



## New Drug Update

<b>Drug Name:</b>	hydrocodone bitartrate
<b>Trade Name (Manufacturer):</b>	Zohydro ER™ (Zogenix, Inc.)
<b>Form:</b>	Extended-Release Capsule
<b>Strength:</b>	10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
<b>FDA Approval:</b>	October 25, 2013
<b>Market Availability:</b>	Available
<b>FDA Approval Classification:</b>	Standard
<b>Classification:</b>	Specific Therapeutic Class (HIC3): Analgesics, Narcotic Long-Acting (H3A)

### INDICATION<sup>1</sup>

Hydrocodone bitartrate extended-release (Zohydro ER) capsule is a C-II medication indicated for the management of severe pain requiring daily, around-the-clock, long-term opioid treatment in cases where alternative treatment options have proven inadequate.

Due to the significant risk of addiction, abuse, and misuse of this medication as with other opioids, even at recommended doses, hydrocodone bitartrate should be limited in use to patients who have failed alternate pain therapy. Since there exists a greater risk of overdose and death with extended-release opioid formulations, hydrocodone bitartrate ER should only be considered for use in patients for whom non-opioid analgesics or immediate-release opioids have been demonstrated to be ineffective, intolerable, or would otherwise provide inadequate pain management. Hydrocodone bitartrate is not indicated to be used for as needed pain relief.

### CONTRAINDICATIONS/WARNINGS

Hydrocodone bitartrate ER, (Zohydro ER), carries a black box warning covering the potential for addiction, abuse, and diversion; potential life-threatening complications of respiratory depression; accidental exposure to the drug; neonatal opioid withdrawal syndrome; and dangerous interactions, if used with alcohol.

As with other hydrocodone products, this Schedule II controlled substance may expose users to the risks of addiction, abuse, and misuse. The extended-release design of the drug also creates a greater risk for overdose and death due to the larger amount of hydrocodone present. While the potential risk of addiction in any individual is unknown, it may occur when hydrocodone bitartrate is appropriately prescribed at recommended doses and if the drug is misused or abused. It may also occur if the drug is misused or obtained through illicit means.

Patients should be assessed, as well as given intensive counseling regarding the risks and proper use of hydrocodone bitartrate, along with routine monitoring for signs of addiction, abuse, and misuse.

Hydrocodone bitartrate is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma, and hypercarbia. Serious and potential fatal cases of respiratory depression have been reported with the use of extended-release opioids, even when used at recommended dosages and strengths. Precautions, including close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status, may be required for the management of respiratory depression. While serious or fatal respiratory depression may occur at any time during therapy, the risk is greatest during the initiation of therapy or following a dose increase. Certain patients including those who are cachectic, debilitated, or elderly are more likely to experience instances of life threatening respiratory depression in comparison to younger and healthier patients. At risk patients should be monitored closer when starting or adjusting hydrocodone bitartrate, as well as when administered with other medications affecting respiratory status. Similarly, extreme caution should be exercised when considering the use of hydrocodone bitartrate in patients with significant chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression, as even normal therapeutic doses may decrease respiratory drive and apnea. Strong consideration should be given for the use of alternative non-opioid analgesics in these patients, if possible.

The accidental consumption of even one dose of hydrocodone bitartrate, particularly by children, may result in a case of respiratory depression leading to potential death due to overdose of hydrocodone.

Prolonged maternal use of hydrocodone bitartrate during pregnancy may result in neonatal opioid withdrawal syndrome requiring treatment. Unlike opioid withdrawal symptoms in adults, neonatal withdrawal may be life threatening and require immediate, specialized therapy.

Consumption of alcoholic beverages or products containing alcohol, whether prescription medications or not, during hydrocodone bitartrate therapy may result in increased plasma hydrocodone levels and a potentially fatal overdose.

Concomitant use of hydrocodone bitartrate with alcohol or other central nervous system depressants may trigger hypotension, profound sedation, coma, respiratory depression, and death. Should it be determined that use of hydrocodone bitartrate is necessary in a patient taking a CNS depressant, the physician should assess the duration of use of the depressant, as well as the degree of any tolerance that has developed. If therapy is indicated, it should be initiated with a lower dose than usual (approximately 20 to 30 percent of the normal dose). Patients should be monitored for symptoms of unusual sedation or respiratory depression. Consideration should also be given to use of a lower dose of the concomitant CNS depressant, as well.

