Get the Facts about Zohydro™ ER (hydrocodone bitartrate) Extended-Release Capsules, CII

Zohydro™ ER (hydrocodone bitartrate) Extended-Release Capsules, CII, fills an unmet need for a subset of severe chronic pain patients who cannot take acetaminophen.

Zohydro™ ER is the first and only extended-release hydrocodone pain product without acetaminophen.

Most other extended-release (ER) opioids are the same or more potent than Zohydro™ ER.

- Zohydro™ ER is approved by the U.S. Food and Drug Administration (FDA) as a safe and effective treatment when taken as prescribed for managing pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.¹
- Zohydro ER was developed specifically for the estimated 2.4 million Americans who are currently taking immediate-release hydrocodone with acetaminophen, the most commonly prescribed hydrocodone product, for management of their severe chronic pain and who may be at risk for liver damage due to overexposure of acetaminophen, which can be fatal or require a liver transplant.²
- Acetaminophen is the leading cause of severe liver failure in this country, leading to liver transplants or even death.³
- Acetaminophen overdose also is a leading cause of acute liver failure in the United States.⁴
- 63 percent of unintentional acetaminophen overdoses are attributed to the use of hydrocodone-acetaminophen combination products.⁴
- To appreciate how the classes of opioids may differ, an understanding of potency, strength and morphine equivalents is required.
  - Potency is a measure of a drug’s activity in the body. Potency is compared on a morphine equivalent basis, a measurement that relates the potencies of different opioids to morphine.
  - Strength, on the other hand, is the amount of the medication administered in a dosage form, such as a tablet or a capsule.
- Hydrocodone in Zohydro ER has the same potency as hydrocodone in Vicodin® (immediate-release hydrocodone). Therefore, Zohydro ER is not 10 times more potent than Vicodin®.
- Oxycodone, the active medication in OxyContin®, has approximately the same potency as hydrocodone, the active medication in Zohydro ER and Vicodin®.⁵,⁶ However, OxyContin® is available on the market in higher doses than Zohydro ER.
- Oxymorphone, the active medication in Opana® ER, is more potent than oxycodone or hydrocodone.⁷ Hydromorphone, the active ingredient in Exalgo® ER, is more potent than oxycodone or hydrocodone.⁸ Therefore, Zohydro ER is not the most potent opioid on the market.
  - FDA Commissioner, Dr. Margaret Hamburg was quoted in a recent article in TIME®, clarifying this point: “It’s been said that Zohydro is super-potent. That surprises me because the highest dosage unit of Zohydro extended release is lower than the highest dosage unit of all the other available extended-release products on a milligram basis.”
The highest dosage strength of Zohydro™ ER is substantially lower than the highest dosage strength of oxycodone ER and morphine ER (on a per milligram basis).

- Two of the most widely prescribed CII extended-release opioids – OxyContin® (oxycodone) and Morphine Sulfate ER (morphine) - have higher dosage strengths per unit than Zohydro™ ER.5,30
- Extended-release opioids are 8 to 40 times stronger than the immediate-release versions of the same opioids.

### Extended-Release vs. Immediate-Release Dosage Comparison

<table>
<thead>
<tr>
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<th>Extended-Release</th>
<th>Immediate-Release</th>
<th>Multiple of ER to IR</th>
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</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>200 mg MS Contin®</td>
<td>5 mg</td>
<td>40 times</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>80 mg OxyContin®</td>
<td>5 mg</td>
<td>16 times</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>32 mg Exalgo® ER</td>
<td>2 mg</td>
<td>16 times</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>50 mg Zohydro™ ER</td>
<td>5 mg</td>
<td>10 times</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>40 mg Opana® ER</td>
<td>5 mg</td>
<td>8 times</td>
</tr>
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**fact**

Zohydro™ ER is the most stringently controlled hydrocodone product available.

**fact**

The total quantity of Zohydro™ ER that could be available is less than 0.3% of the total amount of opioids that the DEA has allocated for 2014.

**fact**

Zohydro™ ER is not more addictive than other opioids.

