Zohydro™ ER (hydrocodone bitartrate) Extended-Release Capsule, CII, is a long-acting (extended-release) type of pain medication called an opioid. Zohydro ER is approved 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.

Zohydro ER capsules are available in six dosage strengths ranging from 10 mg to 50 mg; Zohydro ER is taken every 12 hours.

A Critical Need for Severe Chronic Pain Patients

Zohydro ER is the first and only extended-release formulation of hydrocodone without acetaminophen (acetaminophen is the ingredient in Tylenol®). Taking medicines containing high doses of acetaminophen can lead to liver injury; acetaminophen overdose is a leading cause of acute liver failure in the United States. In fact, 63 percent of unintentional acetaminophen overdoses can be attributed to the use of hydrocodone-acetaminophen combination pain medicines.¹

Zohydro ER was developed to address the need for those with pain severe enough to require daily, around-the-clock, long-term treatment and for whom alternative treatment options are inadequate. It is unique because it is the first and only extended-release hydrocodone medication without acetaminophen that has been available in a 12-hour dose.

Common causes of chronic pain include, but are not limited to low back pain, cancer pain, osteoarthritis and neurogenic pain (pain resulting from damage to the peripheral nerves or to the central nervous system itself).²

Clinical Trials Demonstrate Safety and Efficacy

Zohydro ER was approved by the U.S. Food and Drug Administration (FDA) on October 25, 2013 after a thorough 18-month review. Zohydro ER was studied in more than 1,100 people living with chronic pain who participated in the pivotal phase 3 efficacy study or an open-label phase 3 long-term safety study. The efficacy study, which enrolled more than 500 subjects with moderate-to-severe chronic low back pain, met its primary endpoint in demonstrating that treatment with Zohydro ER resulted in significantly improved chronic pain relief compared to placebo.
The key secondary endpoint was also achieved: a significantly higher number of subjects experienced at least 30 percent improvement in pain intensity from screening to end of study (67.5 percent, Zohydro™ ER versus 31.1 percent, placebo). The safety profile of Zohydro ER in both phase 3 studies was consistent with other opioids; the most frequent treatment-emergent adverse events were constipation, nausea, drowsiness (somnolence), fatigue, headache, dizziness, dry mouth, vomiting and itching (pruritus).

Comprehensive Educational Efforts and Surveillance Systems Support Responsible Use of Zohydro™ ER

Zogenix understands that the benefits of opioid pain medicines are best realized when they are taken as directed. However, current abuse-deterrent technology (ADT) has significant limitations and new formulations are needed. To support the appropriate use of Zohydro ER, Zogenix is committed to responsible management of product distribution and commercialization and has implemented, from the first day of product availability, the following voluntary initiatives:

1. Integrated broad-ranging educational resources for patients, physicians and pharmacists, that complement and build upon the extended-release/long-acting opioid analgesics Risk Evaluation and Mitigation Strategy (REMS), including assessment tools and case-based simulated training

2. Ongoing surveillance and monitoring of key measures from the date of launch, which are intended to detect potential misuse, abuse and diversion of Zohydro ER

3. External Safe Use Board of experts, including pain management, addiction and law-enforcement specialists who will independently make assessments and recommendations, which will be shared with the FDA if patterns of abuse by prescribers, pharmacists or patients are detected

4. Commercial activity focused on selected physicians who are experienced in the prescribing of Schedule II extended-release opioids, as well as proactive medical outreach to those who have expressed an interest in prescribing Zohydro ER

5. 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

6. 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.

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

References
