CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206627Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HYSINGLA ER safely and effectively. See full prescribing information for HYSINGLA ER.

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets, for oral use, CII
Initial U.S. Approval: 1943

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION
See full prescribing information for complete boxed warning.

- **HYSINGLA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow HYSINGLA ER whole to avoid exposure to a potentially fatal dose of hydrocodone. (5.2)**
- **Accidental ingestion of HYSINGLA ER, especially by children, can result in fatal overdose of hydrocodone. (5.2)**
- **Prolonged use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**
- **Initiation of CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone from HYSINGLA ER.**

----------INDICATIONS AND USAGE----------
HYSINGLA ER is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

Limitations of Use
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve HYSINGLA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- HYSINGLA ER is not indicated as an as-needed (prn) analgesic. (1)

----------DOSAGE AND ADMINISTRATION----------
- For opioid-naïve patients, initiate with 20 mg tablets orally every 24 hours. (2.1)
- To convert to HYSINGLA ER from another opioid, follow the conversion instructions to obtain an estimated dose. (2.1)
- Dose titration of HYSINGLA ER may occur every 3 to 5 days (2.2)
- Tablets must be swallowed intact and are not to be crushed, dissolved, or chewed, due to the risk of overdose or death. (2.3, 5.1)
- Do not abruptly discontinue HYSINGLA ER in a physically dependent patient. (2.6)
- HYSINGLA ER tablets should be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth (5.9)

----------DOSAGE FORMS AND STRENGTHS----------
Extended-release Tablets: 20, 30, 40, 60, 80, 100, and 120 mg (3)

----------CONTRAINDICATIONS----------
- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus and GI obstruction (4)
- Hypersensitivity to any components of HYSINGLA ER or the active ingredient, hydrocodone bitartrate (4)

----------WARNINGS AND PRECAUTIONS----------
- Misuse, abuse, and diversion: HYSINGLA ER is an opioid agonist and a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. (5.1)
- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If co-administration is required, consider dose reduction of one or both drugs. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of HYSINGLA ER in patients with impaired consciousness or coma susceptible to intracranial effects of CO_2 retention. (5.7)
- Risk of Choking/GI Obstruction: Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. (5.9, 5.10)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.11)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities. (5.12)
- QTc prolongation has been observed with HYSINGLA ER following daily doses of 160 mg. Avoid use in patients with congenital long 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 the QTc interval. In patients who develop QTc prolongation, consider reducing the dose (5.14, 12.2)

----------ADVERSE REACTIONS----------
Most common treatment-emergent adverse events (≥ 5%) are constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- The CYP3A4 isoenzyme plays a major role in the metabolism of HYSINGLA ER. Drugs that inhibit CYP3A4 activity may cause decreased clearance of hydrocodone which could lead to an increase in hydrocodone plasma concentrations. (7.1)
- CNS depressants: Increased risk of respiratory depression, hypotension, profound sedation, coma or death. When combined therapy with CNS depressant is contemplated, the dose of one or both agents should be reduced. (7.2)
- Mixed Agonists/Antagonists: May precipitate withdrawal or decrease analgesic effect if given concurrently with HYSINGLA ER. (7.3)
- The use of MAO inhibitors or tricyclic antidepressants with HYSINGLA ER may increase the effect of either the antidepressant or HYSINGLA ER. (7.4)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue nursing or discontinue drug. (8.3)
- Hepatic impairment: Use half the initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression. (8.6)
- Renal impairment: Use half the initial dose of HYSINGLA ER in patients with moderate and severe renal impairment and end-stage renal disease and monitor closely for adverse events such as respiratory depression. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATON

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

1 INDICATIONS AND USAGE

HYSINGLA 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, reserve HYSINGLA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- HYSINGLA ER is not indicated as an as-needed analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

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

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with HYSINGLA ER. *[see Warnings and Precautions (5.2)]*

HYSINGLA ER is administered orally once daily (every 24 hours).

HYSINGLA ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*. Crushing, chewing, or dissolving HYSINGLA ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

Use of HYSINGLA ER as the First Opioid Analgesic
Initiate therapy with HYSINGLA ER 20 mg orally every 24 hours.

Use of HYSINGLA ER in Patients who are not Opioid Tolerant
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. *[see Warnings and Precautions (5.2)]*

Daily doses of HYSINGLA ER greater than or equal to 80 mg are only for use in opioid tolerant patients.

Conversion from Oral Hydrocodone Formulations to HYSINGLA ER
Patients receiving other oral hydrocodone-containing formulations may be converted to HYSINGLA ER by administering the patient's total daily oral hydrocodone dose as HYSINGLA ER once daily.

