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# Hydrocodone Bitartrate Extended-Release Tablets (Hysingla ER), C-II

## National Abbreviated Drug Monograph

### October 2015

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

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*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 Documents will be placed in the Archive section when the information is deemed to be no longer current.*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<sup>1-3</sup>

##### Description / Mechanism of Action

Hydrocodone bitartrate extended-release (HYDRO ER) is a once-daily, extended release opioid analgesic tablet formulated with abuse-deterrent properties designed to deter abuse through manipulation and subsequent injection or snorting.

The ER and abuse deterrent properties of HYDRO ER tablets result from a proprietary extended-release solid oral dose platform (Resistec™; which consists of a polymer and special processing) that controls tablet hardness and imparts viscosity when dissolved in aqueous solution.

Hydrocodone bitartrate is a semi-synthetic opioid agonist with relative selectivity for the mu receptor; the pharmacological effects, including analgesia, euphoria, respiratory depression and physiological dependence are believed to be primarily mediated through mu opioid receptors.

Hydrocodone bitartrate is a schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. Despite the abuse-deterrent properties, HYDRO ER is subject to misuse, abuse, addiction and criminal diversion. The high drug content in the ER formulation adds to the risk of adverse outcomes from abuse and misuse.

##### Indication(s) Under Review in this Document

FDA-approved Indication(s): HYDRO ER 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, HYDRO ER should be reserved 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. HYDRO ER is not indicated for as-needed (prn) analgesia.

##### Dosing and Administration

Refer to the Prescribing Information for complete and up-to-date dosing and administration information.

The dosing regimen for HYDRO ER should be initiated for each patient individually, taking into account the patient's prior analgesic treatment experience, concomitant medications, hepatic and renal function, and risk factors for addiction, abuse, and misuse (see *Other Considerations* and *Special Populations*).

The recommended initial dosage of HYDRO ER in opioid-naïve patients is 20mg daily; see *Other Considerations* for dosing recommendations in opioid-experienced/opioid tolerant patients.

HYDRO ER tablets should be swallowed whole without breaking, chewing, crushing, cutting dissolving, or splitting; these actions can result in uncontrolled delivery of hydrocodone and possibly lead to overdose or death. Tablets should be taken with adequate water to ensure complete swallowing immediately after placing in mouth. HYDRO ER may be administered without regard to meals.

The dose of HYDRO ER can be adjusted every 3 to 5 days at increments of 10 or 20mg until pain relief is adequate and tolerance is acceptable.

Patients who may be physically dependent on HYDRO ER and no longer require therapy should have a gradual downward titration of the dose of 50% every 2 to 4 days to prevent signs and symptoms of withdrawal. After reaching the 20mg daily dose for 2 to 4 days, the HYDRO ER can be discontinued.

##### Dosage Form(s) Under Review

Extended-release tablets, each containing hydrocodone bitartrate 20, 30, 40, 60, 80, 100, or 120mg.

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**REMS**  REMS  No REMS  
*See Other Considerations for additional REMS Information.*

