

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZOHYDRO® ER (hydrocodone bitartrate) extended-release capsules, for oral use, CII  
Initial U.S. Approval: 1943

### WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANT; INTERACTION WITH ALCOHOL

See full prescribing information for complete boxed warning.

- ZOHYDRO ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1)
- To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow ZOHYDRO ER whole to avoid exposure to a potentially fatal dose of hydrocodone. (5.3)
- Accidental ingestion of ZOHYDRO ER, especially in children, can result in a fatal overdose of hydrocodone. (5.3)
- Prolonged use of ZOHYDRO ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone. (5.5)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.6, 7)
- Instruct patients not to consume alcohol or any products containing alcohol while taking ZOHYDRO ER because co-ingestion can result in fatal plasma hydrocodone levels. (5.6)

### RECENT MAJOR CHANGES

Boxed Warning 09/2018  
Warnings and Precautions (5.2) 09/2018

### INDICATIONS AND USAGE

ZOHYDRO ER is an opioid agonist 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. (1)

### 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. (1)
- ZOHYDRO ER is not indicated as an as-needed (prn) analgesic. (1)

### DOSAGE AND ADMINISTRATION

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain
- Daily doses of ZOHYDRO ER, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal

fenentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Instruct patients to swallow ZOHYDRO ER intact and not to cut, break, chew, crush, or dissolve the capsules (risk of potentially fatal overdose). (2.1, 5.1)
- For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg capsules orally every 12 hours. (2.2)
- To convert to ZOHYDRO ER from another opioid, use available conversion factors to obtain estimated dose. (2.2)
- Dose titration of ZOHYDRO ER may occur every 3 to 7 days, using increments of 10 mg every 12 hours (i.e., 20 mg per day). (2.3)
- Patients with Severe Hepatic Impairment: Initiate dosing with 10 mg every 12 hours and titrate carefully, while monitoring for respiratory depression, sedation, and hypotension. No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment. (2.4)
- Do not abruptly discontinue ZOHYDRO ER in a physically dependent patient. (2.5)

### DOSAGE FORMS AND STRENGTHS

Extended-release capsules: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg (3)

### CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to hydrocodone or to any other components of ZOHYDRO ER (4)

### WARNINGS AND PRECAUTIONS

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.3)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of ZOHYDRO ER in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of ZOHYDRO ER in patients with circulatory shock. (5.10)

### ADVERSE REACTIONS

Adverse reactions in ≥2% of patients in placebo-controlled trials include constipation, nausea, somnolence, fatigue, headache, dizziness, dry mouth, vomiting, pruritus, abdominal pain, edema peripheral, upper respiratory tract infection, muscle spasms, urinary tract infection, back pain, and tremor. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pernix Therapeutics, LLC at 1-800-793-2145 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue ZOHYDRO ER if serotonin syndrome is suspected. (7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of hydrocodone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping an MAOI. (7)
- Mixed Agonists/Antagonists and Partial Agonist Opioid Analgesics: Avoid use with ZOHYDRO ER because they may reduce analgesic effect of ZOHYDRO ER or precipitate withdrawal symptoms. (7)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2018

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## FULL PRESCRIBING INFORMATION

**WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS; 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 and conditions [*see Warnings and Precautions (5.1)*].

### Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [*see Warnings and Precautions (5.2)*]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

### 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 [*see Warnings and Precautions (5.3)*].

### Accidental Ingestion

Accidental ingestion of even one dose of ZOHYDRO ER, especially by children, can result in a fatal overdose of hydrocodone [*see Warnings and Precautions (5.3)*].

### Neonatal Opioid Withdrawal Syndrome

Prolonged use of ZOHYDRO ER 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 [*see Warnings and Precautions (5.4)*].

### Cytochrome P450 3A4 Interaction

The concomitant use of ZOHYDRO ER with all cytochrome P450 3A4 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 and any CYP3A4 inhibitor or inducer [*see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)*].

### **Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.6)*, *Drug Interactions (7)*].

- Reserve concomitant prescribing of ZOHYDRO ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

### **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 [see *Warnings and Precautions (5.6)* and *Clinical Pharmacology (12.3)*].

## **1 INDICATIONS AND USAGE**

ZOHYDRO<sup>®</sup> ER (hydrocodone bitartrate) is 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 [see *Warnings and Precautions (5.1)*], 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 as an as-needed (prn) analgesic.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Important Dosage and Administration Information**

ZOHYDRO ER should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

Daily doses of ZOHYDRO ER, a single dose of greater than 40 mg, or a total daily dose of greater than 80 mg, are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5)*].
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.1)*].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with ZOHYDRO ER and adjust the dosage accordingly [see *Warnings and Precautions (5.3)*].

Instruct patients to swallow ZOHYDRO ER capsules whole [see Patient Counseling Information (17)]. Crushing, chewing, or dissolving the beads in ZOHYDRO ER capsules will result in uncontrolled delivery of hydrocodone and can lead to overdose or death [see Warnings and Precautions (5.1)].

ZOHYDRO ER is administered orally twice daily (every 12 hours).

## 2.2 Initial Dosage

### Use of ZOHYDRO ER as the First Opioid Analgesic (opioid-naïve patients)

Initiate therapy with ZOHYDRO ER with one 10 mg capsule every 12 hours.

### Use of ZOHYDRO ER in Patients Who Are Not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is ZOHYDRO ER 10 mg orally every 12 hours.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression [see Warnings and Precautions (5.3)].

### Conversion from Oral Hydrocodone Formulations to ZOHYDRO ER

Patients receiving other oral hydrocodone-containing formulations may be converted to ZOHYDRO ER by dividing the patient's total daily oral hydrocodone dose in half and administering as ZOHYDRO ER every 12 hours.

### Conversion from Other Oral Opioid to ZOHYDRO ER

Discontinue all other around-the-clock opioid drugs when ZOHYDRO ER therapy is initiated.

There is inter-patient variability in the relative potency of different opioid drugs and products. Therefore, a conservative approach is advised when determining the total daily dosage of ZOHYDRO ER. It is safer to underestimate a patient's 24-hour oral hydrocodone dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral hydrocodone dosage and manage an adverse reaction due to an overdose.

In a ZOHYDRO ER clinical trial with an open label titration period, patients were converted from their prior opioid to ZOHYDRO ER using Table 1 as a guide for the initial ZOHYDRO ER dose. To obtain the initial ZOHYDRO ER dose, first use Table 1 to convert the prior oral opioids to a total hydrocodone daily dose and then reduce the calculated daily hydrocodone dose by 25% to account for interpatient variability in relative potency of different opioids.