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

Although tables of oral and parenteral equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and formulations. As such, it is preferable to underestimate a patient's 24-hour oral hydrocodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral hydrocodone requirements and manage an adverse reaction.

To obtain the initial HYSINGLA ER dose, first use Table 1 to convert the prior oral opioids to a total hydrocodone daily dose and then reduce the calculated daily hydrocodone dose by 25% to account for interpatient variability in relative potency of different opioids.

Consider the following when using the information found in Table 1.

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics to HYSINGLA ER.
- The table **cannot** be used to convert **from** HYSINGLA ER to another opioid. Doing so will result in an over-estimation of the dose of the new opioid and may result in fatal overdose

Table 1. Conversion factors to HYSINGLA ER (Not Equianalgesic Doses)

Opioid	Oral dose (mg)	Approximate oral conversion factor
Codeine	133	0.15
Hydromorphone	5	4
Methadone	30	1.5
Morphine	40	0.5
Oxycodone	20	1
Oxymorphone	10	2
Tramadol	200	0.1

To calculate the estimated total hydrocodone daily dose using Table 1:

- For patients on a single opioid, sum the current total daily dose of the opioid and then multiply the total daily dose by the approximate oral conversion factor to calculate the approximate oral hydrocodone daily dose.
- For patients on a regimen of more than one opioid, calculate the approximate oral hydrocodone dose for each opioid and sum the totals to obtain the approximate oral hydrocodone daily dose.
- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.
- Reduce the calculated daily oral hydrocodone dose by 25%

Always round the dose down, if necessary, to the nearest HYSINGLA ER tablet strength available and initiate therapy with that dose. If the converted HYSINGLA ER dose using Table 1 is less than 20 mg, initiate therapy with HYSINGLA ER 20 mg.

Example conversion from a single opioid to HYSINGLA ER:
For example, a total daily dose of oxycodone 50 mg would be converted to hydrocodone 50 mg based on the table above, and then multiplied by 0.75 (ie, take a 25 % reduction) resulting in a dose of 37.5 mg hydrocodone. Round this down to the nearest dose strength available, HYSINGLA ER 30 mg, to initiate therapy.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to HYSINGLA ER.

The dose of HYSINGLA ER can be gradually adjusted every three to five days, using increments of 10 to 20 mg, until adequate pain relief and acceptable tolerability have been achieved.

Conversion from Methadone to HYSINGLA ER
Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to HYSINGLA ER
Eighteen hours following the removal of the transdermal fentanyl patch, HYSINGLA ER treatment can be initiated. For each 25 mcg/hr fentanyl transdermal patch, a dose of HYSINGLA ER 20 mg every 24 hours represents a conservative initial dose. Follow the patient closely during conversion from transdermal fentanyl to HYSINGLA ER, as there is limited experience with this conversion.

Conversion from Transdermal Buprenorphine to HYSINGLA ER
All patients receiving transdermal buprenorphine (≤ 20 mcg/hr) should initiate therapy with HYSINGLA ER 20 mg every 24 hours. Follow the patient closely during conversion from transdermal buprenorphine to HYSINGLA ER, as there is limited experience with this conversion.

2.2 Titration and Maintenance of Therapy

Individually titrate HYSINGLA ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually re-evaluate patients receiving HYSINGLA ER to assess the maintenance of pain control and the relative incidence of adverse reactions as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Adjust the dose of HYSINGLA ER in increments of 10 mg to 20 mg every 3 to 5 days as needed to achieve adequate analgesia.

Patients who experience breakthrough pain may require a dose increase of HYSINGLA ER, or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the HYSINGLA ER dose.

If unacceptable opioid-related adverse reactions are observed, the next daily dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.3 Administration of HYSINGLA ER

HYSINGLA ER is administered once daily (every 24 hours).

HYSINGLA ER must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*.

Crushing, chewing, or dissolving HYSINGLA ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

Multiple tablets of lower dose strengths that provide the desired total daily dose can be taken as a once daily dose.

2.4 Patients with Hepatic Impairment

Patients with severe hepatic impairment may have higher plasma concentrations than those with normal function. Initiate therapy with ½ the initial dose of HYSINGLA ER in these patients and monitor closely for respiratory depression and sedation *[see Clinical Pharmacology (12.3)]*.

2.5 Patients with Renal Impairment

Patients with moderate to severe renal impairment, and end-stage renal disease may have higher plasma concentrations than those with normal function. Initiate therapy with ½ the initial dose of HYSINGLA ER in these patients and monitor closely for respiratory depression and sedation *[see Clinical Pharmacology (12.3)]*.

