About Purdue's Hysingla™ ER (hydrocodone bitartrate) Extended-Release Tablets CII

What is Hysingla™ ER?
Hysingla ER (hydrocodone bitartrate) extended-release tablets CII is single-entity hydrocodone bitartrate formulated using Purdue's proprietary extended-release solid oral platform, RESISTEC™. Hysingla ER is the first and only hydrocodone product to be recognized by the U.S. Food & Drug Administration (FDA) as having abuse-deterrent properties that are expected to deter misuse and abuse via chewing, snorting and injection. However, abuse of Hysingla ER by the intravenous, intranasal, and oral routes is still possible.[1] Hysingla ER has been formulated for once-daily (every 24 hours) dosing and is acetaminophen free.

Please see the Boxed Warning, Warnings and Precautions, and Adverse Reactions information below.

What is RESISTEC?
RESISTEC is Purdue Pharma's proprietary solid oral dosage formulation platform, which uses a unique combination of polymer and processing that result in barriers to misuse and abuse by:

- conferring tablet hardness
- imparting viscosity when dissolved in aqueous solutions

What is the significance of Hysingla ER being acetaminophen free?
The overuse of acetaminophen has been reported to be a leading cause of acute liver failure in the United States.[2,3] Prescription products containing hydrocodone and acetaminophen are among the most prescribed and widely abused (nonmedical use) medications in the United States.[4,5]

What are the dosage strengths for Hysingla ER?
Hysingla ER is available in dosage strengths of 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg and 120 mg to be taken once every 24 hours. The starting dose for patients who are not opioid tolerant is Hysingla ER 20 mg orally every 24 hours. Opioid tolerant patients 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.

When was Hysingla ER approved by the FDA?
Hysingla ER was approved by the FDA on November 20, 2014[6] and the approval was accompanied by an FDA press release and blog post[7] from Janet Woodcock, M.D., Director of the FDA's Center for Drug Evaluation and Research.

What were the Phase 3 clinical trial results for Hysingla ER?
In the pivotal Phase 3 clinical trial leading to the FDA approval of Hysingla ER, Hysingla ER met its primary efficacy endpoint mean "average pain over the last 24 hours" score at week 12 by showing that patients with chronic low back pain experienced statistically significant reduction in pain compared with placebo.[8]

What is the indication for Hysingla ER?
Hysingla ER is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment in patients for whom alternative treatment options are inadequate. Hysingla ER has the following 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, Hysingla 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. Hysingla ER is not indicated as an as-needed analgesic.

Hysingla 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 and gastrointestinal obstruction, and hypersensitivity to any component of Hysingla ER or the active ingredient, hydrocodone bitartrate.[1]

Does Hysingla ER have a Boxed Warning?
The Full Prescribing Information for Hysingla ER contains the following Boxed Warning:

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

Addiction, Abuse, and Misuse
Hysingla 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 Hysingla 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 Hysingla ER. Monitor for respiratory depression, especially during initiation of Hysingla ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving Hysingla ER tablets 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 Hysingla 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 Hysingla 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)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of Hysingla ER with all cytochrome P450 CYP3A4 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 Hysingla ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.11), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

Hysingla ER contains hydrocodone, a Schedule II controlled substance. Hysingla ER exposes users to the risks of opioid addiction, abuse, and misuse. As extended-release products such as Hysingla 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. 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 Hysingla ER, and monitor all patients during therapy for the development of these behaviors or conditions. Abuse or misuse of Hysingla 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.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with modified-release opioids, even when used as recommended, and if not immediately recognized and treated, may lead to respiratory arrest and death. The risk of respiratory depression is greatest during the initiation of therapy or following a dose increase; therefore, closely monitor patients for respiratory depression. Proper dosing and titration of Hysingla ER are essential. Overestimating the Hysingla 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 Hysingla ER, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of Hysingla ER during pregnancy can result in neonatal opioid withdrawal syndrome which may be life-threatening to the neonate if not recognized and treated, and requires management according to protocols developed by neonatology experts.

