
Drug Monograph

Generic Name: hydrocodone extended-release

Trade Name: Zohydro ER[®]

Dosage Form: Extended-release capsules

NDCs: 43376-310-60, 43376-315-60, 43376-320-60, 43376-330-60, 43376-340-60, 43376-350-60

Manufacturer: Pernix Ireland Pain Limited

ADF Product Classification: Not yet determined

Executive Summary

Zohydro ER[®] (hydrocodone extended-release) is an extended-release formulation of hydrocodone that is approved by the Food and Drug Administration (FDA) to treat pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.¹ Zohydro ER[®] (hydrocodone extended-release) is formulated as an extended-release capsule for twice-daily administration. Zohydro ER[®] (hydrocodone extended-release) is being evaluated by the Drug Formulary Commission, as it was recently reformulated and is being considered for inclusion on the Massachusetts formulary of therapeutically equivalent substitutions, as outlined in Chapter 258 of the Acts of 2014.

Originally approved by the FDA in 2013, Zohydro ER[®] (hydrocodone extended-release), the first sole-ingredient hydrocodone product, was determined not to have abuse deterrent properties.² The approval was granted despite a 11-2-1 recommendation from the Anesthetic and Analgesic Drug Advisory Committee against the approval, citing the primary concern of the potential for abuse.³ This concern resulted in an executive order from Governor Deval Patrick banning the dispensing of Zohydro ER[®] (hydrocodone extended-release) in the Commonwealth of Massachusetts. Subsequently, in January 2015 the FDA approved the updated version, Zohydro ER[®] (hydrocodone extended-release), after safety concerns were addressed through reformulation with BeadTek[™] technology.⁴

The efficacy and safety of Zohydro ER[®] (hydrocodone extended-release) were established in a 12 week randomized double-blind, placebo controlled trial of 510 subjects. There was a statistically significant difference in the mean change from baseline in weekly average pain scores at week 12 between the hydrocodone extended-release and placebo groups (0.48 ± 1.56 versus 0.96 ± 1.55 , respectively; $P=0.008$). In addition, a higher proportion of subjects with at least a 30% and 50% improvement was noted in the hydrocodone extended-release group ($P<0.001$).^{1,2}

The recommended initial dosing and administration of Zohydro ER[®] (hydrocodone extended-release) in opioid naïve patients or patients without opioid tolerance for whom Zohydro ER[®] (hydrocodone extended-release) is the first opioid analgesic is 10 mg every 12 hours.¹ In patients who are converting from other opioids, the initial dosing recommendation is based upon the dosing conversion factors in the provided table (Table 7.). Maintenance dosing can be achieved by titrating the dose to efficacy in increments of 10 mg every 12 hours every three to seven days as necessary. No maximum dose has been established by the manufacturer.¹ Similar to other extended-release/long-acting opioids, the manufacturer is subject to adhering to the class-wise Risk Evaluation and Mitigation Strategy (REMS)⁵ requirements for preventing inappropriate prescribing, misuse, and abuse of extended release opioids.

Zohydro ER[®] (hydrocodone extended-release) capsules have been reformulated using BeadTek[™] technology. The capsules are comprised of an indistinguishable mix of inactive beads, active immediate-release hydrocodone beads and active extended-release hydrocodone beads which provide 12-hour dose duration. Attempts to crush and dissolve the tablets result in the formation of a viscous gel, which may cause difficulty passing through a hypodermic needle.⁴ When ingested as directed, the inactive beads within the capsule remain inert. The inactive beads dissolve independently of the active beads, thereby not affecting the 12-hour release properties. There is currently no data regarding T_{max} and bioavailability of Zohydro ER[®] (hydrocodone extended-release) if capsules are crushed versus intact.

The demonstrated efficacy of Zohydro ER® (hydrocodone extended-release) in the treatment of chronic pain is a potential strength of the formulation. Potential weaknesses of Zohydro ER® (hydrocodone extended-release) include the high cost relative to generic long-acting opioid formulations and the potential for the BeadTek™ technology to be circumvented if the medication is crushed or chewed and swallowed or crushed and insufflated. There is a lack of postmarketing data demonstrating a reduction of abuse in the community.