2.6 Discontinuation of HYSINGLA ER

Do not abruptly discontinue HYSINGLA ER. When the patient no longer requires opioid therapy, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically dependent patient. The dose may be reduced every 2-4 days. The next dose should be at least 50% of the prior dose. After reaching HYSINGLA ER 20 mg dose for 2-4 days, HYSINGLA ER can be discontinued.

3 DOSAGE FORMS AND STRENGTHS

- 20 mg film-coated extended-release tablets (round, green-colored, bi-convex tablets printed with "HYD 20")
- 30 mg film-coated extended-release tablets (round, yellow-colored, bi-convex tablets printed with "HYD 30")
- 40 mg film-coated extended-release tablets (round, grey-colored, bi-convex tablets printed with "HYD 40")
- 60 mg film-coated extended-release tablets (round, beige-colored, bi-convex tablets printed with "HYD 60")
- 80 mg film-coated extended-release tablets* (round, pink-colored, bi-convex tablets printed with "HYD 80")
- 100 mg film-coated extended-release tablets (round, blue-colored, bi-convex tablets printed with "HYD 100")
- 120 mg film-coated extended-release tablets (round, white-colored, bi-convex tablets printed with "HYD 120")

4 CONTRAINDICATIONS

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

- Hypersensitivity to any component of HYSINGLA ER or the active ingredient, hydrocodone bitartrate

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

HYSINGLA ER contains hydrocodone, a Schedule II controlled substance. As an opioid, HYSINGLA ER exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9.1)]*. 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.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed HYSINGLA ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing HYSINGLA ER, and monitor all patients receiving HYSINGLA ER for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of HYSINGLA ER for the proper management of pain in any given patient.

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 *[see Drug Abuse and Dependence (9.1), and Overdosage (10)]*.

Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing HYSINGLA ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10.2)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of HYSINGLA ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with HYSINGLA ER and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of HYSINGLA ER are essential *[see Dosage and Administration (2.1, 2.2)]*. 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.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

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

5.4 Interactions with Central Nervous System Depressants

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

When considering the use of HYSINGLA ER in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin HYSINGLA ER is made, 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 *[see Drug Interactions (7.2)]*.

5.5 Use in Elderly, Cachectic, and Debilitated Patients

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

5.6 Use in Patients with Chronic Pulmonary Disease

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

5.7 Use in Patients with Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Monitor patients closely who may be susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury.

Avoid the use of HYSINGLA ER in patients with impaired consciousness or coma.

5.8 Hypotensive Effect

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

5.9 Gastrointestinal Obstruction, Dysphagia, and Choking

In the clinical studies with specific instructions to take HYSINGLA ER with adequate water to swallow the tablet, 11 out of 2476 subjects reported difficulty swallowing HYSINGLA ER. These reports included esophageal obstruction, dysphagia, and choking, one of which had required medical intervention to remove the tablet *[see Adverse Reactions (6)]*.

Instruct patients not to pre-soak, lick, or otherwise wet HYSINGLA ER tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*.

Patients with underlying gastrointestinal disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying gastrointestinal disorders resulting in a small gastrointestinal lumen.

5.10 Decreased Bowel Motility

HYSINGLA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of 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.

5.11 Cytochrome P450 CYP3A4 Inhibitors and Inducers

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

The clinical results with CYP3A4 inhibitors show an increase in hydrocodone plasma concentrations and possibly increased or prolonged opioid effects, which could be more pronounced with concomitant use of CYP3A4 inhibitors. The expected clinical result with CYP3A4 inducers is a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to hydrocodone.

If co-administration is necessary, caution is advised when initiating HYSINGLA ER treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent

intervals and consider dose adjustments until stable drug effects are achieved *[see Dosage and Administration 2.6, Drug Interactions (7.1)]*.

5.12 Driving and Operating Machinery

HYSINGLA ER may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Peak blood levels of hydrocodone may occur 14 – 16 hours (range 6 – 30 hours) after initial dosing of HYSINGLA ER tablet administration. Blood levels of hydrocodone, in some patients, may be high at the end of 24 hours after repeated-dose administration. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of HYSINGLA ER and know how they will react to the medication *[see Clinical Pharmacology (12.3)]*.

5.13 Interaction with Mixed Agonist/Antagonist Opioid Analgesics

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

5.14 QTc Interval Prolongation

QTc prolongation has been observed with HYSINGLA ER following daily doses of 160 mg *[see Clinical Pharmacology (12.2)]*. 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 the QTc interval.

