

IMPORTANT SAFETY INFORMATION (cont)

USE IN SPECIFIC POPULATIONS (cont)

Geriatric Use

Clinical studies of nalmefene hydrochloride injection did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Please see additional IMPORTANT SAFETY INFORMATION throughout and Full Prescribing Information.

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CLINICALLY DEMONSTRATED SAFETY PROFILE¹

The safety of ZURNAL is supported by a pharmacokinetic study of healthy adults under normal conditions, and by a pharmacodynamic study evaluating the effects of ZURNAL under steady-state opioid infusion.

ZURNAL: Important considerations

- ZURNAL is not a substitute for emergency care¹
- Use ZURNAL with extreme caution in patients with known physical dependence on opioids, as acute withdrawal symptoms may occur¹
- Any attempt to overcome receptor blockade from opioid antagonists such as ZURNAL with large doses of opioids may lead to opioid intoxication and death¹
- Reversal of respiratory depression caused by partial agonists or mixed agonist/antagonists, such as buprenorphine and pentazocine, may be incomplete and may require repeated administration of ZURNAL using a new auto-injector¹

INDICATIONS AND USAGE

ZURNAL is indicated for the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression.

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**Relative frequencies of most common adverse reactions that occurred
in greater than 5% of subjects in Study NAL1004 and Study NAL1005¹**

| System organ class Adverse event | Pooled NAL1004 and NAL1005 N=44 n (%) | System organ class Adverse event | Pooled NAL1004 and NAL1005 N=44 n (%) |
|--|---|--|---|
| Any adverse reaction | 28 (63.6) | Cardiac disorders Palpitations | 4 (9.1) |
| Nervous system disorders Dizziness Headache Allodynia Burning sensation | 7 (15.9) 8 (18.2) 5 (11.4) 3 (6.8) | General disorders and administration-site conditions Feeling hot Chills Feeling abnormal | 11 (25.0) 6 (13.6) 3 (6.8) |
| Gastrointestinal disorders Nausea Vomiting | 8 (18.2) 5 (11.4) | Vascular disorders Hot flush | 3 (6.8) |
| Ear and labyrinth Tinnitus Ear discomfort | 4 (9.1) 3 (6.8) | Psychiatric disorders Irritability | 3 (6.8) |

It is necessary to seek emergency medical assistance immediately after administration of the first dose of ZURNAL and to keep the patient under continued surveillance.¹

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ZURNAL is contraindicated in patients known to be hypersensitive to nalmeferene hydrochloride or to any other ingredients in the product.

Please see additional IMPORTANT SAFETY INFORMATION throughout and Full Prescribing Information.