**Pregnancy Rating** Category C  
*See Special Populations for additional information*

**Executive Summary**<sup>1-6</sup>

<b>Efficacy</b>	<ul style="list-style-type: none"> <li>An extended-release formulation of hydrocodone bitartrate (HYDRO ER) given 20 to 120mg once daily was shown to provide effective analgesia over 12 weeks in a randomized, double-blind, placebo-controlled study of patients with uncontrolled moderate to severe chronic low back pain (LBP) of at least 3 months duration.</li> <li>No active comparator studies were found.</li> </ul>
<b>Safety</b>	<ul style="list-style-type: none"> <li>The most common adverse events associated with HYDRO ER are those known to occur with the use of opioid analgesics (Nausea, vomiting, constipation, dizziness; long term (&gt;1 year) safety data is lacking.</li> <li>Boxed Warnings for HYDRO ER are similar to other CII ER opioid analgesics</li> <li>Choking, obstruction of the airway, and GI obstruction are potential risks associated with HYDRO ER due to its polyethylene oxide content which causes the tablet to swell and become sticky when wet.</li> <li>QT prolongation has been reported with recommended and greater than recommended doses of HYDRO ER.</li> <li>There is a risk for LASA confusion with twice-daily hydrocodone bitartrate capsules (Zohydro ER).</li> <li>As an extended-release CII opioid analgesic, HYDRO ER poses a risk of abuse/misuse, tolerance, dependence, and withdrawal syndrome. There are labeling requirements and a risk evaluation and mitigation strategy (REMS) required by FDA which are intended to reduce the risks of abuse/misuse, addiction, overdose, and death with this agent.</li> </ul>
<b>Other Considerations</b>	<ul style="list-style-type: none"> <li>HYDRO ER resists crushing, breaking, and dissolution while retaining some ER properties. When placed in an aqueous environment, HYDRO ER forms a viscous hydrogel which resists passage through a hypodermic needle.</li> <li>HYDRO ER is not susceptible to vaporizing (smoking) and is resistant to dose-dumping in the presence of alcoholic beverages.</li> </ul>
<b>Potential Impact</b>	<ul style="list-style-type: none"> <li>Projected Place in Therapy: HYDRO ER may be a consideration in the management of severe pain that requires continuous/24-hour, long-term opioid treatment, where alternate pain management options (including long-acting opioid formulary agents) have been shown to be inadequate/not tolerated and where the perceived benefits of its abuse-deterrent properties outweigh the potential risks.</li> </ul>

**Background**

**Purposes for review** HYDRO ER was approved by the FDA in November, 2014; it is the second extended release hydrocodone product with abuse-deterrent properties (the other is Zohydro ER).

**The purposes of this abbreviated monograph** are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to considering HYDRO ER for addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

**Also to be determined:** Does HYDRO ER have clinical advantages over existing alternatives? What safety issues need to be considered?

**Other therapeutic options**

Formulary Alternatives	Other Considerations
Morphine sulfate sustained action tablets (various)	
Fentanyl transdermal patch (various)	
Nonformulary Alternatives	Other Considerations
Hydrocodone bitartrate ER capsules (Zohydro ER)	Abuse-deterrent formulation
Buprenorphine transdermal patch (Butrans)	
Oxycodone HCL ER tablets (OxyContin)	Abuse-deterrent formulation
Morphine sulfate ER capsules (Kadian, Avinza)	
Oxymorphone HCL ER tablets (Opana ER)	Abuse-deterrent formulation
Tapentadol ER tablets (Nucynta ER)	
Morphine sulfate and naltrexone HCL ER capsules (Embeda)	Abuse-deterrent formulation
Hydromorphone HCL ER tablets (Exalgo)	Abuse-deterrent formulation

Products listed are oral or transdermal extended-release or long-acting opioids, indicated for the long-term treatment of severe pain (all are CII with exception of buprenorphine transdermal patch).

**Efficacy (in FDA-approved Indications)**<sup>1-4, 7, 8</sup>**Literature Search Summary**

A literature search was performed on PubMed/Medline (2011 to August 2015) using multiple search terms and combinations of terms including hydrocodone, extended-release, and Hysingla ER. The search was limited to studies performed in adult humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials.

The HYDRO ER clinical development program included 14 phase I studies and 2 phase III studies [a 12-week multicenter, double-blind, randomized withdrawal design, placebo-controlled efficacy study (study HYD3002) and a 12-month open label safety study in patients with chronic moderate to severe nonmalignant and non-neuropathic pain (study HYD3003; see *Safety Considerations*)].

**Review of Efficacy**

Following decades of clinical experience with hydrocodone and the agency's prior findings for the product Vicoprofen®, FDA agreed that one positive adequate and well-controlled clinical trial would be sufficient to support the efficacy of HYDRO ER and to confirm that the once daily dosing was appropriate for the proposed chronic pain indication.

