ZOHYDRO- hydrocodone bitartrate capsule, extended release
Zogenix, Inc.

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; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and CYTOCHROME P450 3A4 INTERACTION

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 each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **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. (5.2)**
- **Accidental ingestion of ZOHYDRO ER, especially in children, can result in a fatal overdose of hydrocodone. (5.2)**
- **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 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. (5.3)**
- **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. (5.4)**
- **Initiation of CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone from ZOHYDRO ER. (5.13)**

RECENT MAJOR CHANGES

Boxed Warning	8/2014
Dosage and Administration (2)	1/2015
Warnings and Precautions (5)	8/2014

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

- ZOHYDRO ER 50 mg capsules, 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)
- For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg capsules orally every 12 hours. (2.1)
- To convert to ZOHYDRO ER from another opioid, use available conversion factors to obtain estimated dose. (2.1)
- Dose can be increased every 3 to 7 days, using increments of 10 mg every 12 hours (i.e., 20 mg per day). (2.1, 2.2)
- Do not abruptly discontinue ZOHYDRO ER in a physically dependent patient. (2.3)
- Capsules must be swallowed intact and are not to be cut, broken, chewed, crushed, or dissolved (risk of fatal overdose). (2.1, 5.1)

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 (4)
- Known or suspected paralytic ileus (4)
- Hypersensitivity to hydrocodone bitartrate (4)

WARNINGS AND PRECAUTIONS

See Boxed WARNINGS

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If coadministration is required, consider dose reduction of one or both drugs. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)
- Hypotensive effects: Monitor during dose initiation and titration. (5.7)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of ZOHYDRO ER in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.8)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.13)

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 Zogenix, Inc. at 1-866-ZOGENIX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Mixed agonists/antagonists and partial agonist analgesics: Avoid use with ZOHYDRO ER because they may reduce analgesic effect of ZOHYDRO ER or precipitate withdrawal symptoms. (7.4)
- The use of MAO inhibitors or tricyclic antidepressants with ZOHYDRO ER may increase the effect of either the antidepressant or ZOHYDRO ER. (7.5)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)
- Hepatic impairment: No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment; however, in patients with severe hepatic impairment, start with the lowest dose, 10 mg. Monitor these patients closely for adverse events such as respiratory depression. (8.6)
- Renal impairment: Use a low initial dose of ZOHYDRO ER in patients with renal impairment and monitor closely for adverse events such as respiratory depression. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and CYTOCHROME P450 3A4 INTERACTION

Addiction, Abuse, and Misuse

ZOHYDRO ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ZOHYDRO ER and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

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 (5.2)]*.

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 (5.2)]*.

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 (5.3)]*.

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 (5.4) and Clinical Pharmacology (12.3)]*.

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 (5.13) and Clinical Pharmacology (12.3)]*.

1 INDICATIONS AND USAGE

ZOHYDRO® 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, 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 Initial Dosing

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

ZOHYDRO ER 50 mg capsules, a single dose of ZOHYDRO ER 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. 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, or an equianalgesic dose of another opioid.

Initiate the dosing regimen for each patient individually, taking into account the patient's 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 with ZOHYDRO ER *[see Warnings and Precautions (5.2)]*.

ZOHYDRO ER must be taken 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)]*.

Use of ZOHYDRO ER as the First Opioid Analgesic
Initiate treatment 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. 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, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Conversion from Other Oral Opioids to ZOHYDRO ER
Discontinue all other around-the-clock opioid drugs when ZOHYDRO ER therapy is initiated.

While there are useful tables of opioid equivalents readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products. As such, it is preferable to underestimate a patient’s 24-hour oral hydrocodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral hydrocodone requirements which could result in adverse reactions. 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.

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.

Table 1.
Conversion Factors to ZOHYDRO ER (Not Equianalgesic Doses)

Prior Oral Opioid	Oral Dose (mg)	Approximate Oral Conversion Factor
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 conversion factor to calculate the approximate oral hydrocodone daily dose. The daily dose should then be divided 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.

Always round the dose down, if necessary, to the appropriate ZOHYDRO ER strength(s) available.

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.

