

Hydrocodone Bitartrate Extended-release Capsules (ZOHYDRO ER), C-II National Abbreviated Drug Monograph November 2014

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description / Mechanism of Action	Hydrocodone extended-release (HC ER, by Zogenix, Inc.) without abuse-deterrent technology is the first single-entity hydrocodone opioid agonist formulation to be marketed. It uses Alkermes' Spheroidal Drug Absorption System (SODAS®) drug delivery technology.
Indication(s) Under Review in this Document	<p>FDA-approved Indication(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.</p> <p>Limitations of Use: Reserve hydrocodone ER for use in patients for whom alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Hydrocodone ER is not indicated as an as-needed (p.r.n.) analgesic.</p>
Dosing and Administration	<p>Refer to the Prescribing Information for complete and up-to-date dosing and administration information.</p> <p>Swallow capsules whole. Crushing, chewing or dissolving the capsules will result in uncontrolled delivery of hydrocodone and can lead to overdose or death.</p> <p>Initial Dosing</p> <ul style="list-style-type: none">• As First Opioid Analgesic: 10 mg every 12 hours• In Opioid Non-tolerant Patients: 10 mg every 12 hours• Conversion from Other Oral Opioids to Hydrocodone ER: According to the Prescribing Information, conversion (not equianalgesic) doses for other opioids when switching to hydrocodone 10 mg are as follows: oxycodone 10 mg; methadone 10 mg¹; oxymorphone 5 mg; hydromorphone 3.75 mg; morphine 15 mg; or codeine 100 mg.• Conversion from Transdermal Fentanyl to Hydrocodone ER: Hydrocodone 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 hydrocodone ER, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to hydrocodone ER, as there is limited documented experience with this conversion. <p>Titration and Maintenance Dosing</p> <ul style="list-style-type: none">• Titrate doses in increments of 10 mg every 12 hours every 3 to 7 days.• Patients who experience breakthrough pain may require a dose increase of hydrocodone ER, or may need a rescue medication with an appropriate dose of an immediate-release analgesic.
Dosage Form(s) Under Review	12-hour extended-release capsules: 10, 15, 20, 30, 40 and 50 mg
REMS	<input checked="" type="checkbox"/> REMS <input type="checkbox"/> No REMS Extended-release (ER) and long-acting (LA) opioid analgesics risk evaluation and mitigation strategy (REMS) See <i>Other Considerations</i> for additional REMS information.
Pregnancy Rating	Category C

¹ The Prescribing Information indicates that methadone 10 mg converts to hydrocodone 10 mg (i.e., oral conversion factor of 1); however, conversion factors for methadone-to-another opioid are highly variable. Conversion factors are NOT bidirectional and the conversion doses shown in the Prescribing Information are conservative. Overdose may occur if the conversion doses shown in the Prescribing Information are used when converting from hydrocodone ER to methadone (or another opioid).

Executive Summary	
Efficacy	<ul style="list-style-type: none"> Hydrocodone in an extended-release (HC ER) formulation was shown to be efficacious, with small to moderate analgesic effects. NNT was 3 (95% CI 2–4) for at least 30% improvement in pain at 12 weeks in a multicenter, double-blind, placebo-controlled randomized trial involving enriched enrollment randomized withdrawal and comprised of 302 opioid-experienced patients with moderate to severe chronic lower back pain. No active comparator studies were found.
Safety	<ul style="list-style-type: none"> Safety profile is typical of other CII ER opioid agonist formulations without abuse-deterrent technology. Long-term safety data beyond 48 weeks is lacking. Boxed Warnings: Similar to other CII ER opioid analgesics.
Other Considerations	<ul style="list-style-type: none"> The Prescribing Information gives recommendations for converting TO HC ER, but gives no guidance on conversions FROM hydrocodone ER to other opioids. The FDA approval of hydrocodone ER capsules without an abuse-deterrent formulation has been highly controversial in the midst of the prescription opioid overdose epidemic. Abuse-deterrent hydrocodone ER products are in the pipeline.
Potential Impact	<ul style="list-style-type: none"> Projected Place in Therapy: <ul style="list-style-type: none"> For initial opioid therapy and for switching from other opioids: Last-line ER opioid. For patients already receiving HC combination products: Consider in selected patients. Patient Convenience: No advantages over other twice-daily ER opioids.