Use of hydrocodone bitartrate should be avoided in patients with impaired consciousness or who are in a coma. Caution should be exercised and close monitoring instituted when using hydrocodone bitartrate in the presence of head injury, intracranial lesions, or a preexisting increase in intracranial pressure, as the possibility of respiratory depression and elevated cerebrospinal fluid pressure may be greatly increased. Administration of hydrocodone bitartrate in such cases may mask neurologic signs and the clinical course of a patient with a head injury.

Hydrocodone bitartrate has the potential to cause severe hypotension, including orthostatic hypotension and syncope, in ambulatory patients. Individuals with decreased blood volume or

currently using medications, such as phenothiazines, that reduce vasomotor tone may be at an increased risk and require careful monitoring for signs of hypotension. The use of hydrocodone bitartrate in patients with circulatory shock should be avoided.

Caution should be used when giving hydrocodone bitartrate with drugs that alter CYP3A4 activity as inhibitors may affect hydrocodone clearance leading to variances in hydrocodone plasma concentrations and potentially increased or prolonged opioid effects. In a similar manner, use with CYP3A4 inducers may decrease hydrocodone plasma concentrations resulting in decreased opioid effect. In either case, patients should be regularly monitored and evaluated to ensure optimal drug effect.

The use of mixed agonist/antagonist analgesics (e.g., pentazocine, nalbuphine, and butorphanol) in patients receiving hydrocodone bitartrate should be avoided as concomitant use may reduce the analgesic effect and/or precipitate withdrawal symptoms.

Hydrocodone bitartrate is contraindicated in patients having, or suspected of having, paralytic ileus as the drug diminishes propulsive peristaltic waves. Additionally, this drug may obscure the diagnosis or disease course for patients with acute abdominal condition. Caution should be used in patients with biliary tract disease as hydrocodone bitartrate may decrease biliary or pancreatic secretions.

Hydrocodone bitartrate is contraindicated in patients with a known hypersensitivity to hydrocodone or other components of the medication. Caution must be exercised in the performance of hazardous tasks and driving as hydrocodone bitartrate has the ability to impair mental and physical abilities.

## **DRUG INTERACTIONS**

As previously noted, concomitant use of alcohol with hydrocodone bitartrate could result in a potentially fatal overdose of hydrocodone. Patients must be counseled not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on hydrocodone bitartrate therapy.

Hydrocodone bitartrate levels may be increased or decreased when given with other medications that inhibit or induce CYP3A4 activity. If co-administration of hydrocodone bitartrate becomes necessary, monitor for signs of opioid withdrawal and make dose adjustments until stable clinical effects are achieved.

As seen in the adverse reactions/contraindications section, concomitant use of hydrocodone bitartrate with other CNS depressants, including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol, may increase the risk of respiratory depression, profound sedation, coma, and death. Close monitoring of patients receiving CNS depressants and hydrocodone bitartrate should be exercised along with strong consideration for the reduction in dosage of one or both agents.

Mixed agonist/antagonist analgesics including pentazocine, nalbuphine, butorphanol, and buprenorphine may reduce the analgesic effect of hydrocodone bitartrate and/or precipitate withdrawal symptoms. Concurrent use of mixed agonist/antagonist analgesics in patients receiving or intended to receive hydrocodone bitartrate should be avoided.

Use of hydrocodone bitartrate is not recommended in patients who have received MAO inhibitors within 14 days of the initiation of therapy due to severe and unpredictable potentiation by MAO inhibitors.

Anticholinergics or drugs demonstrating anticholinergic activity may increase the risk of urinary retention or severe constipation possibly leading to paralytic ileus when used in patients receiving or due to receive hydrocodone bitartrate therapy. Patients should be monitored for any signs of urinary retention, constipation, along with respiratory and central nervous system depression.