2.2 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. 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 dose increase 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 while adjusting the ZOHYDRO ER dose to decrease the level of pain. 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, the subsequent doses may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.3 Discontinuation of ZOHYDRO ER

When a patient no longer requires therapy with ZOHYDRO ER, use a gradual downward titration of the dose every 2 to 4 days to prevent signs and symptoms of withdrawal in the physically-dependent patient. During the Phase 3 study, the following taper schedule was utilized for patients assigned to placebo in the treatment phase of the study (Table 2):

Table 2.
ZOHYDRO ER Taper Schedule Used in Phase 3 Study

Stabilized Dose At Time of Taper Initiation	Taper Schedule
20 mg to 30 mg q12h*	• 10 mg q12h on Days 1 and 2 • Day 3, stop
40 mg to 70 mg q12h	• 40 mg q12h on Days 1 and 2 • 20 mg q12h on Days 3 and 4 • 10 mg q12h on Days 5 and 6 • Day 7, stop
80 mg to 100 mg q12h	• 80 mg q12h on Days 1 and 2 • 60 mg q12h on Days 3 and 4 • 40 mg q12h on Days 5 and 6 • 20 mg q12h on Days 7 and 8 • 10 mg q12h on Days 9 and 10 • Day 11, stop

*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. Do not abruptly discontinue ZOHYDRO ER.

2.4 Administration of ZOHYDRO ER

Instruct patients to swallow ZOHYDRO ER capsules whole. The beads in the capsules are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of hydrocodone *[see Warnings and Precautions (5.1)]*.

2.5 Hepatic Impairment

Patients with hepatic impairment may have higher plasma concentrations of hydrocodone than those with normal function. No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment. However, in patients with severe hepatic impairment, start with the lowest dose, 10 mg every 12 hours. Monitor these patients closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

2.6 Renal Impairment

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

3 DOSAGE FORMS AND STRENGTHS

ZOHYDRO ER (hydrocodone) extended-release capsules are available in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg hard gelatin capsules for oral administration, containing white to off-white beads, roughly spherical in shape, and uniform in appearance.

4 CONTRAINDICATIONS

ZOHYDRO ER is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (e.g., anaphylaxis) to hydrocodone bitartrate or any other ingredients in ZOHYDRO ER

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

ZOHYDRO ER contains hydrocodone, a Schedule II controlled substance. As an opioid, ZOHYDRO ER exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*. As modified-release products such as ZOHYDRO ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ZOHYDRO ER and in those who obtain the drug illicitly. 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 ZOHYDRO ER, and monitor all patients receiving ZOHYDRO ER for the development of these behaviors or 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 ZOHYDRO ER for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations 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 Overdosage (10)]*.

Opioid agonists such as ZOHYDRO ER 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 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, 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_2) 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 dose increase. Closely monitor patients for respiratory depression when initiating therapy with ZOHYDRO ER and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of ZOHYDRO ER are essential *[see Dosage and Administration (2)]*. 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.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of ZOHYDRO ER during pregnancy can result in withdrawal signs 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. 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. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.4 Interactions with Central Nervous System Depressants

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)]*.

Hypotension, profound sedation, coma, respiratory depression, and death may result if ZOHYDRO ER is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of ZOHYDRO ER in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin ZOHYDRO ER is made, start with a lower ZOHYDRO ER dose than usual (i.e., 20%-30% less), monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.2)]*.

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating ZOHYDRO ER and when ZOHYDRO ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*.

5.6 Use in Patients with Chronic Pulmonary Disease

Monitor for respiratory depression in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression, particularly when initiating therapy and titrating with ZOHYDRO ER, as in these patients, even usual therapeutic doses of ZOHYDRO ER may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.7 Hypotensive Effect

ZOHYDRO ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Monitor these patients for signs of hypotension after initiating or titrating the dose 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.

5.8 Use in Patients with Head Injury and Increased Intracranial Pressure

Monitor patients taking ZOHYDRO ER who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with ZOHYDRO ER. ZOHYDRO ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. 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.

5.9 Use in Patients with Gastrointestinal Conditions

ZOHYDRO ER is contraindicated in patients with known or suspected paralytic ileus. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Monitor for

decreased bowel motility in post-operative patients receiving opioids. The administration of ZOHYDRO ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Hydrocodone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis.