- The November, 2014 FDA approval of HYDRO ER was based upon a multicenter, double-blinded, placebo-controlled, randomized study (HYD3002) in patients with uncontrolled moderate to severe chronic low back pain (LBP) of at least 3 months duration given either placebo or HYDRO ER 20 to 120mg daily for 12 weeks. The LBP was required to be nonradiating or radiating no further than above the knee [Quebec Task Force Classification 1 or 2; see *footnote, page 4*]. Patients were either previously on opioids or had had an inadequate response to other analgesics and were considered appropriate for initiating chronic opioid therapy.
  - o The primary efficacy outcome was the change in mean weekly pain intensity from baseline at randomization to the end of the 12 weeks of double-blind treatment. Secondary efficacy variables were 1) proportions of patients achieving 30 and 50% reduction in pain intensity 2) improvements in sleep disturbance and 3) patient global impression of change (PGIC).
  - o A total of 905 patients entered the up to 45 day open-label titration period. Opioid naïve patients began treatment with HYDRO ER 20mg daily and opioid-experienced patients were converted to a HYDRO ER dose 25 to 50% of their incoming opioid total daily dosage. Patients were allowed to take 5mg of immediate-release (IR) oxycodone as needed up to twice daily during this period.
  - o At Day 45, patients who tolerated HYDRO ER and had achieved adequate analgesia (defined as same dose of HYDRO ER for 7 ± 2 days with pain score ≤ 4 over each of the last 3 days) were randomized 1:1 to either remain on HYDRO ER or to begin a blinded taper to placebo (25-50% reduction every 3-4 days). During the double-blind period, patients receiving HYDRO ER 20, 40, 60, 80 and 120mg daily were permitted to take maximum daily doses of IR oxycodone of 10, 10, 15, 20 and 30mg respectively.
  - o A total of 592 patients met the criteria for randomization; of the 313 patients not randomized, 94 discontinued due to an adverse event, 46 failed due to inadequate analgesia, and 23 were suspected or confirmed as diverting study drug.
  - o At week 12, but not prior, pain scores were significantly lower ( $p < 0.0016$ ) in patients taking HYDRO ER ( $n = 229$ ) versus those taking placebo ( $n = 210$ ).
  - o For the secondary measures, HYDRO ER-treated subjects had consistently higher ≥ 30% and ≥ 50% responder rates than placebo-treated subjects (65 vs 53%,  $p = 0.0033$  and 48 versus 39%,  $p = 0.0225$ ; respectively). The proportion of patients reporting “very much improved” or “much improved” on the PGIC rating scale was higher in the HYDRO ER treatment group versus the placebo group (61 versus 49%; respectively,  $p = 0.0036$ ). HYDRO ER did not significantly change sleep

disturbance and there was no significant difference reported in use of rescue IR oxycodone between groups treated with active drug versus placebo.

- Bartoli et al. (2015) conducted a 12-month, phase III, open-label, multicenter study to assess the long-term effectiveness and safety of HYDRO ER 20 to 120mg in opioid-naïve and opioid-experienced subjects with controlled or non-controlled moderate to severe nonmalignant and non-neuropathic chronic pain (study HYD3003).
  - o 728 patients discontinued controlled-release and long-acting opioid medications prior to treatment with HYDRO ER. Patients were converted to HYDRO ER dosages of 20, 40, 60, 80, or 120 mg/day, based on their incoming opioid dose. The HYDRO ER dose could be adjusted during a titration period of up to 45 days. Patients who could not achieve a stable dose were discontinued from the trial. During the 1-year maintenance period, further adjustments of HYDRO ER doses were allowed as needed. IR opioid supplementation (IR oxycodone, IR morphine, and others) and supplemental non-opioid analgesics were also permitted.
  - o Only 226 patients (31%) completed the titration period and even fewer (129; 18%) finished the 52-week trial. One-third of the 52-week study drop-outs were due to adverse events (36/97) and 6% (13/97) for lack of therapeutic effect.
  - o The mean (SD) dose in hydrocodone equivalents at trial baseline was 24 mg (13). Average daily dose of HYDRO ER at the end of titration was 61.7mg and was 60.8mg at week 52. 61% of patients had no change in HYDRO ER dose over the 52 week trial, 28% had an increase and 11% had a decrease. 58% of patients required concomitant IR opioid supplementation; 77% used concomitant non-opioids.
  - o The most common adverse events were those known to be associated with the use of opioid analgesics (see page 5). Three deaths occurred, one of which was considered related to trial drug (multi-drug overdose, *see page 5*).