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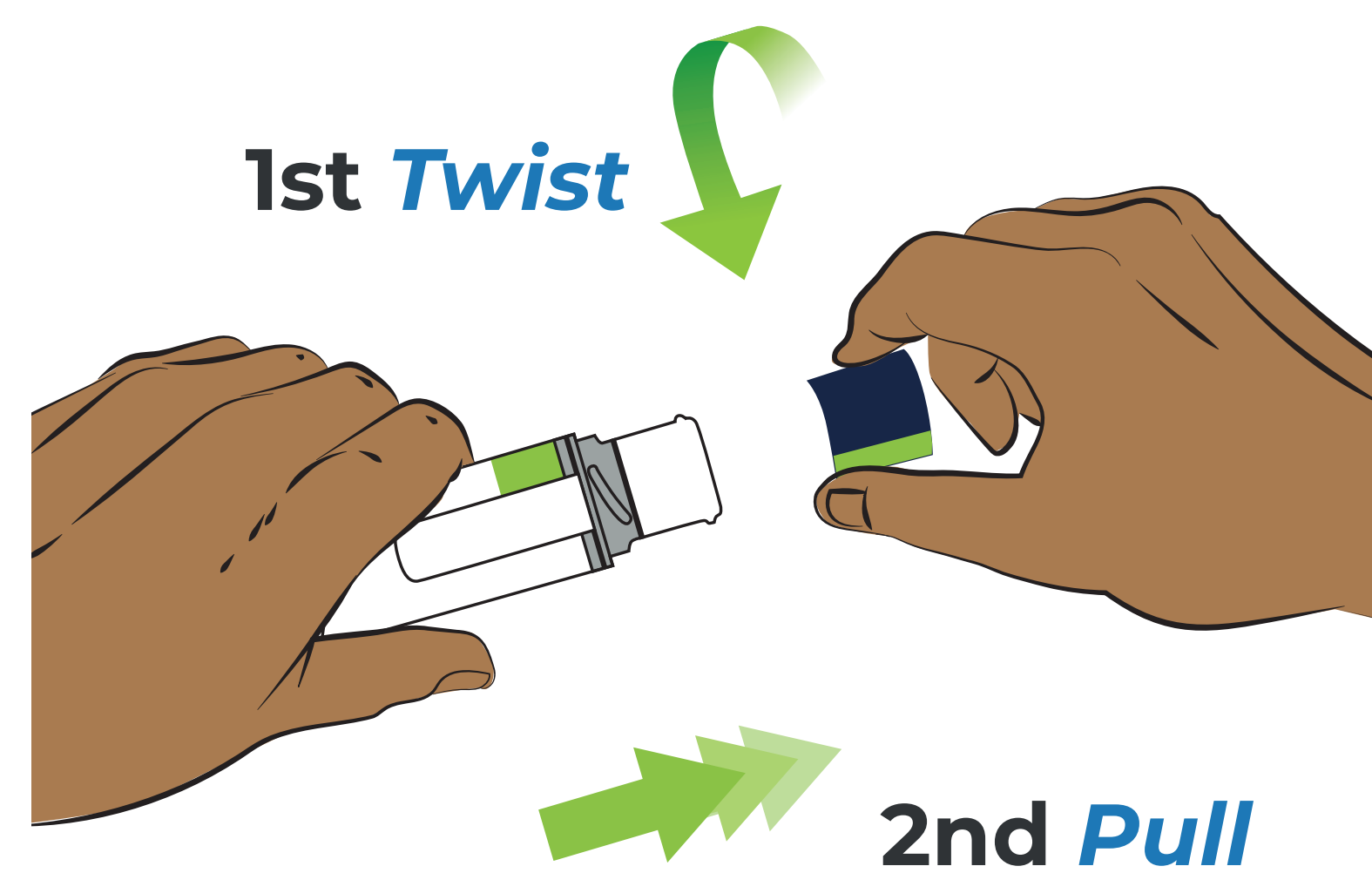
Designed to be used by anyone in the community—
from first responders to family members

HOW TO USE ZURNAI²²

Instruct patients and their family members or caregivers to become familiar with all information contained in the carton as soon as they receive ZURNAI.

Refer to **Instructions for Use** for additional administration details.