Background

Purpose for review

New single-entity hydrocodone product.

Issue to be determined: Does hydrocodone ER have clinical advantages over existing alternatives.

Other therapeutic options

Formulary Alternatives	Other Considerations
Acetaminophen / Hydrocodone (oral liquid, tab)	Dosage titration of hydrocodone is limited by the acetaminophen dose. Immediate-release formulation. No abuse-deterrent formulation.
Fentanyl patch	No abuse-deterrent formulation.
Methadone	No abuse-deterrent formulation.
Morphine SA cap, tab	No abuse-deterrent formulation. Capsules: 24-hour. Tablets: 8–12-hours.
Nonformulary Alternatives	Other Considerations
Hydromorphone 24-hour ER tab CII (EXALGO)	No abuse-deterrent formulation. [†]
Levorphanol tab (LEVODROMORAN)	No abuse-deterrent formulation
Morphine-naltrexone ER CII (EMBEDA)	Abuse-deterrent formulation
Oxycodone 12-hour ER tab CII (OXYCONTIN)	Abuse deterrent formulation
Oxymorphone 12-hour ER tab CII (OPANA ER)	No abuse-deterrent formulation. [†]
Tapentadol 12-hour ER tab CII (NUCYNTA)	No abuse-deterrent formulation

[†] Based on information in Prescribing Information. Other sources refer to an ‘abuse-deterrent’ formulation, but the product didn’t meet FDA’s criteria for abuse-deterrent labelling.

Efficacy (in FDA-approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to August 2014) using the search terms *hydrocodone* and *ZOHYDRO*. The search was limited to studies performed in humans and published in the English language. A single placebo-controlled trial was found.

Review of Efficacy

- There is fair quality evidence from one manufacturer-sponsored RCT that HC ER has a small to moderate analgesic effect in non-neuropathic chronic low back pain (Table 1).
- Potential Efficacy Advantages over Other ER CII Opioids: None identified; no active comparator studies.
- Potential Efficacy Advantages over HC combination products: Dosage titration is not limited by the maximum recommended daily doses of the nonopioid (e.g., acetaminophen)

Table 1 Results of RCT with Enriched Enrollment Withdrawal Design

Outcome Measure	HC ER (N = 151)	PBO (N = 151)	Difference	P-value	NNT (95% CI)	Effect Size
Discontinued due to lack of efficacy, n (%)	14 (9.3)	64 (42.4)	-33.1	< 0.001	3 (4-2)	Medium
Mean (SD) change in ADPI, BL to day 85	0.48 (1.563)	0.96 (1.550)	-0.47	0.008	—	Small
NRS-30 Responder Rates, screening to day 85, n (%)	102 (68)	47 (31)	37	< 0.001	3 (2-4)	Medium
SGAM, mean (SD) change from screening to day 85	0.8 (1.3)	0.0 (1.4)	0.8	≤ 0.001	—	Medium
'Very much' or 'Completely' Satisfied, day 85, n (%)	79 (52)	51 (34)	18	< 0.001	6 (4-15)	Small
Rescue medication, mean (SD) total daily dose, mg	6.0 (3.4)	7.5 (3.9)	-1.5	—	—	—

Sources: Rauck, et al. (2014)¹; FDA Summary Review¹¹

ADPI, Average daily pain intensity; BL, Baseline (start of randomized phase); NRS-30, At least 30% improvement in pain intensity score on the numerical rating scale; SGAM, Subject Global Assessment of Medication on scale of 1/Not at all-5/Completely Satisfied

Potential Off-Label Use

- Management of pain NOT severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are NEITHER TRIED NOR SHOWN TO BE INADEQUATE.

Safety

(For more detailed information refer to the Prescribing Information.)