5.10 Use in Patients with Convulsive or Seizure Disorders

The hydrocodone in ZOHYDRO ER may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during ZOHYDRO ER therapy.

5.11 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received, or are receiving, a course of therapy with a full opioid agonist analgesic, including ZOHYDRO ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms *[see Drug Interactions (7.4)*]

5.12 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.

5.13 Cytochrome P450 CYP3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of ZOHYDRO ER, drugs that alter CYP3A4 activity may cause changes in clearance of hydrocodone which could lead to changes in hydrocodone plasma concentrations.

Inhibition of CYP3A4 activity by its inhibitors 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 effects.

CYP3A4 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of hydrocodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to hydrocodone.

If co-administration is necessary, monitor patients closely who are currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

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 (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Hypotensive Effect *[see Warnings and Precautions (5.7)]*
- Gastrointestinal Conditions *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*

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.

Table 3. Treatment-Emergent Adverse Events in ≥2% 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)

	Open-Label Titration Period	**Double-Blind Treatment Period**	
	ZOHYDRO ER	**ZOHYDRO ER**	**Placebo**
Preferred Term	**(N = 510)**	**(n = 151)**	**(n = 151)**
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** (≥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

7 DRUG INTERACTIONS

7.1 Alcohol

Concomitant use of alcohol with ZOHYDRO ER can result in an increase of hydrocodone plasma levels and potentially fatal overdose of hydrocodone. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on ZOHYDRO ER therapy *[see Clinical Pharmacology (12.3)]*.

7.2 CNS Depressants

The concomitant use of ZOHYDRO ER with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol, can increase the risk of respiratory depression, profound sedation, coma, or death. Monitor patients receiving CNS depressants and ZOHYDRO ER for signs of respiratory depression, sedation, and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*.

7.3 Drugs Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4 and 2D6
Because the CYP3A4 isoenzyme plays a major role in the metabolism of hydrocodone, drugs that inhibit CYP3A4 activity may cause decreased clearance of hydrocodone which could lead to an increase in hydrocodone plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of CYP2D6 and 3A4 inhibitors. If co-administration with ZOHYDRO ER is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP3A4
Cytochrome P450 3A4 inducers may induce the metabolism of hydrocodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration with ZOHYDRO ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

After stopping the treatment of a CYP3A4 inducer, as the effects of the inducer decline, the hydrocodone plasma concentration will increase which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression *[see Clinical Pharmacology (12.3)]*.

7.4 Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of hydrocodone or precipitate withdrawal symptoms. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving ZOHYDRO ER.

7.5 Monoamine Oxidase Inhibitors

The effects of opioid analgesics may be potentiated by monoamine oxidase (MAO) inhibitors. ZOHYDRO ER is not recommended for use in patients who have received MAO inhibitors within 14 days as severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between hydrocodone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

7.6 Anticholinergics

Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid

analgesics may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation in addition to respiratory and central nervous system depression when ZOHYDRO ER is used concurrently 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 (5.3)]*. There are no studies of ZOHYDRO ER use in pregnant women. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. 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.

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 (5.3)]*.

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^2 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^2 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^2 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^2 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^2 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

Infants exposed to ZOHYDRO ER through breast milk should be monitored 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

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 (13.1)]*.

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. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, 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.

Hydrocodone is known to be substantially secreted by the kidney. Thus the risk of toxic reactions may be greater in patients with impaired renal function due to the accumulation of the parent compound and/or metabolites in the plasma. 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.

Hydrocodone may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of hydrocodone bitartrate and observed closely for adverse events such as respiratory depression.

8.6 Hepatic Impairment

Patients with hepatic impairment may have higher plasma concentrations than those with normal function. No adjustment in starting dose with ZOHYDRO ER is required in patients with mild or moderate hepatic impairment; however, in patients with severe hepatic impairment, start with the lowest dose, 10 mg. Monitor these patients closely for adverse events such as respiratory depression *[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 adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ZOHYDRO ER contains hydrocodone bitartrate, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. The high drug content in the extended-release formulation adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse

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.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high,” or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: 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 to addicts and drug abusers. Drug seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers, people with untreated addiction, and criminals seeking drugs to sell. 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. Physicians 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 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, and increased risk of endocarditis and valvular heart injury. 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 dose 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 (pentazocine, butorphanol, nalbuphine), or partial agonists (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 (2.3)]*. If ZOHYDRO ER is abruptly discontinued in a physically-dependent patient, an abstinence 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 symptoms *[see Use in Specific Populations (8.1, 8.2, 8.3)]*.