Reference Data

Zohydro ER[®] (hydrocodone extended-release) is a long-acting formulation of hydrocodone. Hydrocodone is an opioid agonist that is relatively selective for the μ opioid receptors; although, other opioid receptor subtypes may be stimulated at higher doses.¹ Stimulation of the μ opioid receptors results in analgesia, decreased gastrointestinal motility, euphoria, physical dependence, respiratory depression and sedation.⁶ Similar drugs within the long-acting opioid class are listed in Table 1.

Table 1. Long-Acting Opioid Availability

| Generic Name (Trade name) | Abuse Deterrent Formulation Available | Commercially Available |
|---|---------------------------------------|------------------------|
| Buprenorphine (Belbuca [®] , Butrans [®]) | - | ✓ |
| Fentanyl (Duragesic [®]) | - | ✓ |
| Hydrocodone (Hysingla ER [®]) | ✓ | ✓ |
| Hydrocodone (Zohydro ER [®]) | - | ✓ |
| Hydromorphone (Exalgo [®]) | - | ✓ |
| Levorphanol (Levo-Dromoran [®]) | - | ✓ |
| Methadone (Diskets Dispersible [®] , Dolophine [®] , Methadose [®] , Methadone Intensol [®]) | - | ✓ |
| Morphine sulfate (Avinza [®] , Kadian [®] , MS Contin [®]) | - | ✓ |
| Morphine sulfate (Morphabond [®]) | ✓ | - |
| Morphine sulfate/naltrexone (Embeda [®]) | ✓ | ✓ |
| Oxycodone (OxyContin [®]) | ✓ | ✓ |
| Oxycodone (Xtampza ER [®])* | ✓ | - |
| Oxycodone/naloxone (Targiniq ER [®]) | ✓ | - |
| Oxymorphone (Opana [®] ER) | - | ✓ |
| Tapentadol (Nucynta ER [®]) | - | ✓ |

*Xtampza ER approval is tentative, pending patent litigation

Therapeutic Indications/Efficacy

Zohydro ER[®] (hydrocodone extended-release) is an extended-release formulation of hydrocodone that is approved by the Food and Drug Administration (FDA) to treat pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.¹ FDA approval of Zohydro ER[®] (hydrocodone extended-release) was based upon the results of two phase III double-blind, multicenter, randomized, placebo controlled trial in patients with moderate to severe chronic low back pain.

The first trial, also referred to as ZX002-0801, evaluated the safety and efficacy of Zohydro ER[®] (hydrocodone extended-release) in opioid-experienced adults with moderate to severe chronic low back pain in a 12 week double-blind, multicenter, randomized, placebo-controlled trial. The study randomized 302 subjects in a 1:1 fashion to receive either Zohydro ER[®] (hydrocodone extended-release) or placebo after a conversion/titration phase of up to six weeks in length to establish each subject's appropriate dose of Zohydro ER[®] (hydrocodone extended-release). Use of rescue medication was allowed during the study in the form of up to two doses (two tablets) of hydrocodone/acetaminophen 5 mg/500 mg per day. The primary endpoint evaluated was the change in mean pain intensity (PI) score from baseline to end of treatment, which was based on the 11-point numerical rating scale (NRS) that was recorded daily in an electronic diary. The NRS scores ranged from zero to ten, with zero equal to "no pain" and ten equal to the "worst pain imaginable." The secondary endpoints measured were "treatment responders," defined by the percentage of subjects with at least a 30% average improvement in pain intensity scores from screening to end of treatment and subject satisfaction with their pain medication, measured by the mean

increase in Subject Global Assessment of Medication (SGAM) scores from baseline to end of treatment. The SGAM is conducted by asking subjects, "How satisfied are you with your pain medicine?" The answers accepted are "not at all," "a little bit," "moderately," "very much" and "completely". The answers are given a score of 1 to 5, respectively, and a higher SGAM indicated greater satisfaction with subjects' treatments. Mean change from baseline to end of treatment in PI score \pm standard deviation (SD) was significantly lower for Zohydro ER[®] (hydrocodone extended-release) versus placebo (0.48 ± 1.56 versus 0.96 ± 1.55 , respectively; $P=0.008$). There was a significantly higher amount of treatment responders in the Zohydro ER[®] (hydrocodone extended-release) group compared to the placebo group (68% versus 31%, respectively; $P<0.001$) at the end of treatment, and SGAM scores increased from baseline significantly in the Zohydro ER[®] (hydrocodone-extended) release group compared to placebo (0.8 ± 1.3 versus 0.0 ± 1.4 , respectively; $P<0.0001$).^{1,2,7}