Boxed Warning

- Addiction, abuse, and misuse
- Life-threatening respiratory depression; accidental exposure
- Neonatal opioid withdrawal syndrome
- Interaction with alcohol

Contraindications

- Significant respiratory depression
- Acute or severe bronchial asthma or hypercarbia
- Paralytic ileus, known or suspected
- Hypersensitivity to any components or hydrocodone bitartrate

Warnings/Precautions

- Misuse, abuse, diversion; CII controlled substance with high potential for abuse
- Interactions with CNS depressants; consider dose reduction of one or both drugs
- In elderly, cachectic, debilitated patients and those with chronic pulmonary disease, monitor closely because of increased risk for life-threatening respiratory depression.
- In patients with head injury or increased intracranial pressure, monitor for sedation and respiratory depression. Avoid use of HC ER in patients with impaired consciousness or coma susceptible to intracranial effects of CO₂ retention.
- Prolonged gastric obstruction may occur in patients with gastrointestinal obstruction.
- Concomitant use of CYP3A4 inhibitors may increase opioid effects.
- Impaired mental or physical abilities; use caution with potentially hazardous activities.

Safety Considerations

- Safety data was available from 1512 subjects in 10 clinical studies including two phase 3 trials, of which one was an open-label, long-term (up to 52 weeks) safety study. A total of 332 subjects were exposed to HC ER for at least 6 months, and 290 subjects for at least one year. Maximum doses were 200 mg per day in the RCT and 600 mg per day in the open-label study.
- In addition to the limited long-term safety data from HC ER clinical studies, actual clinical experience with chronic use of immediate-release HC combination products has resulted in a substantial risk of misuse, abuse, addiction and diversion, which led the Drug Enforcement Agency to reschedule hydrocodone combination products from CIII to CII as of 6 October 2014.
- Except for reduction in abuse potential shown with opioids available in abuse-deterrent formulations, the safety profile of HC ER is comparable to those of other CII ER full agonist opioids.
- Potential Disadvantage: No abuse-deterrent formulation technology.

Adverse Events

Common Adverse Events

- Incidence of treatment-emergent adverse events in $\geq 2\%$ of patients in placebo-controlled trial in opioid-experienced patients with moderate-to-severe chronic low back pain: 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.
- Of AEs that occurred in $\geq 5\%$ of patients in at least one treatment group, only constipation occurred at a statistically significant higher incidence on HC ER than placebo (7.9% vs. 0%).

Deaths/Serious Adverse Reactions

- The authors of the published RCT reported that no deaths occurred.
- The FDA Summary Review reported 5 deaths among the 575 subjects exposed to HC ER, one of which was notable for involving toxicity to methadone and oxycodone; one notable for involving completed suicide by carbon monoxide poisoning; and one notable for one patient who apparently committed suicide about a year after study completion from an overdose in which about 40 HC ER capsules that the patient hoarded during the study were opened and ingested. Four of the five deaths were considered by the manufacturer to be unrelated and the fifth (the overdose) was related but occurred one year after the study.
- Serious Adverse Reactions listed in the prescribing information:
 - Respiratory depression
 - Misuse and abuse
 - CNS depressant effects
- Overall incidence of Serious Adverse Events reported in the FDA Summary Review: 5 (3.3%) on HC ER and none (0%) on placebo; in addition, 52 (12.0%) of 424 patients exposed to HC ER experienced at least one medical SAE. SAEs considered to be related to study drug were anxiety (n = 1), mental impairment (2), small bowel obstruction (2) and abdominal distension / constipation (3).
- Misuse, Abuse and Diversion Events During Phase 3 Clinical Trialsⁱⁱ:
 - Of 92 diversion-related AEs reported in the two phase 3 trials, 63 possible cases of drug diversion were reported, 13 (2.5%) during the RCT and 50 (7.8%) during the long-term open-label study.
 - There were also 6 cases of possible abuse (e.g., tampering with urine drug screen sample; tampering with rescue HC / acetaminophen product to extract HC; seeking HC / acetaminophen rescue medication from more than one prescriber).