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, sometimes, pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose

In case of overdose, priorities are the re-establishment 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 overdose. Opioid antagonists should not be administered in the absence of

clinically significant respiratory or circulatory depression secondary to hydrocodone overdose. Such agents should be administered cautiously to persons who are known, or suspected to be, physically dependent on ZOHYDRO ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

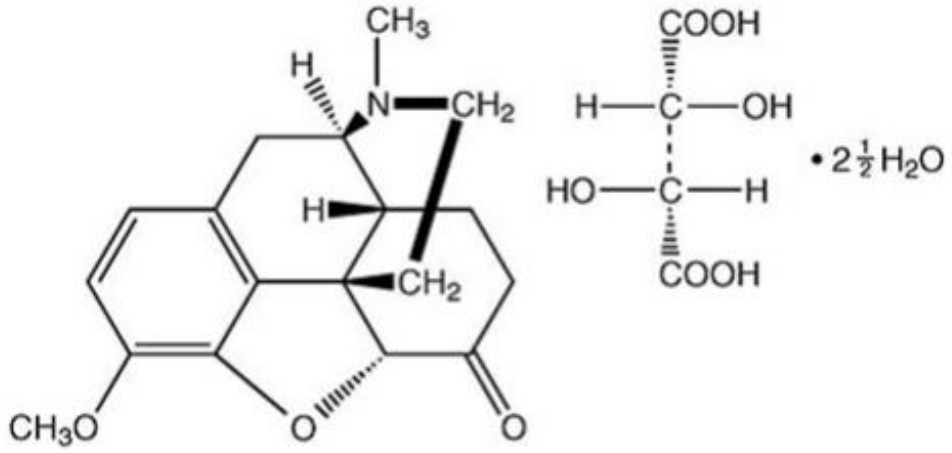
Because the duration of reversal would be expected to be less than the duration of action of ZOHYDRO ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. ZOHYDRO ER will continue to release hydrocodone and add to the hydrocodone load for 24 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be administered as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of the usual 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 begin 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:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}\ H_2O$ MW = 494.50

Each ZOHYDRO ER capsule contains either 10, 15, 20, 30, 40, or 50 mg of hydrocodone bitartrate USP 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 semi-synthetic opioid agonist with relative selectivity for the mu-opioid (μ) receptor, although it can interact with other opioid receptors at higher doses. Hydrocodone acts as a full agonist, binding to and activating opioid receptors at sites in the peri-aquaductal and peri-ventricular gray matter, the ventro-medial medulla and the spinal cord to produce analgesia. The analgesia, as well as the euphoriant, respiratory depressant and physiologic dependence properties of μ agonist opioids like hydrocodone, result principally from agonist action at the μ receptors.

12.2 Pharmacodynamics

Effects on the Central Nervous System
The principal therapeutic action of hydrocodone is analgesia. In common with other opioids, hydrocodone causes respiratory depression, in part by a direct effect on the brainstem 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. Opioids depress the cough reflex by direct effect on the cough center in the medulla.

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)]*. In addition to analgesia, the widely diverse effects of hydrocodone include drowsiness, changes in mood, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system *[see Clinical Pharmacology (12.1)]*.

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 may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Hydrocodone may produce release of histamine with or without associated peripheral vasodilation. 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 may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may manifest from these hormonal changes.

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.

Concentration—Efficacy Relationships
The minimum effective plasma concentration of hydrocodone for analgesia varies widely among patients, especially among patients who have been previously treated with agonist opioids. As a result, individually titrate patients to achieve a balance between therapeutic and adverse effects. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, progression of disease, development of a new pain syndrome and/or potential development of analgesic tolerance.

Concentration—Adverse Experience Relationships

There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.