*\*The Quebec Task Force Classification (QTFC) is a commonly used validated classification system for severity of low back pain based on pain and neurological examination data, imaging test results, and response to treatment. The classification system is validated for the purposes of clinical decision making, determining prognosis, and evaluating quality of care (reference 8).*

## Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s [Guidance on “Off-label” Prescribing](#) (available on the VA PBM intranet site only).

There is potential use of HYDRO ER in the management of pain *not severe enough* to require daily, around-the-clock, long-term opioid treatment and/or for which alternative treatment options *have not yet* been trialed or shown to be inadequate.

There are 10 trials of HYDRO ER listed at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (accessed August 31, 2015). One completed study (NCT02197156) was a multicenter active comparator study of HYDRO ER in adults following bunionectomy surgery (*acute pain model*).

## Safety<sup>1-4,6,7</sup>

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

### Boxed Warning

- Addiction, abuse, and misuse which can lead to overdose and death
- Serious, life-threatening or fatal respiratory depression may occur
- Accidental exposure, especially in children, can result in fatal overdose
- Neonatal opioid withdrawal syndrome when used during pregnancy
- Initiation of CYP3A4 inhibitors or discontinuation of CYP3A4 inducers can result in fatal overdose.

### Contraindications

- Significant respiratory depression
- Acute or severe bronchial asthma
- Paralytic ileus or GI obstruction, known or suspected
- Hypersensitivity to hydrocodone bitartrate or any other component of HYDRO ER

### Warnings/Precautions

(also see *Boxed Warnings*)

- HYDRO ER should not be interchanged with other extended-release hydrocodone products because of differing pharmacokinetic profiles that affect the frequency of administration.
- HYDRO ER, as with any opioid medication, should be used with caution in patients who are experiencing or who are at risk for:
  - o Misuse, abuse, or diversion of opioid medications
  - o CNS depression from other medications; profound sedation, respiratory depression, and death may occur; consider dose reduction of one or both drugs
  - o Life-threatening respiratory depression; in particular, in the elderly, or in cachectic or debilitated patients, or those with chronic pulmonary disease
  - o Head injury/increased intracranial pressure
  - o Choking or GI obstruction (*see Other Considerations*)
  - o Hypotension
- HYDRO ER, as with any opioid medication, may impair the mental and physical abilities; use

caution when performing potentially hazardous activities

- Combination of HYDRO ER with mixed agonist/antagonist analgesics may reduce its analgesic effect
- QTc prolongation has been observed following administration of HYDRO ER 160mg daily. Use caution in patients with heart failure, bradyarrhythmias, electrolyte abnormalities or those taking medications known to prolong the QTc interval. Consider dose reduction in patients with QTc prolongation (see *Other Considerations*).

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## Safety Considerations

FDA recognized that hydrocodone had been marketed for decades and that safety concerns were generally well-known; it was determined that a safety database of at least 300 patients exposed for 6 months and 100 patients exposed for at least 1 year would sufficiently demonstrate whether the formulation had any unexpected effects not related to the active drug component.

In the pooled Phase 3 studies, a total of 1827 subjects were exposed to at least one dose of HYDRO ER ranging from 20 to 120 mg. A total of 364 subjects were exposed for at least 12 months, and 374 were exposed to at least one dose of 120 mg. Twelve percent of subjects who took 120 mg were exposed for at least 12 months. Mean age of subjects receiving HYDRO ER in pooled chronic pain studies was 50 years and mean BMI was 31.4 kg/m<sup>2</sup>. There were more opioid-experienced subjects than opioid-naïve subjects (56% versus 44%).

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## Adverse Events<sup>1-4, 6,7</sup>

### Common Adverse Events

The common treatment-related adverse events (TEAEs) reported for HYDRO ER are those typically associated with opioid analgesics.

The overall incidence of TEAEs reported during the double-blind portion of the placebo-controlled trial HYD3002 (*page 3*) was 41%. A higher percentage of HYDRO ER-treated subjects compared to placebo subjects experienced any TEAE (46% versus 35% respectively); TEAEs that occurred with at least a 2% incidence included: nausea (8%), vomiting (6%), constipation (3%), dizziness (3%), insomnia (3%), headache (2%), decreased appetite (2%) and influenza (2%).