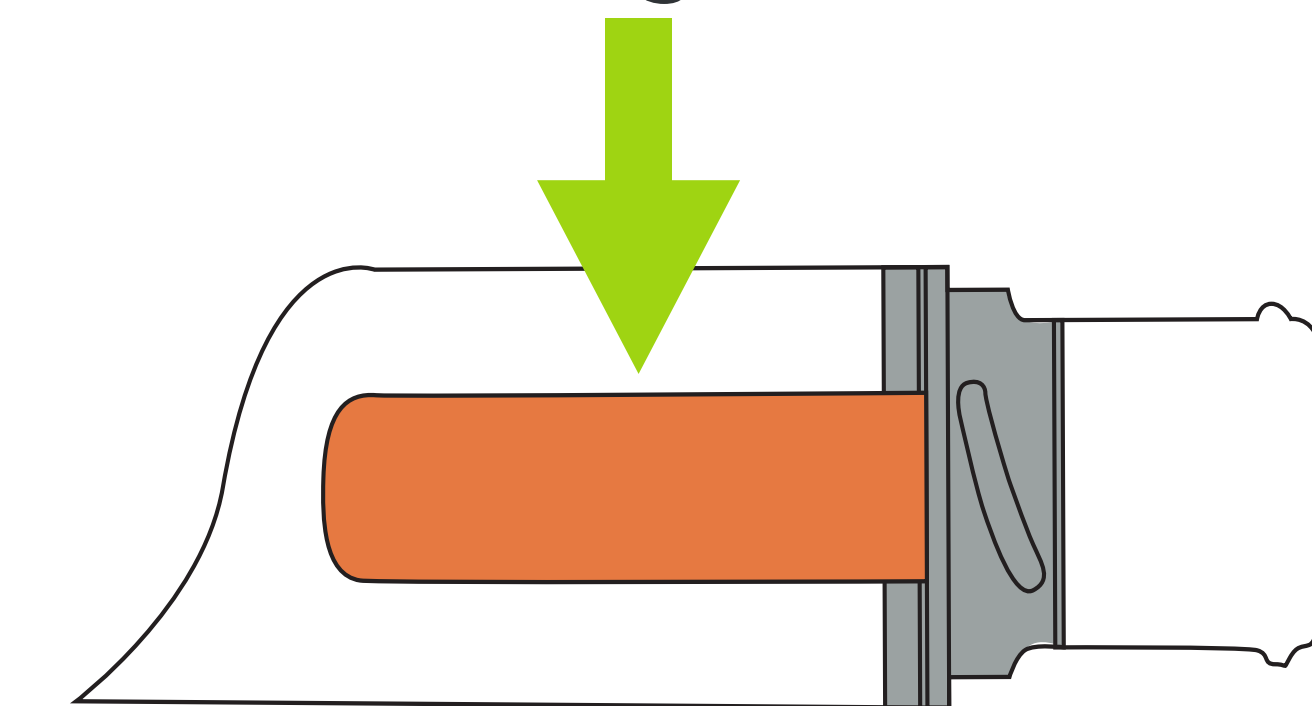
- 1** Twist blue cap and then pull



- 2** Push needle end into outer thigh until click—then hold



- 3** Injection complete when window is orange



ZURNAI can be administered through clothing.¹

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Risk of Recurrent Respiratory and Central Nervous System Depression

A recurrence of respiratory depression is possible, therefore, keep the patient under continued surveillance and administer repeat doses of ZURNAI if necessary, using a new auto-injector with each dose while awaiting emergency medical assistance.

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WHAT TO DO AFTER ADMINISTERING ZURNAI²²

- 4** Call 911 and watch the person. **Stay until the ambulance arrives**



If the person does not wake up within 2–5 minutes after injection, repeat steps 1–3 with a new ZURNAI Auto-Injector.¹



Always seek emergency medical assistance after administration of the first dose of ZURNAI in the event of a suspected, potentially life-threatening opioid emergency.¹

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Risk of Limited Efficacy with Partial Agonists or Mixed Agonist/Antagonists

Reversal of respiratory depression by partial agonists or mixed agonists/antagonists such as buprenorphine and pentazocine, may be incomplete. Repeat doses of ZURNAI may be required.

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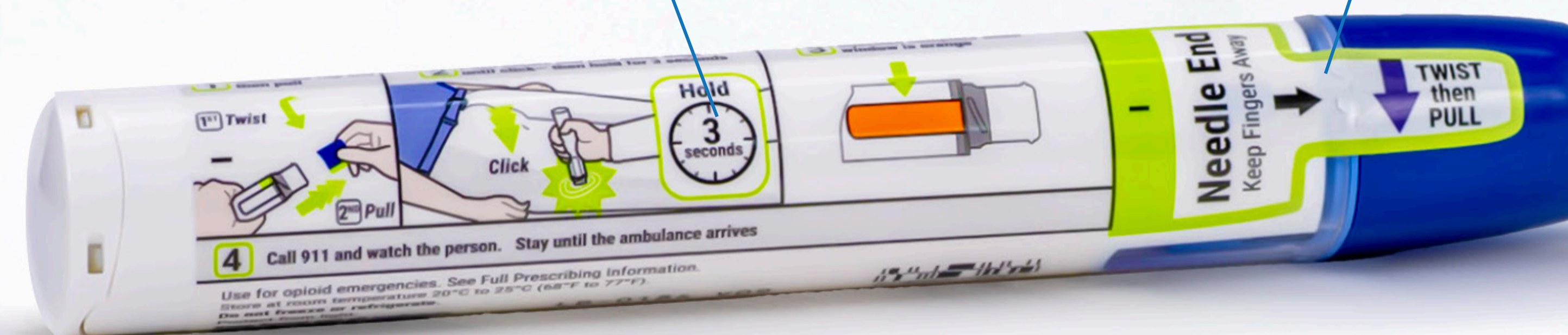
Storage and handling

Advise patients and caregivers of important storage and handling information^{1,22}:

- **Do not freeze or refrigerate**
- Store in a clean, dry place
- Protect from light
- Discard in sharps container after use
- Store ZURNAI at controlled room temperature (68°F to 77°F)
- Periodically check the expiration date and replace expired product as needed
- Cannot be reused

Administration instructions

Safety seal



Needle guard



Not actual size.