Discontinuations Due to Adverse Events

HC ER vs. Placebo:

- Opioid Withdrawal: 0% vs. 4.6%
- Other AEs: 1% vs. 3%

Drug Interactions

Drug-Drug Interactions

- **Alcohol:** May increase HC plasma concentrations (2.4-fold mean increase in C_{max}; 1.2-fold increase in extent of absorption). Instruct patient not to consume alcoholic beverages or alcohol-containing nonprescription products.
- **CYP3A4 Inhibitors:** May decrease clearance of HC and thereby increase HC plasma concentrations. Monitor patients for respiratory depression and sedation at frequent intervals; consider dose adjustments.
- **CYP3A4 Inducers:** May increase clearance of HC and decrease HC plasma concentrations, which may lead to lack of efficacy or withdrawal syndrome in patients with physical dependence to HC. Monitor patients for signs of opioid withdrawal; consider dose adjustments.
- **CNS Depressants:** May increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients for signs of respiratory depression, sedation and hypotension.
- **Mixed Agonist / Antagonist Opioid Analgesics:** May reduce analgesic effects of HC or precipitate withdrawal symptoms. Avoid their use in patients receiving HC ER.
- **MAO Inhibitors:** Avoid using HC ER in patients who have received MAO inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.
- **Anticholinergics:** May increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention, constipation, respiratory depression and central nervous system depression.

Risk Evaluation

As of 28 October 2014

Sentinel event advisories	Use of opioids in hospitals: Respiratory depression, generally preceded by sedation. ⁱⁱⁱ				
Look-alike / sound-alike error potential	Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:				
	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
	Hydrocodone ER cap	Hydromorphone Oxycodone Oxymorphone	Oxycodone Oxycontin MS contin	Oxycodone	Hydrocodone regular Hydrocortisone tab
	ZOXYDRO ER	None	None	None	Zofran ZutriproZyflo

Other Considerations

- **Safety Concerns When Converting FROM HC ER:** The Prescribing Information gives recommendations for converting TO HC ER, but gives no guidance on conversions FROM HC ER to other opioids. *Overdose may occur if the dose conversions provided in the Prescribing Information are used to convert FROM HC ER to other opioids, particularly to methadone.*
- **Public Health Concerns:** The FDA approval of hydrocodone ER capsules without an abuse-deterrent formulation has been highly controversial in the midst of the prescription opioid overdose epidemic.
- **FDA Concerns during Deliberations:** The FDA's Advisory Committee voted 11 to 2, with 1 abstention, to recommend that the Agency not approve the application because of their concerns about the risks for misuse and abuse of HC ER and its impact on public health. Since HC is a well-understood opioid analgesic, the FDA required Zogenix to conduct only one adequately designed clinical trial to show that the agent remained effective in the new formulation and that the dosing regimen was appropriate given the pharmacokinetic and pharmacodynamics profiles of the product.
- **Issues with Procurement:** Abuse-deterrent hydrocodone ER products are in the pipeline: (1) Zogenix has submitted a supplemental NDA for an abuse-deterrent formulation of ZOXYDRO, and the manufacturer expects review for approval in Q1FY15 and, if approved, it will likely be marketed in Q2FY15; (2) Teva submitted an NDA for an abuse-deterrent hydrocodone product; (3) Purdue has developed its own abuse-deterrent hydrocodone product that is under FDA review. It is unknown whether Zogenix plans to continue marketing HC ER if their abuse-deterrent product is approved by the FDA.
- **REMS:** Extended-release (ER) and long-acting (LA) opioid analgesics risk evaluation and mitigation strategy (REMS).
- **Clinical Postmarketing Study Requirements (PMRs) for Adults:** 5 postmarketing studies are required to measure, quantitate and characterize misuse, abuse, addiction, overdose, and death, including "doctor / pharmacy shopping," hyperalgesia and tolerance.
- **Special Storage Requirements:** Secure storage required for CII controlled substances.
- **Pertinent Pharmacokinetic/Pharmacodynamic Considerations:** The mean apparent plasma half-life of HC ER is about 8 hours. Steady-state should be obtained after 3 days of dosing. A population pharmacokinetic study of HC ER provided the first in-depth description of HC pharmacokinetics.^{iv}
- **Physical Function and Quality of Life Data:** Not evaluated in clinical trials.