The second phase III trial, also referred to as ZX002-0802, evaluated long-term safety and tolerability of Zohydro ER[®] (hydrocodone extended-release) in a 48 week multi-center, open label study. The study enrolled a total of 638 subjects, and all were included in the safety population data. In total, 424 subjects completed the conversion/titration phase, and were included in the intention to treat population, with 285 subjects completing the study. The primary endpoint was long-term safety and tolerability. Adverse events that occurred in at least 5% of subjects in the safety population ($n=638$) were constipation, nausea, headache and somnolence. There were four reported deaths during the study, and all were considered not likely to be related to the treatment. One subject committed suicide 13 months after the study, and authors noted that hoarding of study medication was likely involved. Authors also noted that the death was caused by mixed drug toxicity with hydromorphone, hydrocodone, dihydrocodeine, trazodone and ethanol. The secondary endpoint was efficacy, as measured by mean daily pain intensity (PI) scores. The mean pain intensity score at screening (prior to conversion/titration) was 6.4, 3.1 at baseline (begin of treatment phase) and 4.0 at the end of treatment.^{1,2}

Two other phase II studies, ELN154088-201 and ELN154088-203, evaluated the safety and effectiveness of Zohydro ER[®] (hydrocodone extended-release) in post-bunionectomy surgery patients and subjects with chronic, moderate to severe osteoarthritis pain, respectively.²

Table 2. Clinical Trials^{2,7}

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|--|--|--------------------------------|---|--|
| Rauck, et al ^{5*} Hydrocodone ER 20 mg to 100 mg every 12 hours vs placebo | DB, MC, PC, RCT Patients 18 to 75 years of age with moderate to severe chronic low back pain, and an average pain score of at least 4 on the NRS for 24 hour period prior to screening | N=302 12 weeks | Primary: Change in mean daily PI score from baseline \pm SD Secondary: Percentage of treatment responders, mean increase in SGAM scores \pm SD from baseline to end of treatment | Primary: The mean change from baseline in daily PI scores \pm SD was significantly lower for hydrocodone ER versus placebo (0.48 ± 1.56 vs 0.96 ± 1.55 ; $P=0.008$, respectively). Secondary: There was a significantly higher percentage of treatment responders in the hydrocodone ER group vs placebo (68% vs 31%; $P<0.001$, respectively) at the end of treatment. In addition, mean SGAM scores \pm SD increased from baseline to end of treatment in the hydrocodone ER group versus placebo (0.8 ± 1.3 vs 0.0 ± 1.4 ; $P<0.0001$, respectively). |
| Product dossier, Zogenix, Inc. ^{2*} Hydrocodone ER \geq 20 mg every 12 hours | MC, OL Patients 18 to 75 years of age with a diagnosis of a moderate to severe chronic pain condition, current opioid use at an average daily dose equivalent to \geq 30 mg hydrocodone | N=638 48 weeks | Primary: Safety and tolerability Secondary: Mean daily PI scores at screening, baseline and end of treatment | Primary: Adverse events that occurred in \geq 5% of subjects in the safety population were constipation, nausea, headache and somnolence. There were four reported deaths during the study. None of the deaths were considered to be related to treatment. Secondary: The mean PI score at screening (prior to conversion/titration) was 6.4, 3.1 at baseline (begin of treatment phase) and 4.0 at the end of treatment. |

*Trial is registered on ClinicalTrials.gov

†No comparative data provided for placebo

Study abbreviations: DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial, SD=standard deviation

Other abbreviations: ER=extended-release, NRS=numerical rating scale, PI=pain intensity, SGAM=Subject Global Assessment of Medication

Pharmacokinetics/Pharmacogenomics

Absorption

The time to peak plasma concentration (T_{max}) for Zohydro ER® (hydrocodone extended-release) was observed to be approximately five hours after dose administration. Food has no significant effect on the extent of absorption of Zohydro ER® (hydrocodone extended-release). The rate of absorption of Zohydro ER® (hydrocodone extended-release) increases with 40% alcohol coadministration in the fasted state, thereby increasing the peak hydrocodone concentration in patients. Prescribing information for Zohydro ER® (hydrocodone extended-release) does not provide the percent oral bioavailability for this product.¹