Consider the following when using the information in Table 1:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics **to** ZOHYDRO ER.
- The table **cannot** be used to convert **from** ZOHYDRO ER to another opioid. Doing so will result in an over-estimation of the dose of the new opioid and may result in fatal overdose.

<b>Prior Oral Opioid</b>	<b>Oral Dose (mg)</b>	<b>Approximate Oral Conversion Factor</b>
Hydrocodone	10	1
Oxycodone	10	1
Methadone	10	1

Oxymorphone	5	2
Hydromorphone	3.75	2.67
Morphine	15	0.67
Codeine	100	0.10
The conversion ratios in this table are only to be used for the conversion from current opioid therapy to ZOHYDRO ER.		

To calculate the estimated daily ZOHYDRO ER dose using Table 1:

- For patients on a single opioid, sum the current total daily dose of the opioid and then multiply the total daily dose by the approximate oral conversion factor to calculate the approximate oral hydrocodone daily dose. Divide the daily dose in half for administration every 12 hours.
- For patients on a regimen of more than one opioid, calculate the approximate oral hydrocodone dose for each opioid and sum the totals to obtain approximate total hydrocodone daily dose. The daily dose should then be divided in half for administration every 12 hours.
- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.
- Reduce the calculated daily oral hydrocodone dose by 25%

Always round the dose down, if necessary, to the nearest ZOHYDRO ER strength(s) available and initiate therapy with that dose.

#### *Example conversion from a single opioid to ZOHYDRO ER*

Step 1: Sum the total daily dose of the opioid (in this case, extended-release oxymorphone); 15 mg oxymorphone twice daily = 30 mg total daily dose of oxymorphone.

Step 2: Calculate the approximate equivalent dose of oral hydrocodone based on the total daily dose of the current opioid using Table 1; 30 mg total daily dose of oxymorphone x 2 = 60 mg of oral hydrocodone daily. The daily dose should then be divided in half for administration every 12 hours.

Step 3: Calculate the approximate starting dose which is 30 mg ZOHYDRO ER every 12 hours. Round down, if necessary, to the appropriate ZOHYDRO ER capsule strengths available. Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to ZOHYDRO ER.

The dose of ZOHYDRO ER can be gradually adjusted preferably at increments of 10 mg every 12 hours every 3 to 7 days, until adequate pain relief and acceptable adverse reactions have been achieved.

#### Conversion from Methadone to ZOHYDRO ER

Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and tends to accumulate in the plasma.

#### Conversion from Transdermal Fentanyl to ZOHYDRO ER

ZOHYDRO ER treatment can be initiated 18 hours following the removal of the transdermal fentanyl patch. Although there has been no systematic assessment of such conversion, a conservative hydrocodone dose, approximately 10 mg every 12 hours of ZOHYDRO ER, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to ZOHYDRO ER, as there is limited documented experience with this conversion.

## 2.3 Titration and Maintenance of Therapy

Individually titrate ZOHYDRO ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving ZOHYDRO ER to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see *Warnings and Precautions (5.1)*]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

Patients who experience breakthrough pain may require a dosage adjustment of ZOHYDRO ER, or may need a rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the ZOHYDRO ER dosage. Because steady-state plasma concentrations are approximated within 3 days, ZOHYDRO ER dosage adjustments, preferably at increments of 10 mg every 12 hours, may be done every 3 to 7 days.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

## 2.4 Dosage Modifications in Patients with Severe Hepatic Impairment

Patients with severe hepatic impairment may have higher plasma concentrations of hydrocodone than those with normal function. Therefore, initiate therapy with 10 mg every 12 hours and titrate carefully, while monitoring for respiratory depression, sedation, and hypotension. No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment [see *Clinical Pharmacology (12.3)*].

## 2.5 Discontinuation of ZOHYDRO ER

Do not abruptly discontinue ZOHYDRO ER. When a patient no longer requires therapy with ZOHYDRO ER, taper the dose gradually, according to the schedule in Table 2, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these sign or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both.

<b>Stabilized Dose At Time of Taper Initiation</b>	<b>Taper Schedule</b>
20 mg to 30 mg q12h*	<ul style="list-style-type: none"><li>• 10 mg q12h on Days 1 and 2</li><li>• Day 3, stop</li></ul>
40 mg to 70 mg q12h	<ul style="list-style-type: none"><li>• 40 mg q12h on Days 1 and 2</li><li>• 20 mg q12h on Days 3 and 4</li><li>• 10 mg q12h on Days 5 and 6</li><li>• Day 7, stop</li></ul>
80 mg to 100 mg q12h	<ul style="list-style-type: none"><li>• 80 mg q12h on Days 1 and 2</li><li>• 60 mg q12h on Days 3 and 4</li><li>• 40 mg q12h on Days 5 and 6</li><li>• 20 mg q12h on Days 7 and 8</li><li>• 10 mg q12h on Days 9 and 10</li><li>• Day 11, stop</li></ul>

\*q12h = every 12 hours

Doses above 100 mg every 12 hours (q12h) were not studied in the Phase 3 trial. For patients exceeding 100 mg q12h use a gradual downward titration of the dose every 2 to 4 days. Patients should be monitored closely for signs and symptoms of opioid withdrawal which may indicate a need to taper more slowly.

### 3 DOSAGE FORMS AND STRENGTHS

10 mg	White opaque	“Z310 10 mg” in black ink
15 mg	Light green and white opaque	“Z315 15 mg” in black ink
20 mg	Light green opaque	“Z320 20 mg” in black ink
30 mg	Dark blue and white opaque	“Z330 30 mg” in black ink
40 mg	Dark brown and white opaque	“Z340 40 mg” in black ink
50 mg	Dark brown opaque	“Z350 50 mg” in black ink

### 4 CONTRAINDICATIONS

ZOXYDRO ER is contraindicated in patients with:

- Significant respiratory depression [see *Warnings and Precautions (5.3)*]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see *Warnings and Precautions (5.7)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions (5.11)*]
- Hypersensitivity (e.g., anaphylaxis) to hydrocodone or any other ingredients in ZOXYDRO ER

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Addiction, Abuse, and Misuse

ZOXYDRO ER contains hydrocodone, a Schedule II controlled substance. As an opioid, ZOXYDRO ER exposes users to the risks of addiction, abuse, and misuse. Because extended-release products such as ZOXYDRO 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 [see *Drug Abuse and Dependence (9.1)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ZOXYDRO ER. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing ZOXYDRO ER, and monitor all patients receiving ZOXYDRO ER for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of ZOXYDRO ER for the proper management of pain in any given patient. Patients at increased



risk may be prescribed opioids such as ZOHYDRO ER, but use in such patients necessitates intensive counseling about the risks and proper use of ZOHYDRO ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of ZOHYDRO ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death [*see Drug Abuse and Dependence (9.1), Overdosage (10)*].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing ZOHYDRO ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [*see Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

## **5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: [www.fda.gov/OpioidAnalgesicREMSPCG](http://www.fda.gov/OpioidAnalgesicREMSPCG).
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to [www.opioidanalgesicrems.com](http://www.opioidanalgesicrems.com). The FDA Blueprint can be found at [www.fda.gov/OpioidAnalgesicREMSBlueprint](http://www.fda.gov/OpioidAnalgesicREMSBlueprint).