The most common TEAEs reported in the pooled phase III studies were nausea (21%), constipation (16%), vomiting (10%), dizziness (10%), headache (8%), and somnolence (8%).

There were no unusual or unexpected findings on laboratory (hematology, serum chemistry, and urinalysis) or vital sign changes in patients taking HYDRO ER.

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### Deaths/Serious Adverse Reactions

There were a total of 7 deaths that occurred during the phase III trials, 6 in the HYDRO ER group and one in the placebo group. Of the HYDRO ER patients that died, one died of a multi-drug overdose (HYDRO ER in combination with citalopram and cyclobenzaprine) and 2 patients with underlying COPD died of respiratory failure/hypoxia. Contribution of HYDRO ER to these deaths could not be ruled out.

There were 120 nonfatal serious adverse events (SAEs) reported in 84 (5%) patients exposed to HYDRO ER. Twelve nonfatal SAEs considered possibly related to the study drug occurred in 10 subjects and included asthma, esophageal obstruction, impaired gastric emptying, lethargy, sedation, drug abuse, and overdose. There was one SAE of QT prolongation (see *Other Considerations*). There were also 2 reports of esophageal obstruction associated with HYDRO ER, one in a patient with a preexisting esophageal stricture (endoscopy showed a glue-like mass lodged in the esophagus after three doses of HYDRO ER), and one in a patient with no apparent structural abnormality of the GI tract (see *Other Considerations*).

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### Discontinuations Due to Adverse Events

In the pooled phase III studies, 17% of patients taking HYDRO ER experienced at least 1 adverse event (AE) that led to discontinuation, typically GI and or CNS-related in nature (7% and 6%, respectively).

The incidence of discontinuation due to AEs in the double-blind study was 10% during the open-label run in phase, and during the double-blind phase was 4% in HYDRO ER -treated subjects versus 3% in placebo-treated subjects. The most common adverse events were GI (nausea, vomitings) and CNS(dizziness, headache) related.

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## Drug Interactions<sup>1</sup>

### Cytochrome P450 Interactions

The CYP3A4 isoenzyme plays a major role in the metabolism of hydrocodone; drugs that alter CYP3A4 activity may cause changes in hydrocodone clearance and alteration of oxycodone plasma concentrations. If co-administration is necessary, caution is advised when initiating HYDRO ER in patients currently taking or discontinuing CYP3A4 inhibitors or inducers.

**CYP3A4 Inhibitors:**

Ketoconazole, a strong CYP3A4 inhibitor, is known to significantly increase plasma concentrations of hydrocodone when the drugs are given concomitantly. CYP3A4 inhibitors such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. Caution is advised when CYP3A4 inhibitors are initiated or discontinued in association with HYDRO ER administration; under these circumstances, frequent monitoring of patients for respiratory depression and sedation at frequent intervals is recommended until stable drug effects are achieved.

**CYP3A4 Inducers:**

CYP450 3A4 inducers may induce the metabolism of hydrocodone and cause increased clearance of the drug with reduction in hydrocodone plasma concentrations. This could lead to a potential lack of efficacy or withdrawal syndrome in patients who have physical dependence to hydrocodone. If co-administration of a CYP3A4 inducer with HYDRO ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved.

**CNS Depressants:**

Concomitant use of HYDRO ER and other CNS depressants (e.g., sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol) may increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving these combinations for signs of respiratory depression, sedation and hypotension; consider dose reduction of one or both agents.

**Mixed Agonist / Antagonist Opioid Analgesics:**

Mixed agonist/antagonist or partial agonist opioid analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) may reduce the analgesic effect of HYDRO ER and/or precipitate withdrawal symptoms in patients with physical dependence to oxycodone. Avoid use of these agents in patients receiving HYDRO ER.