Distribution

The extent of protein binding of hydrocodone in human plasma is not precisely known; however, the structural similarities of Zohydro ER® (hydrocodone extended-release) to those of opioid analgesics are suggestive that hydrocodone is not extensively protein bound.¹

Metabolism

The primary metabolic pathway for hydrocodone is via CYP3A4 isozyme N-demethylation to norhydrocodone, an inactive metabolite. Norhydrocodone is also produced to a lesser extent by CYP2B6 and CYP2C19. The active metabolite hydromorphone is produced to a minor extent, <3% of circulating parent hydrocodone, primarily by CYP2D6 O-demethylation. CYP2B6 and CYP2C19 also contribute to the formation of hydromorphone to a lesser extent. It is thought that hydromorphone may contribute to the overall analgesia produced by hydrocodone administration.¹

Excretion

The primary route of excretion for hydrocodone and its metabolites is via renal excretion. The mean apparent plasma half-life following Zohydro ER® (hydrocodone extended-release) administration is approximately eight hours.¹

Pharmacogenomic Considerations:

A minor active metabolite of hydrocodone is hydromorphone, an opioid analgesic that may contribute to the overall analgesic effect of hydrocodone.¹ A polymorphism of CYP2D6 metabolism that results in a portion of the general population being ultra-rapid CYP2D6 metabolizers has been well documented as an item of great clinical significance, as evidenced by the boxed warning on codeine products that states respiratory depression and death has occurred in children with this polymorphism.⁸ It has not been apparent that ultra-rapid CYP2D6 metabolism is of as much concern with hydrocodone, but it has been demonstrated in a relatively small amount of subjects that production of hydromorphone as a metabolite is related to the CYP2D6 genotype. Increased plasma concentrations of hydromorphone were correlated with increased pain relief among extensive and ultra-rapid CYP2D6 metabolizers.⁹

Table 3. Pharmacokinetics¹

| Generic Name | T_{max} (hours) | Duration (hours) | Renal Clearance (L/h) | Active Metabolites | Serum Half-Life (hours) |
|--------------|----------------------|---------------------|--------------------------|--------------------------|----------------------------|
| Hydrocodone | 5 | N/A | N/A | Hydromorphone (minor) | 8 |

Special Populations

Table 4. Special Populations¹

| Population | Precaution |
|-------------------|--|
| Elderly | No significant differences in pharmacokinetic data have been identified. |
| Renal Dysfunction | Initiate therapy with a low dose in patients with renal impairment and monitor closely for adverse |

| Population | Precaution |
|---------------------|---|
| | events. |
| Hepatic Dysfunction | No adjustment in the starting dose is required in patients with mild or moderate hepatic impairment. Initiate therapy with the lowest dose, 10 mg, in patients with severe hepatic impairment and monitor closely for adverse events. |
| Pregnancy/Nursing | Category: C Hydrocodone is present in human milk. Due to potential risk for serious adverse reactions in nursing infants, either the medication or nursing should be discontinued, taking into account the importance of the drug to the mother. |
| Children | Safety and efficacy in children have not been established. |
| Gender/Race | No specific differences in pharmacokinetic data have been identified. |

Dosage Forms**Table 5. Availability, Storage and Handling¹**

| Dosage Form | Strength | Special Handling or Storage |
|--------------------------|--|--|
| Extended-release capsule | 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg | Store at 25°C (77°F); excursions between 15°C to 30°C (59°F to 86°F) permitted. Dispense and store in a tight, light-resistant container. |

Dosage Range**Table 6. Dosing and Administration¹**

| Adult Dose | Pediatric Dose | Renal Dose | Hepatic Dose |
|--|--|---|---|
| <u>Pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate:</u> Initial (opioid naïve or patients without opioid tolerance for whom Zohydro ER® is the first opioid analgesic): 10 mg every 12 hours. Initial (conversion from other opioids): use provided table (Table 7) to calculate starting dose. | Safety and efficacy in pediatric patients have not been established. | Initiate therapy with a low dose and monitor closely for respiratory depression and sedation. | Initiate dosing with the lowest dose, 10 mg, and monitor closely for respiratory depression and sedation. |

| Adult Dose | Pediatric Dose | Renal Dose | Hepatic Dose |
|---|----------------|------------|--------------|
| Maintenance: titrate dose to efficacy in increments of 10 mg every 12 hours every three to seven days as necessary. Maximum: no maximum dose provided. | | | |

For patients converting from a different opioid to Zohydro ER[®] (hydrocodone extended-release), the manufacturer provides a table to estimate a total hydrocodone daily dose.