- Zohydro™ ER is the first and only hydrocodone product that is currently prescribed and dispensed under Schedule II rules, the most restrictive schedule available under the U.S. Drug Enforcement Agency’s (DEA) Controlled Drugs Act.
- Zohydro ER is the first hydrocodone product to be part of the FDA’s required class-wide REMS – Risk Evaluation and Mitigation Strategy – for extended-release/long-acting (ER/LA) opioid analgesics.
- There is no evidence that the abuse liability of hydrocodone is higher than other opioids.
  - A conclusion from a recent comprehensive review of clinical studies evaluating abuse potential was that oral oxycodone has an elevated abuse liability compared to oral morphine and hydrocodone.\(^{12}\)
  - Zohydro ER has the same class labeling, shares the same REMS, as all other extended-release/long-acting opioid analgesics.

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**Zohydro™ ER represents less than 0.3% of 2014 Pharmaceutical Opioid Production**

100% = 326,000 kilograms\(^{11}\)

- **Oxycodone**: 45.7%
- **Hydrocodone**: 30.5%
- **Morphine**: 19.1%
- **Oxymorphone**: 2.4%
- **Hydromorphone**: 2.1%
- **Zohydro™ ER**: <0.3%
Current abuse-deterrent technology (ADT) is flawed and new improved formulations are needed.

- Of the more than 30 FDA-approved extended-release/long-acting opioids currently on the market, only one product has a label claim that the formulation is “expected to make abuse via injection difficult and to reduce abuse via the intranasal route (snorting)” compared to a legacy non-abuse deterrent formulation of the same drug. However, that medication does not address the most acute form of abuse – which is oral (swallowing the medicine whole).
- Given the state of current science and technologies, ADT is not a requirement for FDA approval.
- FDA Commissioner Margaret A. Hamburg, M.D., recently stated: “… And right now, unfortunately the technology is poor, and there’s one abuse-deterrent formulation that is in the marketplace, recently approved… It doesn’t prevent abuse or misuse when taken orally, and it’s frankly not where we need to be…”
- Zogenix is investing heavily and actively developing two ADTs with the intent of introducing a next-generation abuse-deterrent formulation of Zohydro ER according to the recently published FDA Guidance for Industry, as soon as possible.

Zogenix is the first pharmaceutical company to voluntarily institute a comprehensive set of educational tools and safeguards prior to launching an opioid product.

- An External Safe Use Board of experts, including pain management, addiction and law-enforcement specialists, independently evaluate data, which will be shared with the FDA if patterns of abuse by prescribers, pharmacists or patients are detected.
- Sales representatives are compensated not on the number of prescriptions written, but instead for our representatives’ efforts to ensure doctors, pharmacists and patients are educated on the risks and benefits of using extended-release opioids.
- Patients receive access to free locking pill bottle caps and discounted safe-storage units to help prevent others from obtaining unauthorized access to Zohydro ER.
About Zohydro™ ER

INDICATION
Zohydro™ ER is an opioid agonist, extended-release, oral formulation of hydrocodone bitartrate indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

LIMITATIONS OF USE
• Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Zohydro ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
• Zohydro ER is not indicated for use as an as-needed analgesic.

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME and INTERACTION WITH ALCOHOL

Addiction, Abuse, and Misuse
Zohydro ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk prior to prescribing Zohydro ER, and monitor all patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Zohydro ER. Monitor for respiratory depression, especially during initiation of Zohydro ER or following a dose increase. Instruct patients to swallow Zohydro ER capsules whole; crushing, chewing, or dissolving Zohydro ER capsules can cause rapid release and absorption of a potentially fatal dose of hydrocodone.

Accidental Exposure
Accidental consumption of even one dose of Zohydro ER, especially by children, can result in a fatal overdose of hydrocodone.

Neonatal Opioid Withdrawal Syndrome
For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Zohydro ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts.

Interaction with Alcohol
Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Zohydro ER. The co-ingestion of alcohol with Zohydro ER may result in increased plasma levels and a potentially fatal overdose of hydrocodone.

CONTRAINDICATIONS
Zohydro ER is contraindicated in patients with: significant respiratory depression; acute or severe bronchial asthma or hypercarbia; known or suspected paralytic ileus; and hypersensitivity to hydrocodone bitartrate or any other ingredients in Zohydro ER.
WARNINGS AND PRECAUTIONS

• **Addiction, Abuse, and Misuse:** Zohydro ER is an opioid agonist and a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. As modified-release products such as Zohydro ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present.