Interactions with Central Nervous System Depressants

Hypotension, profound sedation, coma, respiratory depression, or death may result if Hysingla ER is used concomitantly with other CNS depressants, including alcohol or illicit drugs that can cause CNS depression. Start with a lower Hysingla 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.

Use in Elderly, Cachectic, and Debilitated Patients and Patients with Chronic Pulmonary Disease

Closely monitor elderly, cachectic, and debilitated patients, and patients with chronic obstructive pulmonary disease because of the increased risk of life-threatening respiratory depression. Consider the use of alternative non-opioid analgesics in patients with chronic obstructive pulmonary disease if possible.

Use in Patients with Head Injury and Increased Intracranial Pressure
Monitor patients closely who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or impaired consciousness). Opioids may obscure the clinical course in a patient with a head injury. Avoid the use of Hysingla ER in patients with impaired consciousness or coma.

Hypotensive Effect
Hysingla ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. Monitor patients during dose initiation or titration. In patients with circulatory shock, Hysingla ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Hysingla ER in patients with circulatory shock.

Gastrointestinal Obstruction, Dysphagia, and Choking
Use caution when prescribing Hysingla ER for patients who have difficulty swallowing, or have underlying gastrointestinal disorders that may predispose them to obstruction, dysphagia, or choking. Consider use of an alternative analgesic in these patients.

Decreased Bowel Motility
Hysingla ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of Hysingla 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.

Cytochrome P450 CYP3A4 Inhibitors and Inducers
Concomitant use of CYP3A4 inhibitors may prolong opioid effects. Use with CYP3A4 inducers may cause lack of efficacy or development of withdrawal symptoms. If co-administration is necessary, evaluate patients frequently and consider dose adjustments until stable drug effects are achieved.

Driving and Operating Machinery
Hysingla ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

Interaction with Mixed Agonist/Antagonist Opioid Analgesics
Avoid the use of mixed agonist/antagonist analgesics in patients who have received or are receiving Hysingla ER, as they may reduce the analgesic effect and/or precipitate withdrawal.

QTc Interval Prolongation
QTc prolongation has been observed following daily doses of 160 mg of Hysingla ER. Avoid use in patients with congenital QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong QTc interval. In patients who develop QTc prolongation, consider reducing the dose.

ADVERSE REACTIONS
Most common treatment-emergent adverse reactions (≥5%) reported by patients treated with Hysingla

ER in the clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence.

The Full Prescribing Information for Hysingla ER, including the Boxed Warning and Medication Guide is available at www.purduepharma.com/hysinglaerpi.

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[1] Full Prescribing Information for Hysingla™ ER (hydrocodone bitartrate) Extended-Release Tablets CII

[2] Larson et al. Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study. Hepatology. 2005; 42(6): 1364-1372.

[3] Michna, E, Duh, MS, Korves, C, Dahl, JL. Removal of opioid/acetaminophen combination prescription pain medications: assessing the evidence for hepatotoxicity and consequences of removal of these medications. Pain Medicine. 2010; 11: 369-378.

[4] IMS Health NPA, based on TRx, Q4 2014. Accessed Jan. 23, 2014.

[5] 2013 National Survey on Drug Use and Health, Table 1.89A. Substance Abuse and Mental Health Services Administration. Accessed Jan. 16, 2014.

[6] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm423977.htm. Accessed Jan. 19, 2015.

[7] http://blogs.fda.gov/fdavoice/index.php/2014/11/additional-progress-on-reducing-the-abuse-of-opioid-pain-relievers/. Accessed Jan. 19, 2015.

[8] http://www.purduepharma.com/news-media/2014/03/purdue-pharma-l-p-announces-positive-phase-3-clinical-trial-results-of-once-daily-hydrocodone-bitartrate-extended-release-tablets/. Accessed Jan. 19, 2015.