Table 7. Opioid Conversion Factors¹

| Opioid | Oral Dose* | Approximate Oral Conversion Factor |
|---------------|------------|------------------------------------|
| Codeine | 100 mg | 0.10 |
| Hydromorphone | 3.75 mg | 2.67 |
| Methadone | 10 mg | 1 |
| Morphine | 15 mg | 0.67 |
| Oxycodone | 10 mg | 1 |
| Oxymorphone | 5 mg | 2 |
| Tramadol | N/A | N/A |

*Oral dose is the dose the manufacturer estimates to be equivalent to the lowest strength of Zohydro ER[®] (hydrocodone extended-release) using the approximate oral conversion factor

Dosing Considerations¹:

- The total daily dose of the opioid a patient is taking should be calculated, and then multiplied by the conversion factor to obtain the approximate daily hydrocodone dose.
- If patients are on multiple opioids, the approximate hydrocodone dose for each opioid should be calculated and added together to obtain the overall approximate daily hydrocodone dose.
- Only the opioid component of combination products such as oxycodone/acetaminophen or codeine/acetaminophen should be used to calculate the approximate daily hydrocodone dose.
- Once the approximate daily hydrocodone dose is calculated, the dose should be divided in half for administration every 12 hours.
- Patients converting from fentanyl transdermal should receive their initial dose of Zohydro ER[®] (hydrocodone extended-release) 18 hours after removal of the last fentanyl transdermal patch.
- Patients converting from methadone should be closely monitored as the half-life of methadone is long, and methadone can accumulate in the plasma. In addition, the equivalency ratio between methadone and other opioids may vary widely.

Precautions

Boxed Warning for Zohydro ER[®] (hydrocodone extended-release)¹

WARNING

Addition, Abuse and Misuse

Zohydro ER[®] (hydrocodone extended-release) 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[®] (hydrocodone extended-release), 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[®]

WARNING

(hydrocodone extended-release). Monitor for respiratory depression, especially during initiation of Zohydro ER[®] (hydrocodone extended-release) or following a dose increase. Instruct patients to swallow Zohydro ER[®] capsules whole to avoid a potentially fatal dose of hydrocodone.

Accidental Ingestion

Accidental ingestion of Zohydro ER[®] (hydrocodone extended-release), especially by children, can result in a fatal overdose of hydrocodone.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of Zohydro ER[®] (hydrocodone extended-release) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Interaction with Alcohol

Co-ingestion of Zohydro ER[®] (hydrocodone extended-release) and alcohol or any products containing alcohol can result in fatal plasma hydrocodone levels. Patients should be instructed not to consume alcohol or any products containing alcohol while taking Zohydro ER[®] (hydrocodone extended-release).

Cytochrome P450 3A4 Interaction

The concomitant use of Zohydro ER[®] (hydrocodone extended-release) with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving Zohydro ER[®] (hydrocodone extended-release) and any CYP3A4 inhibitor or inducer.

Table 8. Warnings/Precautions¹

| | |
|--------------------------------|---|
| Warning/ Precaution | Addiction, Abuse and Misuse; Zohydro ER [®] (hydrocodone extended-release) 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 [®] (hydrocodone extended-release), 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 [®] (hydrocodone extended-release). Monitor for respiratory depression, especially during initiation of Zohydro ER [®] (hydrocodone extended-release) or following a dose increase. Instruct patients to swallow Zohydro ER [®] capsules whole to avoid a potentially fatal dose of hydrocodone. |
| | Neonatal Opioid Withdrawal Syndrome; Prolonged use of Zohydro ER [®] (hydrocodone extended-release) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. |
| | Interactions with Central Nervous System (CNS) Depressants; Hypotension, profound sedation, coma, respiratory depression and death may result if Zohydro ER [®] (hydrocodone extended-release) is used concomitantly with alcohol or other CNS depressants. |
| | Use in Elderly, Cachectic and Debilitated Patients; Life-threatening respiratory |