HYSINGLA ER should be avoided in patients with congenital long QT syndrome. In patients who develop QTc prolongation, consider reducing the dose by 33 – 50%, or changing to an alternate analgesic.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Hypotensive effects *[see Warnings and Precautions (5.8)]*
- Gastrointestinal Effects *[see Warnings and Precautions (5.9, 5.10)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1,827 patients were treated with HYSINGLA ER in controlled and open-label chronic pain clinical trials. Five hundred patients were treated for 6 months and 364 patients were treated for 12 months. The clinical trial population consisted of opioid-naïve and opioid-experienced patients with persistent moderate to severe chronic pain.

The common adverse reactions (≥2%) reported by patients in clinical trials comparing HYSINGLA ER (20-120 mg/day) with placebo are shown in Table 2 below:

Table 2: Adverse Reactions Reported in ≥2% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Naïve and Opioid-Experienced Patients

MedDRA Preferred Term	Open-label Titration Period (N=905) (%)	Double-blind Treatment Period Placebo (N=292) (%)	Double-blind Treatment Period HYSINGLA ER (N=296) (%)
Nausea	16	5	8
Constipation	9	2	3
Vomiting	7	3	6
Dizziness	7	2	3
Headache	7	2	2
Somnolence	5	1	1
Fatigue	4	1	1
Pruritus	3	<1	0
Tinnitus	2	1	2
Insomnia	2	2	3
Decreased appetite	1	1	2
Influenza	1	1	3

The adverse reactions seen in controlled and open-label chronic pain studies are presented below in the following manner: most common (≥5%), common (≥1% to <5%), and less common (<1%).

The most common adverse reactions (≥5%) reported by patients treated with HYSINGLA ER in the chronic pain clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, somnolence.

The common (≥1% to <5%) adverse events reported by patients treated with HYSINGLA ER in the chronic pain clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were:

Ear and labyrinth disorders	tinnitus
Gastrointestinal disorders	abdominal pain, abdominal pain upper, diarrhea, dry mouth, dyspepsia, gastroesophageal reflux disease
General disorders and administration site conditions	chest pain, chills, edema peripheral, pain, pyrexia
Infections and infestations	bronchitis, gastroenteritis, gastroenteritis viral, influenza, nasopharyngitis, sinusitis, urinary tract infection
Injury, poisoning and procedural complications	fall, muscle strain

Metabolism and nutrition disorders	decreased appetite
Musculoskeletal and connective tissue disorders	arthralgia, back pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity
Nervous system disorders	lethargy, migraine, sedation
Psychiatric disorders	anxiety, depression, insomnia
Respiratory, thoracic and mediastinal disorders	cough, nasal congestion, oropharyngeal pain
Skin and subcutaneous tissue disorders	hyperhidrosis, pruritus, rash
Vascular disorders	hot flush, hypertension

Other less common adverse reactions that were seen in <1% of the patients in the HYSINGLA ER chronic pain clinical trials include the following in alphabetical order: abdominal discomfort, abdominal distention, agitation, asthenia, choking, confusional state, depressed mood, drug hypersensitivity, drug withdrawal syndrome, dysphagia, dyspnea, esophageal obstruction, flushing, hypogonadism, hypotension, hypoxia, irritability, libido decreased, malaise, mental impairment, mood altered, muscle twitching, edema, orthostatic hypotension, palpitations, presyncope, retching, syncope, thinking abnormal, thirst, tremor, and urinary retention.

7 DRUG INTERACTIONS

7.1 Drugs Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4
Co-administration of HYSINGLA ER with ketoconazole, a strong CYP3A4 inhibitor, significantly increased the plasma concentrations of hydrocodone. Inhibition of CYP3A4 activity by 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 initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

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

7.2 Central Nervous System Depressants

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

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

7.3 Interactions with Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

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

7.4 MAO Inhibitors

HYSINGLA ER is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between hydrocodone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

7.5 Anticholinergics

Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation in addition to respiratory and central nervous system depression when HYSINGLA ER is used concurrently with anticholinergic drugs.

7.6 Strong Laxatives

Concomitant use of HYSINGLA ER with strong laxatives (e.g., lactulose), that rapidly increase gastrointestinal motility, may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. If HYSINGLA ER is used in these patients, closely monitor for the development of adverse events as well as changing analgesic requirements.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary
There are no adequate and well-controlled studies of HYSINGLA ER use during pregnancy. Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. In animal reproduction studies with hydrocodone in rats and rabbits no embryotoxicity or teratogenicity was observed. However, reduced pup survival rates, reduced fetal/pup body weights, and delayed ossification were observed at doses causing maternal toxicity. In all of the studies conducted, the exposures in animals were less than the human exposure (see Animal Data). HYSINGLA ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
<u>Fetal/neonatal adverse reactions</u>
Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*.