## **5.3 Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [*see Overdosage (10)*]. Carbon dioxide (CO<sub>2</sub>) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of ZOHYDRO ER, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of ZOHYDRO ER.

To reduce the risk of respiratory depression, proper dosing and titration of ZOHYDRO ER are essential [*see Dosage and Administration (2.3)*]. Overestimating the ZOHYDRO ER dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of even one dose of ZOHYDRO ER, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone.

#### **5.4 Neonatal Opioid Withdrawal Syndrome**

Prolonged use of ZOHYDRO ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [*see Use in Specific Populations (8.1), Patient Counseling Information (17)*].

#### **5.5 Risks from Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers**

Concomitant use of ZOHYDRO ER with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of hydrocodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [*see Warnings and Precautions (5.3)*], particularly when an inhibitor is added after a stable dose of ZOHYDRO ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in ZOHYDRO ER-treated patients may increase hydrocodone plasma concentrations and prolong opioid adverse reactions. When using ZOHYDRO ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in ZOHYDRO ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of ZOHYDRO ER until stable drug effects are achieved [*see Drug Interactions (7)*].

Concomitant use of ZOHYDRO ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease hydrocodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. When using ZOHYDRO ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [*see Drug Interactions (7)*].

#### **5.6 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants**

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of ZOHYDRO ER with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [*see Drug Interactions (7)*].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum duration of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid

analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when ZOHYDRO ER is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk of overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [*see Drug Interactions (7) and Patient Counseling Information (17)*].

Patients must not consume alcoholic beverages, or prescription or non-prescription products containing alcohol, while on ZOHYDRO ER therapy. The co-ingestion of alcohol with ZOHYDRO ER may result in increased plasma levels and a potentially fatal overdose of hydrocodone [*see Clinical Pharmacology (12.3)*].

### **5.7 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients**

The use of ZOHYDRO ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: ZOHYDRO ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of ZOHYDRO ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particular when initiating and titrating ZOHYDRO ER and when ZOHYDRO ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

### **5.8 Adrenal Insufficiency**

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioid as being more likely to be associated with adrenal insufficiency.

### **5.9 Severe Hypotension**

ZOHYDRO ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an added risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or after concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [*see Drug Interactions (7)*]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of ZOHYDRO ER. In patients with circulatory shock, ZOHYDRO ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of ZOHYDRO ER in patients with circulatory shock.

### **5.10 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**

In patients who may be susceptible to the intracranial effects of CO<sub>2</sub> retention (e.g., those with evidence of increased intracranial pressure or brain tumors), ZOHYDRO ER may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with ZOHYDRO ER.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of ZOHYDRO ER in patients with impaired consciousness or coma.

### **5.11 Risks of Use in Patients with Gastrointestinal Conditions**

ZOHYDRO ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Hydrocodone in ZOHYDRO ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening of symptoms.

### **5.12 Increased Risk of Seizures in Patients with Seizure Disorders**

The hydrocodone in ZOHYDRO ER may increase the frequency of seizures in patients with seizure disorders, and may increase the risk occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during ZOHYDRO ER therapy.

### **5.13 Withdrawal**

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including ZOHYDRO ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms [*see Drug Interactions (7)*].

When discontinuing ZOHYDRO ER, gradually taper the dosage [*see Dosage and Administration (2.4)*]. Do not abruptly discontinue ZOHYDRO ER [*see Drug Abuse and Dependence (9.3)*].

### **5.14 Risks of Driving and Operating Machinery**

ZOHYDRO ER may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of ZOHYDRO ER and know how they will react to the medication [*see Clinical Pharmacology (12.3), Patient Counseling Information (17)*].

## **6 ADVERSE REACTIONS**

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

- Addiction, Abuse, and Misuse [*see Warnings and Precautions (5.1)*]
- Life-Threatening Respiratory Depression [*see Warnings and Precautions (5.3)*]
- Neonatal Opioid Withdrawal Syndrome [*see Warnings and Precautions (5.4)*]
- Interactions with Benzodiazepines and Other CNS Depressants [*see Warnings and Precautions (5.6)*]
- Adrenal Insufficiency [*see Warnings and Precautions (5.8)*]
- Severe Hypotension [*see Warnings and Precautions (5.9)*]
- Gastrointestinal Adverse Reactions [*see Warnings and Precautions (5.11)*]
- Seizures [*see Warnings and Precautions (5.12)*]
- Withdrawal [*see Warnings and Precautions (5.13)*]

## **6.1 Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of ZOHYDRO ER was evaluated in a total of 1,148 subjects in Phase 3 clinical trials.

Table 3 lists the most frequently occurring adverse reactions occurring at a greater frequency than placebo from the placebo-controlled trial in subjects with moderate-to-severe chronic lower back pain.

<b>Table 3. Treatment-Emergent Adverse Events in <math>\geq 2\%</math> of Subjects During the Open-Label Titration Period and/or the Double-Blind Treatment Period, by Preferred Term — Number (%) of Treated Subjects (Placebo-Controlled Study in Opioid-Experienced Subjects with Moderate-to-Severe Chronic Lower Back Pain)</b>			
	<b>Open-Label Titration Period</b>	<b>Double-Blind Treatment Period</b>	
	<b>ZOHYDRO ER</b>	<b>ZOHYDRO ER</b>	<b>Placebo</b>
<b>Preferred Term</b>	<b>(N = 510)</b>	<b>(n = 151)</b>	<b>(n = 151)</b>
Constipation	56 (11%)	12 (8%)	0 (0%)
Nausea	50 (10%)	11 (7%)	5 (3%)
Somnolence	24 (5%)	1 (1%)	0 (0%)
Fatigue	21 (4%)	1 (1%)	2 (1%)
Headache	19 (4%)	0 (0%)	2 (1%)
Dizziness	17 (3%)	3 (2%)	1 (1%)
Dry mouth	16 (3%)	0 (0%)	0 (0%)
Vomiting	14 (3%)	7 (5%)	1 (1%)
Pruritus	13 (3%)	0 (0%)	0 (0%)
Abdominal pain	8 (2%)	4 (3%)	0 (0%)
Edema peripheral	7 (1%)	4 (3%)	0 (0%)
Upper respiratory tract infection	7 (1%)	5 (3%)	1 (1%)
Muscle spasms	6 (1%)	4 (3%)	2 (1%)
Urinary tract infection	4 (1%)	8 (5%)	3 (2%)
Back pain	4 (1%)	6 (4%)	5 (3%)
Tremor	1 (0%)	4 (3%)	1 (1%)