| | |
|--|--|
| | depression is more likely to occur in elderly, cachectic or debilitated patients due to potential for altered pharmacokinetics or clearance compared to younger, healthier patients. These patients should be monitored closely, particularly upon initiating and titrating Zohydro ER® (hydrocodone extended-release) and when other drugs that depress respiration are concomitantly administered. |
| | Use in Patients with Chronic Pulmonary Disease; Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients that have a substantially decreased respiratory reserve, hypoxia, hypercapnia or preexisting respiratory depression for respiratory depression, particularly when initiating therapy with Zohydro ER® (hydrocodone extended-release), as even usual therapeutic doses of Zohydro ER® (hydrocodone extended-release) may decrease respiratory drive to the point of apnea in these patients. Consider the use of non-opioid analgesics in these patients if possible. |
| | Hypotensive Effect; Zohydro ER® (hydrocodone extended-release) may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is additional risk for patients with compromised ability to maintain blood pressure due to depleted blood volume or concomitant administration of drugs that compromise vasomotor tone, such as phenothiazines. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Zohydro ER® (hydrocodone extended-release). The use of Zohydro ER® (hydrocodone extended-release) should be avoided in patients with circulatory shock, as Zohydro ER® (hydrocodone extended-release) may cause vasodilation that can further reduce cardiac output and blood pressure. |
| | Use in Patients with Head Injury and Increased Intracranial Pressure; In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioids and their potential to elevate cerebrospinal fluid pressure may be markedly exaggerated. Opioid analgesics can also produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. |
| | Decreased Bowel Motility; Zohydro ER® (hydrocodone extended-release) is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Monitor for decreased bowel motility in post-operative patients receiving opioids. Administration of Zohydro ER® (hydrocodone extended-release) may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Hydrocodone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis. |
| | Use in Patients with Convulsive or Seizure Disorders; Zohydro ER® (hydrocodone extended-release) may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during Zohydro ER® (hydrocodone extended-release) therapy. |
| | Avoidance of Withdrawal; The use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received, or are receiving, a course of therapy with a full opioid agonist analgesic, including Zohydro ER® (hydrocodone extended-release) should be avoided. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms |
| | Driving and Operating Machinery; Zohydro ER® (hydrocodone extended-release) may impair the mental and physical abilities necessary to perform potentially hazardous activities such as driving a vehicle or operating machinery. Patients |

| | |
|--|--|
| | should be warned not to drive or operate dangerous machinery unless they are tolerant to the effects of Zohydro ER [®] (hydrocodone extended-release) and know how they will react to the medication. |
| | Cytochrome P450 3A4 Inhibitors and Inducers; Since the CYP3A4 isoenzyme plays a major role in metabolism of Zohydro ER [®] (hydrocodone extended-release), drugs that alter CYP3A4 activity may cause changes in clearance of hydrocodone which could lead to changes in hydrocodone plasma concentrations. Concomitant use CYP3A4 inhibitors have shown an increase in plasma hydrocodone concentrations which can increase or prolong opioid effects, and this may be more pronounced if multiple CYP3A4 inhibitors are used concomitantly. The expected clinical result with CYP3A4 inducers is decreased plasma hydrocodone concentrations, lack of efficacy or possible development of an abstinence syndrome if patients are physically dependent upon hydrocodone. If concomitant administration is necessary, caution is advised when initiating treatment with Zohydro ER [®] (hydrocodone extended-release) in patients taking or discontinuing CYP3A4 inhibitors or inducers. Patients should be evaluated frequently, and dose adjustments should be considered until drug effects are stable. |

Contraindications

Table 9. Contraindications¹

| | |
|-------------------------|---|
| Contraindication | Zohydro ER [®] (hydrocodone extended-release) is contraindicated in patients with severe respiratory depression. |
| | Zohydro ER [®] (hydrocodone extended-release) is contraindicated in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment. |
| | Zohydro ER [®] (hydrocodone extended-release) is contraindicated in patients with known or suspected paralytic ileus and gastrointestinal obstruction. |
| | Zohydro ER [®] (hydrocodone extended-release) is contraindicated in patients with hypersensitivity to any component of Zohydro ER [®] (hydrocodone extended-release). |

Adverse Effects

Table 10 represents adverse reactions reported in $\geq 2\%$ of subjects from both the open-label titration period and double-blind treatment period of a clinical trial for Zohydro ER[®] (hydrocodone extended-release). Figures reported during the open-label titration phase are reported in the active drug column.