Special Populations (Adults)

Elderly \geq 65 years	<ul style="list-style-type: none"> No significant pharmacokinetic differences. In general, use caution when dosing opioids in the elderly. Monitoring of renal function may be useful since HC is excreted by the kidney.
Pregnancy	<ul style="list-style-type: none"> Pregnancy Category C. No adequate and well-controlled studies in pregnant women. Use HC ER during pregnancy only if the potential benefits justifies the potential risk to the fetus. Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. HC ER should not be used in women during and immediately prior to labor, when short-acting opioids or other analgesic techniques are more appropriate. Inconsistent effects of opioids on the uterine muscle and cervix may result in either prolongation or shortening of labor.
Lactation	<ul style="list-style-type: none"> Low concentrations of HC and hydromorphone have been detected in breast milk. Weigh risks versus benefits given the potential for serious adverse reactions in nursing infants. Monitor infants for excess sedation and respiratory depression. Nursing infants may develop opioid withdrawal symptoms when maternal opioid intake is discontinued or breastfeeding is stopped.
Renal Impairment	<ul style="list-style-type: none"> HC plasma concentrations are increased. Use low initial dose of HC ER and monitor closely for adverse events such as excessive sedation and respiratory depression.
Hepatic Impairment	<ul style="list-style-type: none"> HC plasma concentrations may be increased. No dosage adjustment is required in mild or moderate hepatic impairment. Start with the lowest dose, 10 mg, in patients with severe hepatic impairment, and monitor these patient closely for adverse events such as excessive sedation and respiratory depression.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> No data found

Projected Place in Therapy

- A trial of opioid therapy for chronic noncancer pain should be reserved for patients who have had an inadequate response, loss of response, intolerance or contraindications to nondrug and nonopioid pain therapies that are part of a comprehensive multimodal treatment approach and when an individualized patient assessment determines that the potential benefits outweigh the potential risks. An opioid trial should be cautiously undertaken only after taking into consideration that there is limited long-term (\geq 1 year) data and low-quality evidence suggesting that long-term opioid therapy may be associated with harms and/or a lack of analgesic or functional benefit.^{v,vi,vii}
- Overall, there is moderate quality evidence of the short-term analgesic efficacy of HC ER, no evidence of the efficacy of HC ER for improving physical function, and very low quality evidence of its safety for up to 1 year. This drug product is likely to have efficacy, safety and tolerability comparable to those of other C-II ER opioids on VANF in opioid-experienced patients with chronic non-neuropathic low back pain who do not have uncontrolled depression.
- Potential place in therapy:
 - For the first ER opioid therapy and for switching from opioids other than HC:
 - In patients who would probably not benefit from abuse-deterrent opioid formulations, consider HC ER after trials of the long-acting formulary opioid products (morphine ER, methadone, and transdermal fentanyl).
 - In patients who would probably benefit from abuse-deterrent opioid formulations, abuse-deterrent oxycodone CR, and other ER opioids with abuse-deterrent technology should be considered rather than non-abuse deterrent opioid products including HC ER.
 - For patients already receiving HC combination products and continuation of HC using an ER formulation is clinically appropriate (e.g., patients who have only partial pain relief despite optimization of the dosage regimen or maximal recommended nonopioid dose or who have increased pain prior to the next dose (end-of-dose breakthrough pain) despite appropriate dosage adjustments): Switching to HC ER may be considered.

References

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- ⁱⁱ Center for Drug Evaluation and Research. Application Number: 202880Orig1s000. Zohydro ER (hydrocodone bitartrate extended-release capsules) Summary Review. 25 October 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202880Orig1s000SumR.pdf. Accessed: 28 October 2014.
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- ^v Sjøgren P, Grønbaek M, Peuckmann V, Ekholm O. A population-based cohort study on chronic pain: the role of opioids. *Clin J Pain*. 2010 Nov-Dec;26(9):763-9
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- ^{vii} Murphy JL, Clark ME, Banou E. Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment. *Clin J Pain*. 2013 Feb;29(2):109-17

Prepared November 2014. Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager – Formulary, PBM Services (10P4P)