The common ( $\geq 1\%$  to  $< 10\%$ ) adverse drug reactions reported at least once by subjects treated with ZOHYDRO ER in the Phase 3 clinical trials and not represented in Table 3 were:

Gastrointestinal Disorders: abdominal discomfort, abdominal pain, gastroesophageal reflux disease

General Disorders and Administration Site Conditions: non-cardiac chest pain, pain, peripheral edema, pyrexia

Injury, Poisoning and Procedural Complications: contusion, fall, foot fracture, joint injury, joint sprain, muscle strain, skin laceration

Investigations: increased blood cholesterol, increased gamma-glutamyltransferase

Metabolism and Nutrition Disorders: dehydration, hypokalemia

Musculoskeletal and Connective Tissue Disorders: arthralgia, musculoskeletal pain, myalgia, neck pain, osteoarthritis, pain in extremity

Nervous System Disorders: lethargy, migraine, paresthesia

Psychiatric Disorders: anxiety, depression, insomnia

Respiratory, Thoracic, and Mediastinal Disorders: cough, dyspnea

Skin and Subcutaneous Tissue Disorders: hyperhidrosis, night sweats, rash

Vascular Disorders: hot flush

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of hydrocodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in ZOHYDRO ER.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see *Clinical Pharmacology (12.2)*].

## 7 DRUG INTERACTIONS

<b>Alcohol</b>	
<i>Clinical Impact:</i>	Concomitant use of alcohol with ZOHYDRO ER can result in an increase of hydrocodone plasma levels and potentially fatal overdose of hydrocodone.
<i>Intervention:</i>	Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on ZOHYDRO ER therapy [see <i>Clinical Pharmacology (12.3)</i> ].
<b>Inhibitors of CYP3A4 and CYP2D6</b>	
<i>Clinical Impact:</i>	The concomitant use of ZOHYDRO ER and CYP3A4 inhibitors can increase the plasma concentration of hydrocodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of ZOHYDRO ER and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of ZOHYDRO ER is achieved [see <i>Warnings and Precautions (5.5)</i> ]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the hydrocodone plasma concentration will decrease [see <i>Clinical Pharmacology (12.3)</i> ], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to hydrocodone.
<i>Intervention:</i>	If concomitant use is necessary, consider dosage reduction of ZOHYDRO ER until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the ZOHYDRO ER dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
<i>Examples:</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
<b>CYP3A4 Inducers</b>	
<i>Clinical Impact:</i>	The concomitant use of ZOHYDRO ER and CYP3A4 inducers can decrease the plasma concentration of hydrocodone [see <i>Clinical Pharmacology (12.3)</i> ],

	<p>resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to hydrocodone [see <i>Warnings and Precautions (5.5)</i>].</p> <p>After stopping a CYP3A4 inducer, as the effects of the inducer decline, the hydrocodone plasma concentration will increase [see <i>Clinical Pharmacology (12.3)</i>], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.</p>
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the ZOHYDRO ER dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider ZOHYDRO ER dosage reduction and monitor for signs of respiratory depression.
<i>Examples:</i>	Rafampin, carbamazepine, phenytoin
<b>Benzodiazepines and other Central Nervous System (CNS) Depressants</b>	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see <i>Warnings and Precautions (5.6)</i> ].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol
<b>Serotonergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue ZOHYDRO ER if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT <sub>3</sub> receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue)
<b>Monoamine Oxidase Inhibitors (MAOIs)</b>	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see <i>Drug Interactions (7)</i> ].
<i>Intervention:</i>	The use of ZOHYDRO ER is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	Phenelzine, tranylcypromine, linezolid
<b>Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics</b>	
<i>Clinical Impact:</i>	May reduce the analgesic effect of ZOHYDRO ER and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine
<b>Muscle Relaxants</b>	
<i>Clinical Impact:</i>	Hydrocodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of ZOHYDRO ER and/or the muscle relaxant as necessary.
<b>Diuretics</b>	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of

	antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
<b>Anticholinergic Drugs</b>	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when ZOHYDRO ER is used concomitantly with anticholinergic drugs.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [*see Warnings and Precautions (5.4)*]. There are no studies of ZOHYDRO ER use in pregnant women. Rats administered oral hydrocodone during gestation and lactation showed increases in stillborn pups and decreases in pup survival at doses equivalent to the human dose of 100 mg/day. Reduced nursing behavior and decreased body weights were observed at 2 times the human dose. Reduced fetal weights were observed in rabbits administered hydrocodone during the period of organogenesis at doses equivalent to 5 times the human dose of 100 mg/day. In this study, increases in the number of umbilical hernias, irregularly shaped bones, and delays in fetal skeletal maturation were observed at doses 15 times the human dose of 100 mg/day. No fetal malformations were observed in animal reproduction studies with oral administration of hydrocodone bitartrate during organogenesis in rats and rabbits at doses approximately 2 and 10 times a human dose of 100 mg/day, respectively [*see Data*]. Based on animal data, advise pregnant women of the potential risks to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Clinical Considerations

##### *Fetal/neonatal adverse reactions*

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the newborn and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [*see Warnings and Precautions (5.4)*].