The dose of ZOHYDRO ER must be individualized *[see Dosage and Administration (2.1)]*. The effective analgesic dose for some patients will be too high to be tolerated by other patients.

12.3 Pharmacokinetics

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_{max} 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.

Absorption
ZOHYDRO ER capsules exhibit peak plasma concentrations occurring 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.

Metabolism
Hydrocodone exhibits a complex pattern of metabolism, including N-demethylation, O-demethylation, and 6-keto reduction to the corresponding 6-α-and 6-β-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.

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 (5.4)]*.

Special Populations
Elderly (≥ 65 years)
No significant pharmacokinetic differences by age were observed based on population pharmacokinetic

analysis.

Gender
No significant pharmacokinetic differences by gender 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 ± 5, 24 ± 5, and 22 ± 3.3 ng/mL for moderate and mild impairment, and normal subjects, respectively. Mean hydrocodone AUC values were 509 ± 157, 440 ± 124, and 391 ± 74 ng•h/mL for moderate and mild impairment, and normal subjects, respectively. Hydrocodone C_{max} values were 8-10% higher in patients with hepatic impairment 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 ± 6.0, 28 ± 7.5, 21 ± 5.1 and 19 ± 4.4 ng/mL for severe, moderate, mild renal impairment, and normal subjects, respectively. Mean hydrocodone AUC values were 487 ± 123, 547 ± 184, 391 ± 122 and 343 ± 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-Drug Interactions
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 (5.13) and Drug Interactions (7.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term animal studies to evaluate the carcinogenic potential of hydrocodone have not been conducted.

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^2 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^2 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

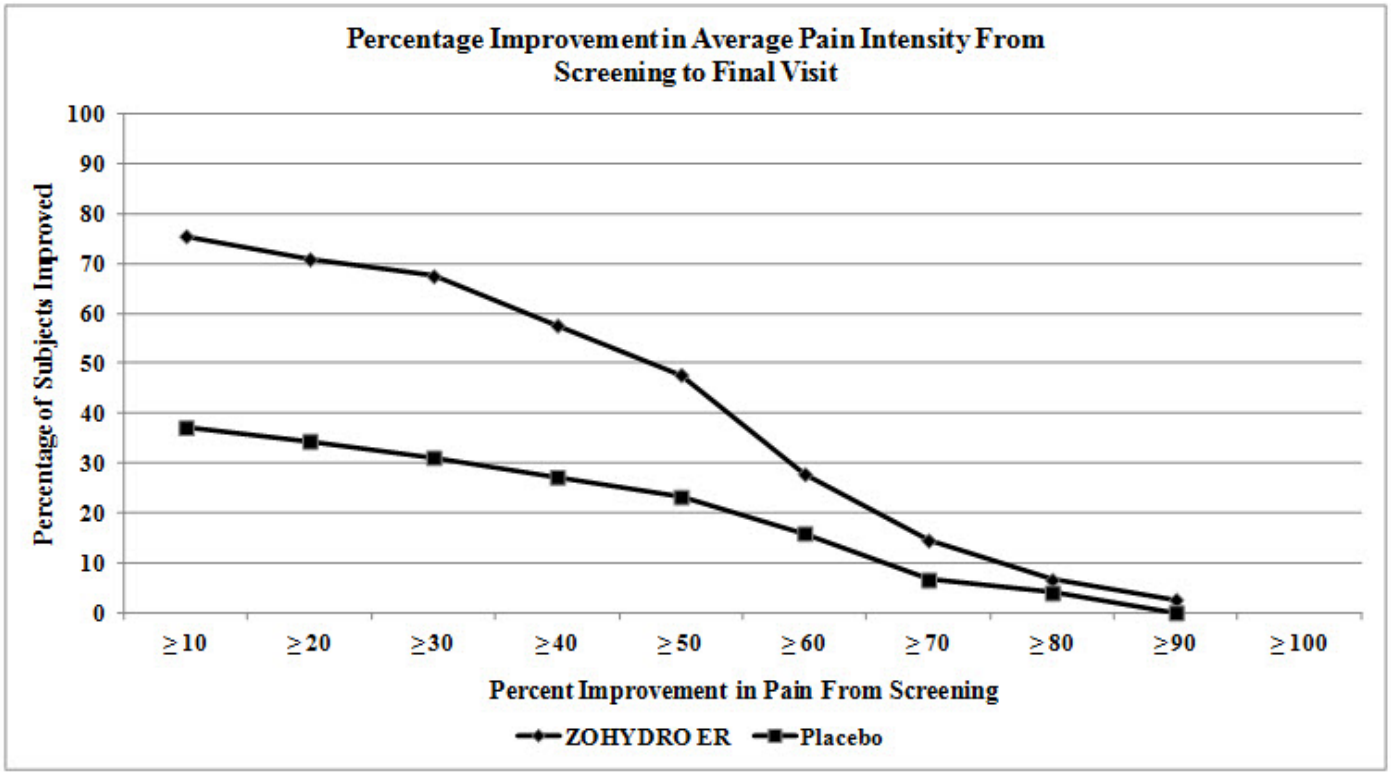
The efficacy and safety of ZOHYDRO ER have been evaluated in a randomized double-blind, placebo-controlled, multi-center clinical trial in opioid-experienced subjects with moderate to severe chronic low back pain.