**Monoamine Oxidase Inhibitors (MAOI):**

The use of HYDRO ER is not recommended for patients taking MAOIs or within 14 days of discontinuation of an MAOI; although not reported specifically for hydrocodone, there is a potential for severe and unpredictable potentiation of opioid analgesics in combination with a MAOI.

**Strong Laxatives:**

Use of HYDRO ER with a strong laxative may decrease hydrocodone absorption and decrease hydrocodone plasma levels; closely monitor patients on this combination for adverse effects and changing analgesic requirements.

**Anticholinergics:**

Medications with anticholinergic activity used concurrently with opioid analgesics may result in increased risk of urinary retention and/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 9 September 2015

**Sentinel event advisories**

- Use of opioids in hospitals: Respiratory depression, generally preceded by sedation.<sup>9</sup>
- Sources: ISMP, FDA, TJC

**Look-alike / sound-alike error potential**

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Hydrocodone 24-hr ER tab	Hydromorphone Oxycodone Oxymorphone	Oxycodone Oxycontin MS contin	Oxycodone	Hydrocodone 12-hr ER cap Hydrocodone (regular) Hydrocortisone
Hysingla ER		None	None	Humira Hycufenix (hydrocodone cough syrup) Hizentra Hyserpin

- **High alert medication:** The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

## Other Considerations<sup>1-3, 6, 10</sup>

### HYDRO ER Dosing in Opioid Experienced/Tolerant patients:

- Patients who are receiving other oral hydrocodone formulations may be converted to HYDRO ER on a mg-to-mg basis (add current total daily hydrocodone dosage to determine once daily dose of HYDRO ER, rounding down as necessary).
- Patients who are receiving another opioid or combination of other opioids may be converted to HYDRO ER through use of a oral relative potency conversion table:
  - Using the appropriate conversion factor(s) from the table, convert the prior total daily oral opioid dose to a total daily hydrocodone dose
  - Reduce the total daily hydrocodone dose by 25% to account for the phenomenon of incomplete cross-tolerance
  - Initiate HYDRO ER at the nearest whole-tablet strength to the calculated dose, rounding down as necessary.
- Patients converted from oral methadone should be closely monitored due to that agent's prolonged half-life and the resultant patient-to-patient variation in response when converted to an alternative opioid.
- Patients converted from transdermal fentanyl patches can be given HYDRO ER 18 hours after patch removal; HYDRO ER 20mg daily is recommended for each 25mcg/hr of fentanyl patch previously applied.
- There is limited experience converting from transdermal buprenorphine; initiate HYDRO ER at 20mg daily in patients being converted from  $\leq 20$ mcg/hr of transdermal buprenorphine.

### QT prolongation:

- QTc interval prolongation was studied in a double-blind, placebo- and positive-controlled (moxifloxacin) 3-treatment parallel-group dose-escalating study of HYDRO ER (80, 120, and 160mg daily) in 196 healthy subjects (NCT02243241). QTc interval prolongation was observed following HYDRO ER 160 mg daily for 3 days where the maximum mean difference in the QTc interval between HYDRO ER and placebo (after baseline-correction) at steady state was 9.85 milliseconds (6.73, 12.97; 90% CI).
- In the pooled phase III studies, seven HYDRO ER-treated subjects were reported to have QT prolongation or syncope, all during the open-label study.
  - Four of these seven subjects experienced syncope
  - The remaining three subjects had documented prolonged QT on HYDRO ER 40 or 80mg daily; two of the cases prolonged QT resolved when drug was discontinued, and one while still taking study drug.
  - Two cases of syncope were documented not to have been associated with QT prolongation.
- FDA concluded that the finding of QT prolongation in the QT study indicated that QT prolongations in the clinical trial were possibly associated with HYDRO ER