• **Life-Threatening Respiratory Depression:** Serious, life-threatening respiratory depression has been reported with the use of modified-release opioids, even when used as recommended, and may lead to respiratory arrest and death if not immediately treated. The risk of respiratory depression is greatest during initiation of therapy or following a dose increase. Proper dosing and titration are essential.

• **Interactions with CNS Depressants:** Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs.

• **Elderly, Cachectic, Debilitated Patients, and Those with Chronic Pulmonary Disease:** Monitor closely because of increased risk for life-threatening respiratory depression.

• **Chronic Pulmonary Disease:** Monitor patients with significant chronic obstructive pulmonary disease for respiratory depression as even the usual therapeutic doses of Zohydro ER may decrease respiratory drive to the point of apnea.

• **Patients with Head Injury or Increased Intracranial Pressure:** Monitor for sedation and respiratory depression. Avoid use of Zohydro ER in patients with impaired consciousness or coma susceptible to intracranial effects of CO₂ retention.

• **Hypotensive Effect:** Zohydro ER may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised. Avoid the use of Zohydro ER in patients with circulatory shock.

• **Prolonged Gastric Obstruction:** May occur in patients with gastrointestinal obstruction. Monitor patients with biliary tract disease, including acute pancreatitis.

• **Cytochrome P450 CYP3A4 Inhibitors and Inducers:** Concomitant use of CYP3A4 inhibitors may increase or prolong opioid effects. CYP3A4 inducers may decrease hydrocodone plasma concentrations.

• **Impaired Mental/Physical Abilities:** Caution must be used with potentially hazardous activities.

• **Interaction with Mixed Agonist/Antagonist Opioid Analgesics:** Avoid the use of mixed agonist/antagonist analgesics with full opioid agonist analgesics, including Zohydro ER.

ADVERSE REACTIONS

• Potential serious adverse events caused by opioids include respiratory depression, potential for misuse and abuse, and CNS depressant effects.

• Adverse reactions in ≥2% of patients in placebo-controlled trials include constipation, nausea, somnolence, fatigue, headache, dizziness, dry mouth, vomiting, pruritus, abdominal pain, peripheral edema, upper respiratory tract infection, muscle spasms, urinary tract infection, back pain and tremor.

DRUG INTERACTIONS

• The CYP3A4 isoenzyme plays a major role in the metabolism of Zohydro ER. Drugs that inhibit CYP3A4 activity may cause decreased clearance of hydrocodone which could lead to an increase in hydrocodone plasma concentrations.

• CNS Depressants: Increased risk of respiratory depression, hypotension, profound sedation, coma or death. When combined therapy with CNS depressant is contemplated, the dose of one or both agents should be reduced.
• Mixed Agonists/Antagonists: May precipitate withdrawal or decrease analgesic effect if given concurrently with Zohydro ER.

• The use of MAO inhibitors or tricyclic antidepressants with Zohydro ER may increase the effect of either the antidepressant or Zohydro ER.

For more information about Zohydro ER, please visit: www.ZohydroER.com or the Zohydro ER REMS website at www.ZohydroERREMS.com.

Please read Full Prescribing Information, including full boxed warning, at www.zogenix.com/pdf/ZOHYDRO%20ER%20Full%20Prescribing%20Information.pdf.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

About Zogenix

Zogenix, Inc. (Nasdaq:ZGNX), with offices in San Diego and Emeryville, California, is a pharmaceutical company committed to developing and commercializing therapies that address specific clinical needs for people living with pain-related conditions and central nervous system disorders who need innovative treatment alternatives to help them return to normal daily functioning. More information about Zogenix is available at www.zogenix.com or 1-866-ZOGENIX.

Zohydro™ ER is a trademark of Zogenix, Inc.

All other trademarks and trade names are the properties of their respective owners.

References

2. FDA analysis of IMS Health Total Patient Tracker data for 2011 (presented at Zohydro ER Advisory Committee, December 2012).
5. OxyContin® Prescribing Information.
6. Vicodin® Prescribing Information.
7. Opana® ER Prescribing Information.
8. Exalgo® ER Prescribing Information.
10. MS Contin® Prescribing Information.