14.1 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 ZOHYDRO ER dosed every 12 hours at an approximated equianalgesic dose of their pre-study opioid medication. For inadequately controlled pain, ZOHYDRO 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 ZOHYDRO 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 ZOHYDRO 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 ZOHYDRO ER and 59 subjects (39%) with placebo.

ZOHYDRO 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 ZOHYDRO 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	"ZGNX 10 mg" in black ink	43376-310-60
15 mg	Light green and white opaque	"ZGNX 15 mg" in black ink	43376-315-60
20 mg	Light green opaque	"ZGNX 20 mg" in black ink	43376-320-60
30 mg	Dark blue and white opaque	"ZGNX 30 mg" in black ink	43376-330-60
40 mg	Dark brown and white opaque	"ZGNX 40 mg" in black ink	43376-340-60
50 mg	Dark brown opaque	"ZGNX 50 mg" in black ink	43376-350-60

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

See FDA-approved patient labeling (Medication Guide).

17.1 Information for Patients and Caregivers

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 dose is increased, and that it can occur even at recommended doses *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Ingestion
Inform patients that accidental ingestion, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store ZOHYDRO ER securely and to dispose of unused ZOHYDRO ER by flushing the capsules down the toilet.

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 (5.3)]*.

Interaction with Alcohol and other CNS Depressants
Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter products that contain alcohol, during treatment with ZOHYDRO ER. The co-ingestion of alcohol with ZOHYDRO ER may result in increased plasma levels and a potentially fatal overdose of hydrocodone.

Inform patients that potentially serious additive effects may occur if ZOHYDRO ER is used with alcohol or other CNS depressants and not to use such drugs unless supervised by a healthcare provider.

Important Administration Instructions

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

- Swallow ZOHYDRO ER capsules whole.
- Do not crush, chew, or dissolve the capsule or its contents.
- Use ZOHYDRO ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression).
- 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).

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. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

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.

Pregnancy
Advise female patients that ZOHYDRO ER can cause fetal harm and neonatal opioid withdrawal syndrome and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.3) and 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)]*.

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

ZOHYDRO® ER is a registered trademark of Zogenix®, Inc.

Manufactured for Zogenix®, Inc., San Diego, CA 92130 by Alkermes Gainesville LLC under license from Alkermes Pharma Ireland Limited (APIL), Ireland.

U.S. Patent Nos.: US 6,228,398 and US 6,902,742

Medication Guide
ZOHYDRO® ER (zoh-hye-droh)
(hydrocodone bitartrate) extended-release capsules, CII

ZOHYDRO ER is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to treat pain severe enough to require daily, around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed, you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about ZOHYDRO ER:

- **Get emergency help right away if you take too much ZOHYDRO ER (overdose).** When you first start taking ZOHYDRO ER, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Never give anyone else your ZOHYDRO ER. They could die from taking it. Store ZOHYDRO ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away ZOHYDRO ER is against the law.

Do not take ZOHYDRO ER if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or narrowing of the stomach or intestines.