### Abuse deterrent properties of HYDRO ER:

- HYDRO ER is formulated with physicochemical properties that prolong its action and deter abuse. These properties result from a proprietary formulation (Resistec™) containing polyethylene oxide (PEO) that is subjected to a process which imparts tablet hardness.
- *In vitro* tests indicate that HYDRO ER resists crushing, breaking, and dissolution using a variety of tools and solvents while retaining some ER properties. These tests included exposure of HYDRO ER to various concentrations of ethanol and simulated gastric fluid with results that indicated resistance of the formulation to dose-dumping in the presence of alcoholic beverages.
- When placed in an aqueous environment, HYDRO ER forms a viscous hydrogel which resists passage through a hypodermic needle.
- Simulated smoking indicated that HYDRO ER is not susceptible to vaporizing.
- Two randomized, double-blind, placebo and active-comparator studies in non-dependent opioid abusers were conducted to characterize the abuse potential of HYDRO ER following physical manipulation and administration via the intranasal and oral routes.
  - In the intranasal abuse potential study (HYD1014), incomplete dosing due to granules falling from the subjects' nostrils occurred in 82% of subjects receiving tampered HYDRO ER compared to no subjects with powdered hydrocodone or placebo. Intranasal administration of tampered HYDRO ER resulted in significantly lower mean and median scores for drug liking and take drug again ( $P < 0.001$  for both), compared with powdered hydrocodone.
  - In the oral abuse potential study (HYD1013), treatments included oral administrations of chewed HYDRO ER 60 mg tablets, intact HYDRO ER 60 mg tablets, 60 mg aqueous hydrocodone bitartrate solution, and placebo. The oral administration of chewed and intact HYDRO ER resulted in lower mean and median scores on scales that measure drug liking and desire to take drug again ( $P < 0.001$ ), compared to hydrocodone solution.
- While the aforementioned properties are expected to deter abuse by the oral, intranasal and intravenous routes, abuse of HYDRO ER via these routes remains possible.
- The FDA has required the manufacturer of HYDRO ER to participate in postmarketing evaluation of the risks of abuse, misuse, addiction, overdose, death and hyperalgesia associated with the long term use of ER/LA opioid analgesics. Specific to HYDRO ER, the manufacturer is required to conduct epidemiologic investigations that address whether the properties intended to deter misuse

and abuse of HYDRO ER actually result in a significant and meaningful decrease in misuse and abuse, and the consequences of addiction, overdose, and death in the community. Target date for final report submission is April, 2020.

**Safety Concerns Regarding Abuse of HYDRO ER:** Taking cut, broken, chewed, crushed or dissolved HYDRO ER increases the risk of overdose or death. With parenteral abuse, the inert ingredients of HYDRO ER can result in local tissue necrosis, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.

**Safety Concerns Regarding Swallowing of HYDRO ER:** Eleven subjects in the HYDRO ER clinical development trials (< 1%) experienced formulation-related choking or GI obstruction AEs. HYDRO ER contains PEO which causes tablets to swell and become sticky when wetted; this can result in tablets sticking in the GI tract, choking, and possible GI obstruction, particularly in patients who have had a prior GI surgery or who have a structural abnormality resulting in a small gastrointestinal lumen. Patients should be instructed not to pre-soak, lick, or otherwise wet HYDRO ER prior to placing in the mouth and to take one tablet at a time with adequate water to ensure complete swallowing immediately after placing in the mouth.

#### Pharmacokinetics of HYDRO ER :

- Median  $T_{max}$  of HYDRO ER is 14 to 16 hours.
- $C_{max}$  and AUC of HYDRO ER 120mg tablets were similar under low fat conditions relative to fasting conditions and AUC of HYDRO ER 120mg tablets was only 20% higher when administered with high fat meals. HYDRO ER may be administered with or without food.