## **COMMON ADVERSE EFFECTS**

Clinical trials are conducted under widely varying conditions, and observed adverse reaction rates often cannot be directly compared to rates observed in clinical practice. Serious adverse reactions associated with the use of hydrocodone bitartrate and previously noted include may include: respiratory depression, central nervous system depression, and misuse/abuse.

The following adverse reactions noted in hydrocodone bitartrate treated patients with an incidence greater than or equivalent to two percent during clinical trials: constipation (eight percent), nausea (seven percent), vomiting (five percent), urinary tract infection (five percent), back pain (four percent), abdominal pain (three percent), peripheral edema (three percent), upper respiratory tract infection (three percent), muscle spasms (three percent), tremor (three percent), and dizziness (two percent).

## **SPECIAL POPULATIONS**

### **Pregnancy**

Hydrocodone bitartrate is listed as Pregnancy Category C.

### **Pediatrics**

Safety and effectiveness of hydrocodone bitartrate in pediatric patients under 18 years of age have not been established.

### **Geriatrics**

Clinical studies did not include adequate numbers of patients 65 years of age or greater to determine if differences exist in clinical response compared to younger patients. Patients aged 65 years or older may demonstrate an increased response to hydrocodone bitartrate therapy. Caution should be exercised when selecting a dose for an elderly patient, commonly starting at the low end of the dosing range, to reflect the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease, and possible use of other drug therapies.

### **Renal Impairment**

Patients with renal impairment may exhibit higher plasma concentrations of hydrocodone bitartrate than subjects with normal renal function. A conservative approach to dosing in patients with renal impairment should be observed utilizing a low initial dose of hydrocodone bitartrate in these patients. Monitor patients closely and adjust the dose based on the clinical response.

### **Hepatic Impairment**

Since hydrocodone bitartrate is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. A conservative approach should be employed when initiating dosing in patients with hepatic impairment. No dosage alteration is required in mild to moderate hepatic

impairment, while patients with severe hepatic impairment should begin therapy at the lowest dose. Patients should be monitored closely and adjusted based on the clinical response.

## Dosages

As with all opioid analgesics, hydrocodone bitartrate should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

The dosing requirements for each patient must be individually evaluated and consider the patient's prior analgesic treatment experience, in addition to the risk factors for addiction, abuse, and misuse. Patients should be monitored closely within the initial 24 to 72 hours following initiation of treatment for respiratory depression.

Hydrocodone bitartrate capsules are to be swallowed whole, one capsule at a time. Capsules must not be crushed, chewed, or allowed to dissolve, as this may result in uncontrolled release of hydrocodone and lead to overdose or death.

The initial dose for patients who are not opioid tolerant is 10 mg orally every 12 hours. Patients who are confirmed to be opioid tolerant are considered those who have received 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 for a period of at least one week.

Single doses of hydrocodone bitartrate greater than 40 mg or total daily dosage greater than 80 mg are to be reserved for patients in whom tolerance to an opioid of comparable potency has been well established. The use of higher doses in patients not confirmed to have opioid tolerant may result in fatal respiratory depression.

Dosage for hydrocodone bitartrate should be titrated to levels that provide adequate analgesic effect, as well as minimize adverse reactions. Patients should be routinely and periodically re-evaluated to assess the maintenance of pain control and the relative incidence of adverse reactions. These evaluations should also monitor and review development of any indications of addiction, abuse, or misuse.

Doses of hydrocodone bitartrate may be increased in increments of 10 mg every 12 hours every three to seven days, as needed, to achieve adequate analgesia.

Patients experiencing episodes of breakthrough pain may require a dosage increase of hydrocodone bitartrate or the addition of an appropriate dose of an immediate-release analgesic. If the reported level of pain increases following titration guidelines, identification of the source of the increased pain should be made prior to considering an increase in the hydrocodone bitartrate dose.

If unacceptable adverse reactions are observed, adjustments to the hydrocodone bitartrate dose may be made to achieve a balance between pain management and adverse reactions.

Hydrocodone bitartrate therapy should not be abruptly stopped. If determined that hydrocodone bitartrate therapy is no longer required, a gradual reduction of the dose every two to four days should be undertaken to prevent any signs and symptoms of withdrawal in patients.