Before taking ZOHYDRO ER, tell your healthcare provider if you have a history of:

• head injury, seizures • liver, kidney, thyroid problems
• problems urinating • pancreas or gallbladder problems
• abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of ZOHYDRO ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended; may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking ZOHYDRO ER with certain other medicines can cause serious side effects that could lead to death.

When taking ZOHYDRO ER:

- Do not change your dose. Take ZOHYDRO ER exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 12 hours, at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.
- Swallow ZOHYDRO ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject ZOHYDRO ER because this may cause you to overdose and die.

Call your healthcare provider if the dose you are taking does not control your pain.

- **Do not stop taking ZOHYDRO ER without talking to your healthcare provider**.
- After you stop taking ZOHYDRO ER, flush any unused capsules down the toilet.

While taking ZOHYDRO ER DO NOT:

- Drive or operate heavy machinery, until you know how ZOHYDRO ER affects you. ZOHYDRO ER can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with ZOHYDRO ER may cause you to overdose and die.

The possible side effects of ZOHYDRO ER are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when you are changing positions, or you are feeling faint.

These are not all the possible side effects of ZOHYDRO ER. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

ZOHYDRO ER is a registered trademark of Zogenix, Inc. Manufactured by: Alkermes Gainesville LLC, Gainesville, GA.. Distributed by: Zogenix, Inc., San Diego, CA 92130, www.ZohydroER.com, 1-866-ZOGENIX (1-866-964-3649).

This Medication Guide has been approved by the U.S. Food and Drug Administration Issue: February 2015

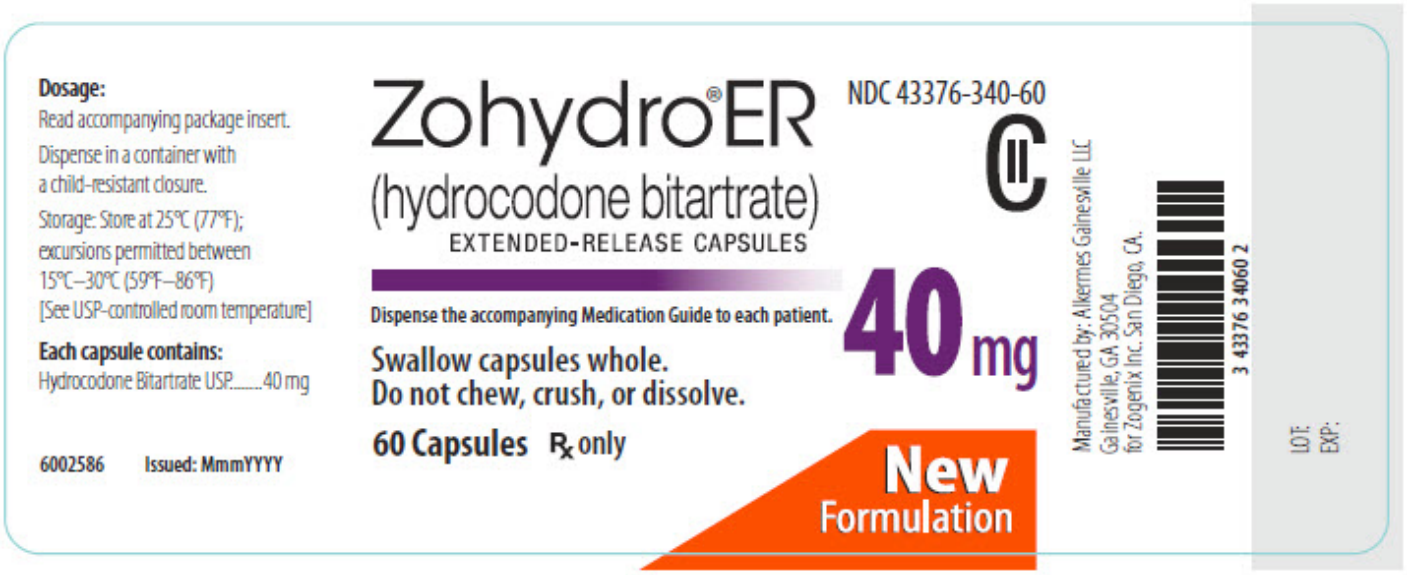
Principal Display Panel
NDC 43376-310-60
Zohydro ER
(hydrocodone bitartrate)
Extended-Release Capsules
10 mg
60 Capsules
Rx Only