##### *Labor or Delivery*

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist such as naloxone must be available for reversal of opioid induced respiratory depression in the neonate. ZOHYDRO ER is not recommended for use in women during and immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including ZOHYDRO ER, can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

#### Data

##### *Animal Data*

Oral doses of hydrocodone bitartrate up to 25 mg/kg/day in rats and 50 mg/kg/day in rabbits, equivalent to 2 and 10 times an adult human dose of 100 mg/day, respectively on a mg/m<sup>2</sup> basis, did not result in any fetal malformations. Fetuses of rabbits administered oral doses of 75 mg/kg/day hydrocodone bitartrate (15 times an adult human dose of 100 mg/day on a mg/m<sup>2</sup> basis) during the period of organogenesis exhibited an increased number of malformations consisting of umbilical hernia, and irregularly shaped bones (ulna, femur, tibia and/or



fibula). Maternal toxicity was evident at this dose (decreased body weight). In addition, oral hydrocodone bitartrate reduced fetal weights at doses greater than or equal to 25 mg/kg/day (equivalent to approximately 5 times an adult human dose of 100 mg/day on a mg/m<sup>2</sup> basis). Delays in fetal skeletal maturation (reduced ossification of hyoid bodies and xiphoid bones) were seen following dosing with 75 mg/kg/day (a dose equivalent to 15 times an adult human dose of 100 mg/day on a mg/m<sup>2</sup> basis).

Hydrocodone bitartrate administered orally to female rats at oral doses of 10 and 25 mg/kg/day during gestation and lactation resulted in pups which were noted as cold to touch and caused a reduction in fetal viability (increases in the number of stillborn pups and/or pups dying postpartum). The doses causing these effects were equivalent to approximately 1 and 2.4 times an adult human dose of 100 mg/day, on a mg/m<sup>2</sup> basis. Nursing was reduced in pups of mothers administered 25 mg/kg/day which correlated with decreased body weight/body weight gain and food consumption in male pups. Minimal maternal toxicity was evident at 25 mg/kg (decreased body weight).

## **8.2 Lactation**

### Risk Summary

Hydrocodone is present in human milk. A published lactation study reports variable concentrations of hydrocodone and hydromorphone (an active metabolite) in breast milk with administration of immediate-release hydrocodone to nursing mothers in the early post-partum period. This lactation study did not assess breastfed infants for potential adverse drug reactions. Lactation studies have not been conducted with extended-release hydrocodone, including ZOHYDRO ER, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ZOHYDRO ER.

### Clinical Considerations

Monitor infants exposed to ZOHYDRO ER through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

## **8.3 Females and Males of Reproductive Potential**

### Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

In rat fertility studies, no effects on male fertility were observed with hydrocodone at doses equivalent to 10 times the human dose of 100 mg/day, however, decreases in the weight of male reproductive organs were observed in all treated groups at doses equivalent to 2.4 times the human dose of 100 mg/day and above. Reductions in female fertility indices were observed at doses of hydrocodone equivalent to 2 times the human dose of 100 mg/day and above. These changes are attributed to a hydrocodone-mediated decrease in prolactin levels in the rat. Unique to rodents, prolactin is required for normal estrous cycling and the effects on fertility observed in this study are most likely rodent-specific and not believed to be clinically relevant [*see Nonclinical Toxicology (13)*].

## **8.4 Pediatric Use**

The safety and effectiveness of ZOHYDRO ER in pediatric patients below the age of 18 years have not been established.

## **8.5 Geriatric Use**

Clinical studies of ZOHYDRO ER did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients (aged 65 years or older) may have increased sensitivity to hydrocodone. In general, use caution when selecting a dosage for an elderly patient,

usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of the concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of ZOHYDRO ER slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [*see Warnings and Precautions (5.7)*].

Hydrocodone is known to be substantially secreted by the kidney and the risk adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

## **8.6 Hepatic Impairment**

No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function [*see Clinical Pharmacology (12.3)*]. Therefore, a dosage reduction is recommended for patients with severe hepatic impairment [*see Dosage and Administration (2.4)*]. Monitor patients with severe hepatic impairment closely for respiratory depression, sedation, and hypotension [*see Clinical Pharmacology (12.3)*].

## **8.7 Renal Impairment**

Patients with renal impairment have higher plasma concentrations than those with normal function. Use a low initial dose of ZOHYDRO ER in patients with renal impairment and monitor closely for respiratory depression, sedation, and hypotension [*see Clinical Pharmacology (12.3)*].

# **9 DRUG ABUSE AND DEPENDENCE**

## **9.1 Controlled Substance**

ZOHYDRO ER contains hydrocodone bitartrate, a Schedule II controlled substance.

## **9.2 Abuse**

ZOHYDRO ER contains hydrocodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. ZOHYDRO ER can be abused and is subject to misuse, abuse, addiction, and criminal diversion [*see Warnings and Precautions (5.1)*].

The high drug content in extended release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction as use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical

records or contact information for other treating healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers, and people with untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

ZOHYDRO ER, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing, storage, and disposal are appropriate measures that help to limit abuse of opioid drugs.

#### Risks Specific to Abuse of ZOHYDRO ER

ZOHYDRO ER is for oral use only. Abuse of ZOHYDRO ER poses a risk of overdose and death. The risk is increased with concurrent use of ZOHYDRO ER with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved ZOHYDRO ER enhances drug release and increases the risk of overdose and death.

With intravenous abuse, the inactive ingredients in ZOHYDRO ER can result in death, local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis and valvular heart injury, embolism, and death. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

### **9.3 Dependence**

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

ZOHYDRO ER should not be abruptly discontinued [*see Dosage and Administration (2.5)*]. If ZOHYDRO ER is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Use in Specific Populations (8.1)*].

## **10 OVERDOSAGE**

### Clinical Presentation

Acute overdosage with ZOHYDRO ER can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and

death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [see *Clinical Pharmacology (12.2)*].

### Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdosage. For clinically significant respiratory or circulatory depression secondary to hydrocodone overdose, administer an opioid antagonist.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydrocodone overdose.

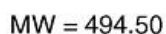
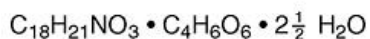
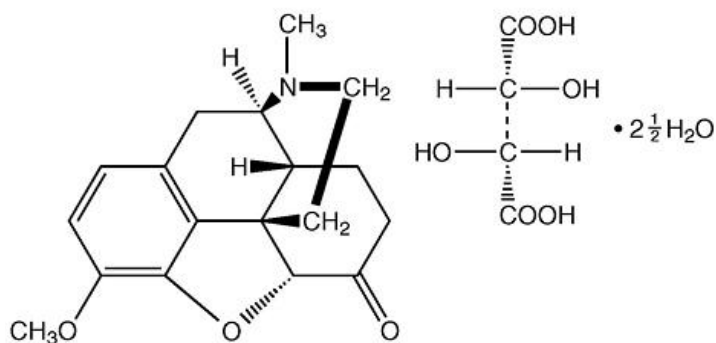
Because the duration of reversal is expected to be less than the duration of action of hydrocodone in ZOHYDRO ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. ZOHYDRO ER will continue to release hydrocodone and add to the hydrocodone load for 24 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

## 11 DESCRIPTION

ZOHYDRO ER (hydrocodone bitartrate) extended-release capsules are hard gelatin capsules for oral administration. Hydrocodone bitartrate is an opioid agonist and occurs as fine, white crystals, or as a crystalline powder.