Viewing window

Safety cap

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Precipitation of Severe Opioid Withdrawal

The use of ZURNAI in patients who are opioid dependent may precipitate opioid withdrawal.

Abrupt postoperative reversal of opioid depression may result in adverse cardiovascular (CV) effects. These events have primarily occurred in patients who had preexisting CV disorders or received other drugs that may have similar adverse CV effects. Monitor these patients closely in an appropriate healthcare setting after use of ZURNAI.

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How to order ZURNAI

PUT AN IMPORTANT TOOL IN THE HANDS OF YOUR COMMUNITY

Order through Knoa Pharma
Authorized Distributors

NDC 59011-962-01

More information available at:

- ZURNAI.com
- 1-800-877-5666



Actor portrayal.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Precipitation of Severe Opioid Withdrawal (cont)

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. Monitor the patient for the development of the signs and symptoms of opioid withdrawal.

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IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Risk of Opioid Overdose from Attempts to Overcome the Blockade

Attempts to overcome opioid withdrawal symptoms caused by opioid antagonists with high or repeated doses of exogenous opioids may lead to opioid intoxication and death.

ADVERSE REACTIONS

Most common adverse reactions (> 5%) are feeling hot, nausea, headache, dizziness, chills, vomiting, allodynia, palpitations, tinnitus, ear discomfort, feeling abnormal, burning sensation, hot flush, and irritability.

USE IN SPECIFIC POPULATIONS

Pregnancy

An opioid overdose is a medical emergency and can be fatal for the pregnant woman and fetus if left untreated. Treatment with ZURNAI for opioid overdose should not be withheld because of potential concerns regarding the effects of ZURNAI in the fetus.

Pediatric Use

The safety and effectiveness of ZURNAI for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, have not been established in pediatric patients younger than 12 years of age.

Geriatric Use

Clinical studies of nalmeferene hydrochloride injection did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects.

To report SUSPECTED ADVERSE REACTIONS, contact Knoa Pharma LLC at 1 888-726-7535, option 2, or FDA at 1-800-FDA-1088 or www.fda.gov/safety/medwatch.

Intended for healthcare professionals of the United States of America only.

Please see [Full Prescribing Information](#).

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ZURNAL Auto-Injector summary

OPIOID OVERDOSES ARE FULL OF UNKNOWN—

the variability and potency of opioids, particularly synthetics, make reversal situations even more challenging.¹

CHOOSE ZURNAL TO HELP SUPPORT YOUR PATIENTS

ZURNAL is the first and only nalmeferene auto-injector.¹

- Reverses fentanyl-induced respiratory depression in **2.5 to 5 minutes**^{1*}
- **>9-hour** mean terminal elimination half-life^{1†}
- Can be **administered through clothing**¹
- The use of ZURNAL in patients who are opioid dependent may precipitate opioid withdrawal. Monitor for the development of opioid withdrawal¹

*Following ZURNAL administration, the time to onset of effect, ie, the onset of reversal of respiratory depression, was observed between 2.5 to 5 minutes, based on a pharmacodynamic study.¹

†ZURNAL mean terminal elimination half-life of 9.07 hours is based on a pharmacokinetic study of 24 healthy adult subjects given a single dose of IM ZURNAL.¹

INDICATIONS AND USAGE

ZURNAL is indicated for the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression.

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

ZURNAL is not a substitute for emergency medical care.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ZURNAL is contraindicated in patients known to be hypersensitive to nalmeferene hydrochloride or to any other ingredients in the product.

Please see additional IMPORTANT SAFETY INFORMATION throughout and Full Prescribing Information.

We are committed to maintaining the highest standards of sales and marketing practices, while continuing to advance the proper treatment of patients. If you have any questions or concerns with our sales and marketing practices, please contact us at 1-877-787-3831.



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Zurnai[™] (nalmeferene injection)
1.5 mg/0.5 mL Auto-Injector

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