Table 10. Adverse Events¹

| Adverse Event (%) | Reported Frequency | |
|--------------------------|---|--------------------------|
| | Active Drug, Dosing Regimen N=510 (open-label titration phase), 151 (double-blind treatment phase) | Placebo N=151 |
| Constipation | 8 to 11 | 0 |
| Nausea | 7 to 10 | 5 |
| Somnolence | 1 to 5 | 0 |
| Fatigue | 1 to 4 | 1 |
| Headache | 0 to 4 | 1 |
| Dizziness | 2 to 3 | 1 |
| Dry mouth | 0 to 3 | 0 |
| Vomiting | 3 to 5 | 1 |
| Pruritus | 0 to 3 | 0 |
| Abdominal pain | 2 to 3 | 0 |

| Adverse Event (%) | Reported Frequency | |
|-----------------------------------|---|------------------|
| | Active Drug, Dosing Regimen N=510 (open-label titration phase), 151 (double-blind treatment phase) | Placebo N=151 |
| Edema peripheral | 1 to 3 | 0 |
| Upper respiratory tract infection | 1 to 3 | 1 |
| Muscle spasms | 1 to 3 | 1 |
| Urinary tract infection | 1 to 5 | 2 |
| Back pain | 1 to 4 | 3 |
| Tremor | 0 to 3 | 1 |

Drug Interactions

Table 11. Drug Interactions^{1,10}

| Interacting Medication or Disease | Interaction Severity Rating* | Potential Result |
|--|------------------------------|---|
| CYP3A4 Inducers | Major | CYP3A4 inducers may induce the metabolism of hydrocodone resulting in increased clearance of hydrocodone and lower plasma concentrations of hydrocodone. This may result in lack of efficacy or possibly withdrawal syndrome. Monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved. |
| CYP3A4 Inhibitors | Major | CYP3A4 inhibitors such as macrolide antibiotics, azole-antifungals and protease inhibitors may inhibit the metabolism of hydrocodone, resulting in increased plasma concentrations of hydrocodone and prolonged opioid effects. When concomitant administration of CYP3A4 inhibitors and hydrocodone is necessary, patients should be evaluated at frequent intervals and dose adjustments should be considered until stable drug effects are achieved. |
| Central Nervous System (CNS) Depressants | Major | Concomitant administration of hydrocodone with other CNS depressants can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving concomitant CNS depressants for signs of respiratory depression, sedation and hypotension. When using hydrocodone and another CNS depressant, the dose of one or both agents should be reduced. |
| Mixed Agonist/Antagonist and Partial Agonist Opioids | Major | Mixed agonist/antagonist and partial agonist opioid analgesics may reduce the analgesic effect of hydrocodone or precipitate withdrawal symptoms. The concomitant use of mixed agonist/antagonist or partial opioid agonist analgesics with hydrocodone should be avoided. |
| Monoamine oxidase inhibitors (MAOIs) | Major | Concomitant use of hydrocodone and MAOIs, or use of hydrocodone within 14 days of using an MAOI is not recommended due to severe and unpredictable potentiation by MAOIs has been reported with opioid analgesics. |
| Escitalopram | Moderate | Concomitant use of hydrocodone and escitalopram may result in an increased risk of serotonin syndrome. |
| Kava | Moderate | Concomitant use of hydrocodone with kava may result in increased CNS depression. |
| Ginseng | Moderate | Concomitant use of hydrocodone with ginseng may result in |

| Interacting Medication or Disease | Interaction Severity Rating* | Potential Result |
|-----------------------------------|------------------------------|--|
| | | decreased efficacy of analgesia of hydrocodone. |
| Valerian | Moderate | Concomitant use of hydrocodone with valerian may result in increased CNS depression. |
| Quinidine | Moderate | Concomitant use of hydrocodone with quinidine may result in decreased efficacy of analgesia of hydrocodone. |
| Anticholinergics | Unknown | Concomitant use of opioids with anticholinergics or other drugs with anticholinergic activity may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation, in addition to respiratory and CNS depression. |

*Severity rating per Micromedex

Patient Monitoring Guidelines¹

It is recommended that patients be monitored continually to assess maintenance of analgesia. In addition, patients should be regularly monitored for adverse events, as well as signs of misuse, abuse or addiction. All patients should be screened for individual risk of opioid misuse, abuse and addiction prior to initiating treatment with Zohydro ER® (hydrocodone extended-release). These risks are increased in patients with a history of substance abuse, family history of substance abuse or mental illness.