Principal Display Panel
NDC 43376-315-60
Zohydro ER
(hydrocodone bitartrate)
Extended-Release Capsules
15 mg
60 Capsules
Rx Only

Principal Display Panel
NDC 43376-320-60
Zohydro ER
(hydrocodone bitartrate)
Extended-Release Capsules
20 mg
60 Capsules
Rx Only

Principal Display Panel
NDC 43376-330-60
Zohydro ER
(hydrocodone bitartrate)
Extended-Release Capsules
30 mg
60 Capsules
Rx Only

Principal Display Panel
NDC 43376-340-60
Zohydro ER
(hydrocodone bitartrate)
Extended-Release Capsules
40 mg
60 Capsules
Rx Only



Principal Display Panel
NDC 43376-350-60
Zohydro ER
(hydrocodone bitartrate)
Extended-Release Capsules
50 mg
60 Capsules
Rx Only

ZOHYDRO

hydrocodone bitartrate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43376-310
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII:6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	10 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SUCROSE (UNII: C151H8M554)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161H3B14U2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
POVIDONES (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics			
Color	WHITE (white opaque)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	ZGNX;10mg
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:43376-310-60	60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202880	10/25/2013	

ZOHYDRO

hydrocodone bitartrate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43376-315
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII:6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	15 mg

Inactive Ingredients

Ingredient Name	Strength
SUCROSE (UNII: C151H8M554)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161H3B14U2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
POVIDONES (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics

Color	GREEN (light green) , WHITE (white opaque)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	ZGNX;15mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:43376-315-60	60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202880	10/25/2013	

ZOHYDRO

hydrocodone bitartrate capsule, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43376-320
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII:6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	20 mg

Inactive Ingredients

Ingredient Name	Strength
SUCROSE (UNII: C151H8M554)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161H3B14U2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
POVIDONES (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics

Color	GREEN (light green opaque)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	ZGNX;20mg
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43376-320-60	60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202880	10/25/2013	

ZOHYDRO

hydrocodone bitartrate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43376-330
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII:6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	30 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SUCROSE (UNII: C151H8M554)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161H3B14U2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
POVIDONES (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics			
Color	BLUE (dark blue) , WHITE (white opaque)	**Score**	no score
Shape	CAPSULE	**Size**	16mm

Flavor		**Imprint Code**	ZGNX;30mg
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:43376-330-60	60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202880	10/25/2013	

ZOHYDRO

hydrocodone bitartrate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43376-340
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII:6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	40 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SUCROSE (UNII: C151H8M554)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161H3B14U2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
POVIDONES (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics			
Color	BROWN (dark brown) , WHITE (white opaque)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	ZGNX;40mg
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:43376-340-60	60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202880	10/25/2013	

ZOHYDRO

hydrocodone bitartrate capsule, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:43376-350
Route of Administration	ORAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HYDROCODONE BITARTRATE (UNII: NO70W886KK) (HYDROCODONE - UNII:6YKS4Y3WQ7)	HYDROCODONE BITARTRATE	50 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SUCROSE (UNII: C151H8M554)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
AMMONIO METHACRYLATE COPOLYMER TYPE B (UNII: 161H3B14U2)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
TALC (UNII: 7SEV7J4R1U)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
POVIDONES (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

GELATIN (UNII: 2G86QN327L)	

Product Characteristics			
Color	BROWN (dark brown opaque)	**Score**	no score
Shape	CAPSULE	**Size**	18mm
Flavor		**Imprint Code**	ZGNX;50mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43376-350-60	60 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202880	10/25/2013	

Labeler - Zogenix, Inc. (867785441)

Establishment

Name	Address	ID/FEI	Business Operations
Alkermes Gainesville, LLC.		057585150	MANUFACTURE(43376-310, 43376-315, 43376-320, 43376-330, 43376-340, 43376-350)

Revised: 2/2015 Zogenix, Inc.