#### Special Populations <sup>1</sup>

<b>Elderly <math>\geq</math> 65 years</b>	<ul style="list-style-type: none"> <li>• In a controlled pharmacokinetic study, subjects &gt; 65 years of age had similar plasma concentrations of HYDRO ER compared to young adults.</li> <li>• No untoward or unexpected adverse reactions were seen in the elderly patients who received HYDRO ER in the pooled chronic pain studies (13% of the 1827 patients were &gt; 65 years old; 2% were &gt; 75).</li> <li>• Hydrocodone may cause confusion and oversedation in the elderly; start elderly patients on low doses of HYDRO ER and monitor closely, especially when concomitant disease (renal, hepatic, cardiac) or concomitant CNS-active medications increase the risk of confusion, sedation or respiratory depression.</li> </ul>
<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>• Pregnancy Category C. No adequate and well-controlled studies in pregnant women. Use HYDRO ER during pregnancy only if the potential benefits justify the potential risk to the fetus. Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. HYDRO ER should not be used in women during and immediately prior to labor, when short-acting opioids or other analgesic techniques are more appropriate.</li> </ul>
<b>Lactation</b>	<ul style="list-style-type: none"> <li>• Hydrocodone is present in human milk; infants exposed to HYDRO ER through breast milk should be monitored for excess sedation and respiratory depression. Because of the potential for serious adverse reactions in nursing infants from HYDRO ER, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.</li> </ul>
<b>Renal Impairment</b>	<ul style="list-style-type: none"> <li>• No adjustment in HYDRO ER dosage is required in patients with mild renal impairment. Patients with moderate or severe renal impairment or ESRD have higher plasma concentrations of hydrocodone than those with normal renal function and should be given initial therapy with <math>\frac{1}{2}</math> the usual starting dose. Monitor closely for respiratory depression.</li> </ul>
<b>Hepatic Impairment</b>	<ul style="list-style-type: none"> <li>• No adjustment in HYDRO ER dosage is required in patients with mild or moderate hepatic impairment; it is recommended that patients with severe impairment be started at <math>\frac{1}{2}</math> the usual initial dose with dose titration as needed. Monitor closely for respiratory depression</li> </ul>
<b>Pharmacogenetics/genomics</b>	<ul style="list-style-type: none"> <li>• There are no data identified in the FDA approved labeling or at this site: <a href="http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm">http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm</a> (accessed August 31, 2015).</li> </ul>

#### Projected Place in Therapy <sup>1-4, 6, 10-12</sup>

- Chronic opioid therapy (COT) should be reserved for patients who have intractable chronic pain that is not adequately managed with more conservative or interventional methods; COT should be prescribed only after thorough patient evaluation, consideration of management alternatives, and development of a patient-specific treatment plan and should include on-going monitoring of treatment efficacy and safety.



- While prescription opioids play an important role in modern pain management, their abuse and misuse have created a serious public health problem. FDA believes the development of opioids formulated to deter abuse is an important step towards the goal of improved safety with these agents. Since opioid products may be manipulated for purposes of abuse by different routes of administration or to defeat ER properties; most abuse-deterrent technologies have been designed to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. In spite of these efforts, no opioid formulation prevents consumption of a large number of intact capsules or tablets which continues to be the most common method of abuse.
- One randomized, placebo-controlled trial of good quality documents the 12 week efficacy of once-daily HYDRO ER in the relief of uncontrolled moderate to severe chronic low back pain in opioid naïve and opioid experienced patients. There are no active comparator trials and evidence for efficacy of HYDRO ER for longer periods (> 12 weeks) appears to be incomplete and of low quality.
- The physicochemical properties of HYDRO ER are expected to deter abuse by the oral, intranasal and intravenous routes; however, abuse of HYDRO ER via these routes remains possible. FDA has required the manufacturer of HYDRO ER to perform post-marketing studies to address whether the properties intended to deter misuse and abuse of HYDRO ER actually result in a significant and meaningful decrease in misuse and abuse.
- The most common adverse events associated with HYDRO ER are those known to occur with the use of opioid analgesics. QT prolongation has been reported with recommended and greater than recommended doses of HYDRO ER. The PEO content of HYDRO ER causes tablets to swell and become sticky when wetted which can result in tablets sticking in the GI tract, choking, and possible GI obstruction. There appears to be a significant risk of LASA drug error with hydrocodone bitartrate ER capsules (Zohydro ER).
- Potential place in therapy: HYDRO ER may be a consideration in the management of severe pain that requires continuous/24-hour, long-term opioid treatment, where alternate pain management options (including long-acting opioid formulary agents) have been shown to be inadequate/not tolerated and where the perceived benefits of its abuse-deterrent properties outweigh the product's potential risks. HYDRO ER should not be made available to patients with a history of any type of dysphagia, esophageal obstruction, or gastrointestinal structural abnormality, nor should it be provided to patients that may be unable to strictly adhere to safe administration practices.

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