Patients should be monitored closely for respiratory depression, especially upon initiation of treatment, following a dose increase or when Zohydro ER® (hydrocodone extended-release) is prescribed to a patient with renal impairment, hepatic impairment, head injury or increased intracranial pressure. Elderly, cachectic, debilitated patients and patients with chronic pulmonary disease are at increased risk for life-threatening respiratory depression; therefore, they should be monitored closely.

Patients receiving treatment with a CYP3A4 inhibitor or inducers must be monitored closely for increased incidence of adverse effects or decreased analgesia. Patients converting from other opioids to Zohydro ER® (hydrocodone extended-release) should be monitored for signs and symptoms of oversedation and respiratory depression and signs and symptoms of opioid withdrawal upon treatment initiation. Other monitoring recommendations are found in Table 8 with the warnings and precautions.

Addendum

Per the request of the Drug Formulary Commission, additional information about the potential abuse-deterrent properties of Zohydro ER® (hydrocodone extended-release) was requested of the manufacturer. A representative of Pernix Ireland Pain Limited provided a brief document that identified polyethylene oxide as the agent used to cause viscous gel formation upon attempts to crush and dissolve the beads within a Zohydro ER® (hydrocodone extended-release) capsule. The document states that the clinical significance of BeadTek™ on abuse or misuse of Zohydro ER® (hydrocodone extended-release) has not been established. In addition, the manufacturer was unable to supply any clinical abuse potential studies or *in vitro* laboratory manipulation and extraction studies for Zohydro ER® (hydrocodone extended-release).¹¹ Review of the Supplemental New Drug Application for reformulated Zohydro ER® (hydrocodone extended-release) with BeadTek™ revealed no information pertinent to the potential abuse-deterrent properties of Zohydro ER® (hydrocodone extended-release).¹²

References

1. Zohydro ER® [package insert]. Morristown (NJ): Pernix Ireland Pain Limited; 2015 May.
2. Zohydro ER® (hydrocodone bitartrate extended-release capsules) product dossier. June 2014. Zogenix, Inc.
3. Hitt E. Panel Recommends Against Approval of Hydrocodone Capsules. Medscape [webpage on the internet]. 2012 Dec 10 [cited 2015 Dec 23].

4. Pernix Launches Zohydro ER® with BeadTek™ [press release on the internet]. Morristown (NJ). 2015 May
5. Zohydro ER® FAQs [webpage on the internet]. Pernix Ireland Pain Limited; 2015 Dec 23 [cited 2015 Dec 23].
6. Trescot AM, Datta S, Lee M, Hansen H. Opioid Pharmacology. Pain Physician. 2008 Mar;11(2 Suppl):S133-153.
7. Rauck RL, Srinivas N, Wild JE, Walker GS, Robinson CY, Davis CS, et al. Single-Entity Hydrocodone Extended-Release Capsules in Opioid-Tolerant Subjects with Moderate-to-Severe Chronic Low Back Pain: A Randomized Double-Blind, Placebo-Controlled Study. Pain Medicine. 2014 Feb 12. doi: 10.1111/pme.12377. [Epub ahead of print]
8. Codeine [package insert on the internet]. Columbus (OH): Roxane Laboratories, Inc.; 2014 Sep. Available from: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Roxane/Codeine+NDA+2009/10005657_03+Codeine+NDA.pdf
9. Stauble ME, Moore AW, Langman LJ, Boswell MV, Baumgartner R, McGee S, et al. Hydrocodone in postoperative personalized pain management: pro-drug or drug? Clinica Chimica Acta. 2014 Feb 15;429:26-29.
10. Micromedex® Healthcare Series DRUGDEX® [database on the internet]. Greenwood Village (CO): Truven Health Analytics; Updated periodically [cited 2015 Dec 15]. Available from: <http://www.micromedexsolutions.com/>.
11. Zohydro ER® Mechanism and Comparison of Abuse Resistance. Pernix Ireland Pain Limited; 2015 Dec 11 [cited 2016 Apr 25].
12. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2016 [cited 2016 Apr 25]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.