The chemical name is 4,5(alpha)-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5) or morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 alpha)-, [R (R\*, R\*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5). It has the following structural formula:



Each ZOHYDRO ER capsule contains either 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, or 50 mg of hydrocodone bitartrate and the following inactive ingredients: sugar spheres NF, hypromellose USP, ammonio methacrylate copolymer NF, silicon dioxide NF, talc USP, polyethylene oxide NF, and povidone USP. The capsule shells collectively contain titanium dioxide, FD&C Blue #1, FD&C Red #40, FDA Yellow iron oxide, FD&C Red #3, FDA Black iron oxide, FDA Red iron oxide, and gelatin.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Hydrocodone is a full opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of hydrocodone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with hydrocodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

### 12.2 Pharmacodynamics

#### Effects on the Central Nervous System

Hydrocodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brainstem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Hydrocodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see Overdosage (10)*].

#### Effects on the Gastrointestinal Tract and Other Smooth Muscle

Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in gastric, in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

#### Effects on the Cardiovascular System

Hydrocodone produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

#### Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [*see Adverse Reactions (6.2)*]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [*see Adverse Reactions (6.2)*].

#### Effects on the Immune System

*In vitro* and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

### Concentration—Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or potential development of analgesic tolerance. [see *Dosage and Administration (2.1, 2.3)*].

### Concentration—Adverse Experience Relationships

There is a relationship between increasing hydrocodone plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see *Dosage and Administration (2.1, 2.2, 2.3)*].

## **12.3 Pharmacokinetics**

### Absorption

As compared to immediate-release hydrocodone combination products, ZOHYDRO ER at similar daily doses results in similar overall exposure but with lower maximum concentrations. The half-life is also longer due to the prolonged duration of absorption. Based on the half-life of hydrocodone, steady-state should be obtained after 3 days of dosing. Following 7 days of dosing, AUC and C<sub>max</sub> increase approximately two-fold as compared to the first day of dosing. The pharmacokinetics of ZOHYDRO ER have been shown to be independent of dose up to a dose of 50 mg.

ZOHYDRO ER capsules exhibit peak plasma concentrations approximately 5 hours after dose administration.

### *Food Effects*

Food has no significant effect on the extent of absorption of hydrocodone from ZOHYDRO ER. Although there was no evidence of dose dumping associated with this formulation under fasted and fed conditions, peak plasma concentration of hydrocodone increased by 27% when a ZOHYDRO ER 20 mg capsule was administered with a high-fat meal.

### Distribution

Although the extent of protein binding of hydrocodone in human plasma has not been definitively determined, structural similarities to related opioid analgesics suggest that hydrocodone is not extensively protein bound. As most agents in the 5-ring morphinan group of semi-synthetic opioids bind plasma protein to a similar degree (range 19% [hydromorphone] to 45% [oxycodone]), hydrocodone is expected to fall within this range.

### Elimination

#### *Metabolism*

Hydrocodone exhibits a complex pattern of metabolism, including N-demethylation, O-demethylation, and 6-keto reduction to the corresponding 6- $\alpha$ - and 6- $\beta$ -hydroxy metabolites. CYP3A4 mediated N-demethylation to norhydrocodone is the primary metabolic pathway of hydrocodone with a lower contribution from CYP2D6 mediated O-demethylation to hydromorphone. Hydromorphone is formed from the O-demethylation of hydrocodone and may contribute to the total analgesic effect of hydrocodone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs [see *Drug Interactions (7.3)*]. Published *in vitro* studies have shown that N-demethylation of hydrocodone to form norhydrocodone can be attributed to CYP3A4 while O-demethylation of hydrocodone to hydromorphone is predominantly catalyzed by CYP2D6 and to a lesser extent by an unknown low affinity CYP enzyme.

#### *Excretion*

Hydrocodone and its metabolites are eliminated primarily in the kidneys, with a mean apparent plasma half-life after ZOHYDRO ER administration of approximately 8 hours.

### Special Populations

#### *Age: Geriatric Patients*

No significant pharmacokinetic differences by age were observed based on population pharmacokinetic analysis.

*Sex:* No significant pharmacokinetic differences by sex were observed based on population pharmacokinetic analysis.

#### *Hepatic Impairment*

After a single dose of 20 mg ZOHYDRO ER in 20 patients with mild to moderate hepatic impairment based on Child-Pugh classifications, mean hydrocodone  $C_{max}$  values were  $25 \pm 5$ ,  $24 \pm 5$ , and  $22 \pm 3.3$  ng/mL for moderate and mild impairment, and normal subjects, respectively. Mean hydrocodone AUC values were  $509 \pm 157$ ,  $440 \pm 124$ , and  $391 \pm 74$  ng·h/mL for moderate and mild impairment, and normal subjects, respectively. Hydrocodone  $C_{max}$  values were 8-10% higher in patients with mild or moderate hepatic impairment, respectively, while AUC values were 10% and 26% higher in patients with mild and moderate hepatic impairment, respectively. Severely impaired subjects were not studied [see *Use in Specific Populations (8.6)*].

#### *Renal Impairment*

After a single dose of 20 mg ZOHYDRO ER in 28 patients with mild, moderate, or severe renal impairment based on Cockcroft-Gault criteria, mean hydrocodone  $C_{max}$  values were  $26 \pm 6.0$ ,  $28 \pm 7.5$ ,  $21 \pm 5.1$  and  $19 \pm 4.4$  ng/mL for severe, moderate, mild renal impairment, and normal subjects, respectively. Mean hydrocodone AUC values were  $487 \pm 123$ ,  $547 \pm 184$ ,  $391 \pm 122$  and  $343 \pm 105$  ng·h/mL for severe, moderate, mild renal impairment, and normal subjects, respectively. Hydrocodone  $C_{max}$  values were 15%, 48%, and 41% higher and AUC values were 15%, 57% and 44% higher in patients with mild, moderate, and severe renal impairment, respectively [see *Use in Specific Populations (8.7)*].