## CLINICAL TRIALS<sup>2</sup>

*A literature search was performed using “hydrocodone bitartrate, Zohydro ER.”*

The efficacy and safety of hydrocodone bitartrate was determined in a randomized double-blind, placebo-controlled, multicenter clinical trial in opioid-experienced subjects presenting with moderate to severe chronic low back pain. A total of 510 subjects currently on routine opioid therapy were enrolled in an open-label conversion and titration phase that lasted for up to 6 weeks. Patients were administered hydrocodone bitartrate every 12 hours at a dose calculated to be equianalgesic to the pre-study opioid medication. If the reported pain was not adequately controlled, the hydrocodone dosage was increased by 10 mg per 12-hour dose once every three to seven days until adequate analgesia was reached or a maximum dosage of 100 mg every 12 hours was given.

Of the initial 510 patients, 302 (59 percent) were randomized at a ratio of 1:1 into a 12-week double-blind treatment phase with their previously achieved dose of for hydrocodone bitartrate (ranging from 40 to 200 mg daily taken as 20 to 100 mg every 12 hours) or a matching dose of placebo. Subjects randomized to the placebo arm of the study were given a blinded reduction taper of hydrocodone bitartrate in accordance with a previously specified schedule. During the active Treatment Phase of the study, participants were allowed to utilize an immediate-release rescue medication (hydrocodone 5 mg/500 mg acetaminophen) up to two doses (two tablets) per day. A total of 124 treated subjects (82 percent) in the hydrocodone bitartrate treatment arm completed the 12-week trial while 59 subjects (39 percent) in the placebo arm were able to complete the trial.

The hydrocodone bitartrate-treated patients reported greater analgesia when compared to placebo-treated patients. Following the open-label conversion period, patients were evaluated for their levels of pain intensity utilizing a Numeric Rating Scale developed and agreed upon for the double-blind portion of the study. Those patients enrolled in the active treatment arm of the 12 week double blind study reported significant differences in the mean changes of their baseline analgesia from the start to week 12 in average weekly pain when compared to those in the placebo arm.

The percentage of subjects in each group who demonstrated improvement in their Numeric Rating Scale (NRS) pain score at End-of-Study revealed a cumulative improvement of 30 percent in analgesia from baseline. Patients not completing the entire course of study were classified as non-responders. Treatment with hydrocodone bitartrate demonstrated a significantly larger number of responders, defined as those patients showing an improvement of at least 30 percent improvement, compared to placebo (67.5 percent versus 31.1 percent).

## OTHER DRUGS USED FOR CONDITION

Long-acting opioid analgesics are considered the medications of choice for severe pain when immediate-release opioids are no longer effective and around-the-clock administration is required. Other CII long-acting narcotic analgesics approved for treatment of moderate to severe pain include extended-release oral formulations of hydromorphone, methadone, morphine sulfate, oxycodone, and oxymorphone, as well as transdermal formulations of fentanyl. These products are available both as branded agents and generic equivalents.

## PLACE IN THERAPY

Hydrocodone bitartrate ER (Zohydro ER) is intended to be used in cases where patients have reached a point where around-the-clock, long-acting opioid analgesia is required. As noted by the manufacturer, this medication is not without risks. There is a history and prevalence of addiction and abuse of opioids including hydrocodone. Hydrocodone bitartrate ER (Zohydro ER), which does not come in an abuse deterrent formulation, may best be reserved for cases where other long-acting analgesics have proven ineffective and then closely monitored and regulated according to the approved indications.

## SUGGESTED UTILIZATION MANAGEMENT

<b>Anticipated Therapeutic Class Review (TCR) Placement</b>	Analgesics, Long Acting Narcotics
<b>Clinical Edit</b>	Patients ≥18 years with a diagnosis severe pain and trials and failure of preferred long-acting opioid analgesic agents. Evaluate patient diagnoses for a history of drug abuse/dependence or addiction.
<b>Quantity Limit</b>	80 mg per day
<b>Duration of Approval</b>	6 months
<b>Drug to Disease Hard Edit</b>	None

## REFERENCES

1 Zohydro ER [package insert], San Diego CA; Zogenix, Inc; October 2013

2 Zohydro ER [package insert], San Diego CA; Zogenix, Inc; October 2013