#### Drug Interaction Studies

##### *Interactions with Alcohol*

The rate of absorption of ZOHYDRO ER 50 mg was affected by co-administration with 40% alcohol in the fasted state, as exhibited by an increase in peak hydrocodone concentrations (on average 2.4-fold increase with maximum increase of 3.9-fold in one subject) and a decrease in the time to peak concentrations. The extent of absorption was increased on average 1.2-fold with maximum increase of 1.7-fold in one subject with 40% alcohol [see *Warnings and Precautions (5.6)*].

##### *Cytochrome P450 Enzymes*

While comprehensive PK drug-drug interaction studies (other than alcohol) have not been performed in humans receiving hydrocodone, published *in vitro* and human PK studies indicate that conversion of hydrocodone to its primary metabolite, norhydrocodone and lesser metabolite, hydromorphone, is mediated by the cytochrome P450 enzyme system. N-demethylation of hydrocodone to form norhydrocodone is attributed to CYP3A4 and O-demethylation of hydrocodone to hydromorphone is predominantly catalyzed by CYP2D6 and to a lesser extent by an unknown low affinity CYP enzyme.

##### *CYP3A4 Inhibitors and Inducers*

An increase in CYP3A4 activity by initiation of CYP3A4 inhibiting drugs or discontinuation of CYP3A4 inducing drugs could alter the metabolic profile of hydrocodone causing a slowing of hydrocodone clearance, and lead to elevated hydrocodone concentrations and effects, which could be more pronounced with concomitant use of cytochrome P450 CYP3A4 inhibitors. Initiation of a CYP3A4 inducing drug can lower hydrocodone plasma levels and may induce an opioid-withdrawal syndrome [see *Warnings and Precautions (5.5) and Drug Interactions (7)*].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

Hydrocodone was evaluated for carcinogenic potential in rats and mice. In a two-year bioassay in rats, doses up to 30 mg/kg in males and 100 mg/kg in females were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 0.1 times and 0.6 times for males and females, respectively, the human

hydrocodone dose of 100 mg/day based on AUC exposure comparisons). In a two-year bioassay in mice, doses up to 100 mg/kg in males and females were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 0.8 times and 1.5 times, respectively, the human hydrocodone dose of 100 mg/day based on AUC exposure comparisons).

### Mutagenesis

Hydrocodone bitartrate was genotoxic in an *in vitro* chromosomal aberration assay in the presence of metabolic activation. No evidence of clastogenicity was observed in this assay in the absence of metabolic activation. No evidence of DNA damage was found in an *in vivo* comet assay in mouse liver. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay (*Salmonella typhimurium* and *Escherichia coli*) or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).

### Impairment of Fertility

In a fertility study, rats were administered once daily by oral gavage the vehicle or hydrocodone bitartrate at doses of 25, 75, and 100 mg/kg/day (equivalent to approximately 2, 7, and 10 times an adult human dose of 100 mg/day, on a mg/m<sup>2</sup> basis). Male and female rats were dosed before cohabitation (up to 28 days), during the cohabitation and until gestation day 7 (females) or necropsy (males; 2-3 weeks post-cohabitation). Hydrocodone bitartrate did not affect reproductive function in males, although the weights of male reproductive organs were decreased at all doses. Doses of 25 mg/kg/day and greater in females reduced the rate at which females became pregnant which correlated with suppression of estrous cyclicity, thought to be due to increases in prolactin. In hydrocodone bitartrate-treated rats that became pregnant, at 25 mg/kg early embryonic development was unaffected (approximately 2 times the adult human daily dose of 100 mg/day on a mg/m<sup>2</sup> basis). In rats, prolactin plays a unique role in the estrous cycle and the clinical relevance of the female rat reproductive findings is uncertain.

## **14 CLINICAL STUDIES**

The efficacy and safety of ZOXYDRO ER have been evaluated in a randomized double-blind, placebo-controlled, multi-center clinical trial in opioid-experienced subjects with moderate to severe chronic low back pain.

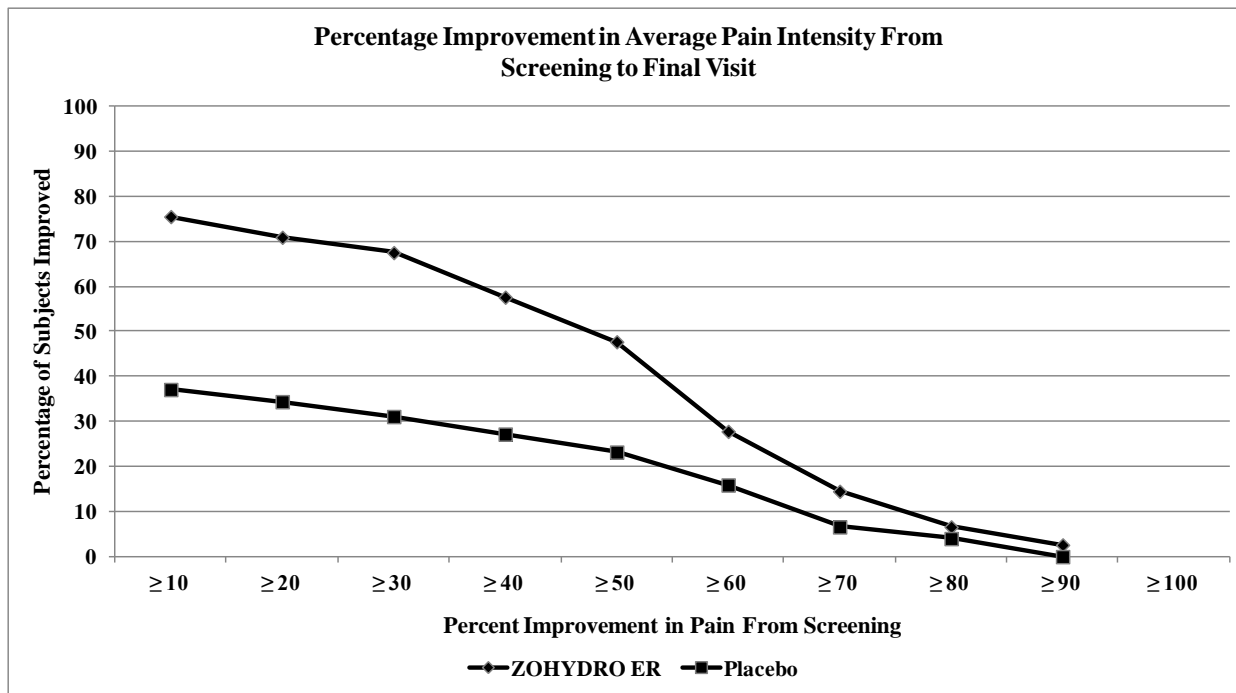
### Placebo-Controlled Study in Opioid-Experienced Subjects with Moderate to Severe Chronic Lower Back Pain

A total of 510 subjects currently on chronic opioid therapy entered an open-label conversion and titration phase (up to 6 weeks) with ZOXYDRO ER dosed every 12 hours at an approximated equianalgesic dose of their pre-study opioid medication. For inadequately controlled pain, ZOXYDRO ER was increased by 10 mg per 12-hour dose, once every 3–7 days until a stabilized dose was identified, or a maximum dosage of 100 mg every 12 hours. There were 302 subjects (59%) randomized at a ratio of 1:1 into a 12-week double-blind treatment phase with their fixed stabilized dose of ZOXYDRO ER (40-200 mg daily taken as 20-100 mg, every 12 hours) or a matching placebo. Subjects randomized to placebo were given a blinded taper of ZOXYDRO ER according to a pre-specified tapering schedule. During the treatment phase, subjects were allowed to use rescue medication (hydrocodone 5 mg/500 mg acetaminophen) up to 2 doses (2 tablets) per day. There were 124 treated subjects (82%) that completed the 12-week treatment with ZOXYDRO ER and 59 subjects (39%) with placebo.

ZOXYDRO ER provided greater analgesia compared to placebo. There was a significant difference in the mean changes from Baseline to Week 12 in average weekly pain intensity Numeric Rating Scale (NRS) scores between the two groups.

The percentage of subjects in each group who demonstrated improvement in their NRS pain score at End-of-Study, as compared to Screening is shown in the figure below. The figure is cumulative, so subjects whose change from Screening is, for example, 30% are also included at every level of improvement below 30%. Subjects who did not complete the study were classified as non-responders. Treatment with ZOXYDRO ER produced a greater number of responders, defined as subjects with at least a 30% improvement, as compared to placebo (67.5% vs. 31.1%).





## 16 HOW SUPPLIED/STORAGE AND HANDLING

ZOHYDRO ER extended-release capsules are supplied in 60-count bottles with a child-resistant closure as follows:

Strength	Capsule Color(s)	Capsule Text	NDC Number
10 mg	White opaque	“Z310 10 mg” in black ink	65224-310-60
15 mg	Light green and white opaque	“Z315 15 mg” in black ink	65224-315-60
20 mg	Light green opaque	“Z320 20 mg” in black ink	65224-320-60
30 mg	Dark blue and white opaque	“Z330 30 mg” in black ink	65224-330-60
40 mg	Dark brown and white opaque	“Z340 40 mg” in black ink	65224-340-60
50 mg	Dark brown opaque	“Z350 50 mg” in black ink	65224-350-60

ZOHYDRO ER contains hydrocodone bitartrate which is a controlled substance and is controlled under Schedule II of the Controlled Substances Act. Hydrocodone, like all opioids, is liable to diversion and misuse and should be handled accordingly. Patients and their families should be instructed to dispose of any ZOHYDRO ER capsules that are no longer needed.

ZOHYDRO ER may be targeted for theft and diversion. Healthcare professionals should contact their State Medical Board, State Board of Pharmacy, or State Control Board for information on how to detect or prevent diversion of this product.

Healthcare professionals should advise patients to store ZOHYDRO ER in a secure place, preferably locked and out of the reach of children and other non-caregivers.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Dispense in tight container as defined in the USP, with a child-resistant closure.

Advise patients to dispose of any unused capsules from a prescription as soon as they are no longer needed in accordance with local State guidelines and/or regulations [see *Patient Counseling Information (17)*].

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA approved patient labeling (Medication Guide).

### Addiction, Abuse, and Misuse

Inform patients that the use of ZOHYDRO ER, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share ZOHYDRO ER with others and to take steps to protect ZOHYDRO ER from theft or misuse.

### Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting ZOHYDRO ER or when the dosage is increased, and that it can occur even at recommended dosages [see *Warnings and Precautions (5.3)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

### Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see *Warnings and Precautions (5.3)*]. Instruct patients to take steps to store ZOHYDRO ER securely and to dispose of unused ZOHYDRO ER by flushing the capsules down the toilet.

### Interaction with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if ZOHYDRO ER is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider. Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter products that contain alcohol, during treatment with ZOHYDRO ER [see *Warnings and Precautions (5.6), Drug Interactions (7)*].

### Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications. [see *Drug Interactions (7)*].

### MAOI Interaction

Inform patients to avoid taking ZOHYDRO ER while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking ZOHYDRO ER [see *Drug Interactions (7)*].

### Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see *Warnings and Precautions (5.8)*].

### Important Administration Instructions [see *Dosage and Administration (2)*]

Instruct patients how to properly take ZOHYDRO ER, including the following:

- Use ZOHYDRO ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) [*see Warnings and Precautions (5.3)*].
- Swallow ZOHYDRO ER capsules whole.
- Do not crush, chew, or dissolve the capsule or its contents.
- Do not discontinue ZOHYDRO ER without first discussing the need for a tapering regimen with the prescriber.

### Hypotension

Inform patients that ZOHYDRO ER may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position [*see Warnings and Precautions (5.9)*]).

### Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in ZOHYDRO ER. Advise patients how to recognize such a reaction and when to seek medical attention [*see Contraindications (4), Adverse Reactions (6)*].

### Pregnancy

#### *Neonatal Opioid Withdrawal Syndrome*

Inform female patients of reproductive potential that prolonged use of ZOHYDRO ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.4), Use in Specific Populations (8.1)*].

#### *Embryo-Fetal Toxicity*

Inform female patients of reproductive potential that ZOHYDRO ER can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

### Lactation

Advise patients that breastfeeding is not recommended during treatment with ZOHYDRO ER [*see Use in Specific Populations (8.2)*].

### Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [*see Adverse Reactions (6.2), Use in Specific Populations (8.3)*].

### Driving or Operating Heavy Machinery

Inform patients that ZOHYDRO ER may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Blood levels of hydrocodone, in some patients, may be high at the end of 24 hours after repeated dose administration. Advise patients not to perform such tasks until they know how they will react to the medication [*see Warnings and Precautions (5.14)*].

### Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention. Instruct patients to monitor their analgesic response following the use of strong laxatives and to contact the prescriber if changes are noted [*see Adverse Reactions (6), Clinical Pharmacology (12.2)*].

### Disposal of Unused ZOHYDRO ER

Advise patients to flush the unused capsules down the toilet when ZOHYDRO ER is no longer needed.

ZOHYDRO<sup>®</sup> ER is a registered trademark of an affiliate of Pernix Therapeutics, LLC.

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