Data
<u>Animal Data</u>
No evidence of embryotoxicity or teratogenicity was observed after oral administration of hydrocodone throughout the period of organogenesis in rats and rabbits at doses up to 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). However, in these studies, reduced fetal body weights and delayed ossification were observed in rat at 30 mg/kg/day and reduced fetal body weights were observed in in rabbit at 30

mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). In a pre- and post-natal development study pregnant rats were administered oral hydrocodone throughout the period of gestation and lactation. At a dose of 30 mg/kg/day decreased pup viability, pup survival indices, litter size and pup body weight were observed. This dose is approximately 0.1-fold the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. HYSINGLA ER is not recommended for use in women immediately prior to and during labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. HYSINGLA ER may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

8.3 Nursing Mothers

Hydrocodone is present in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue HYSINGLA ER, taking into account the importance of the drug to the mother. Infants exposed to HYSINGLA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.4 Pediatric Use

The safety and effectiveness of HYSINGLA ER in pediatric patients have not been established.

Accidental ingestion of a single dose of HYSINGLA ER in children can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) when exposed to water or other fluids. Pediatric patients may be at increased risk of esophageal obstruction, dysphagia, and choking because of a smaller gastrointestinal lumen if they ingest HYSINGLA ER *[see Warnings and Precautions (5.9)]*.

8.5 Geriatric Use

In a controlled pharmacokinetic study, elderly subjects (greater than 65 years) compared to young adults had similar plasma concentrations of hydrocodone *[see Clinical Pharmacology (12.3)]*. Of the 1827 subjects exposed to HYSINGLA ER in the pooled chronic pain studies, 241 (13%) were age 65 and older (including those age 75 and older), while 42 (2%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received HYSINGLA ER.

Hydrocodone may cause confusion and over-sedation in the elderly. In addition, because of the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease and concomitant use of CNS active medications, start elderly patients on low doses of HYSINGLA ER and monitor closely for adverse events such as respiratory depression, sedation, and confusion.

8.6 Hepatic Impairment

No adjustment in starting dose with HYSINGLA ER is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dose adjustment is need in patients with mild renal impairment. Patients with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations than those with normal renal function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in these patients and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

HYSINGLA ER contains hydrocodone bitartrate, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, abuse, addiction and criminal diversion. The high drug content in the extended-release formulation adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

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

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common to addicts and drug abusers. Drug seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers, people with untreated addiction, and criminals seeking drugs to sell. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

HYSINGLA ER can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk is increased with concurrent use of HYSINGLA ER with alcohol or other central nervous system depressants

Risks Specific to Abuse of HYSINGLA ER
HYSINGLA ER is for oral use only. Abuse of HYSINGLA ER poses a risk of overdose and death.. Taking cut, broken, chewed, crushed, or dissolved HYSINGLA ER increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in HYSINGLA ER can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies
HYSINGLA ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse, and maintains some extended release characteristics even if the tablet is physically compromised. To evaluate the ability of these physicochemical properties to reduce the potential for abuse of HYSINGLA ER, a series of *in vitro* laboratory studies, pharmacokinetic studies and clinical abuse potential studies was conducted. A summary is provided at the end of this section.

In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that HYSINGLA ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation. When subjected to an aqueous environment, HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

Clinical Abuse Potential Studies
Studies in Non-dependent Opioid Abusers
Two randomized, double-blind, placebo and active-comparator studies in non-dependent opioid abusers were conducted to characterize the abuse potential of HYSINGLA ER following physical manipulation and administration via the intranasal and oral routes. For both studies, drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100 where 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again").

Intranasal Abuse Potential Study
In the intranasal abuse potential study, 31 subjects were dosed and 25 subjects completed the study. Treatments studied included intranasally administered tampered HYSINGLA ER 60 mg tablets, powdered hydrocodone bitartrate 60 mg, and placebo. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 82% (n = 23) of subjects receiving tampered HYSINGLA ER compared to no subjects with powdered hydrocodone or placebo.

The intranasal administration of tampered HYSINGLA ER was associated with statistically significantly lower mean and median scores for drug liking and take drug again ($P<0.001$ for both), compared with powdered hydrocodone as summarized in Table 3.

Table 3. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again VAS Following intranasal Administration of HYSINGLA ER and Hydrocodone Powder in Non-dependent Opioid Abusers

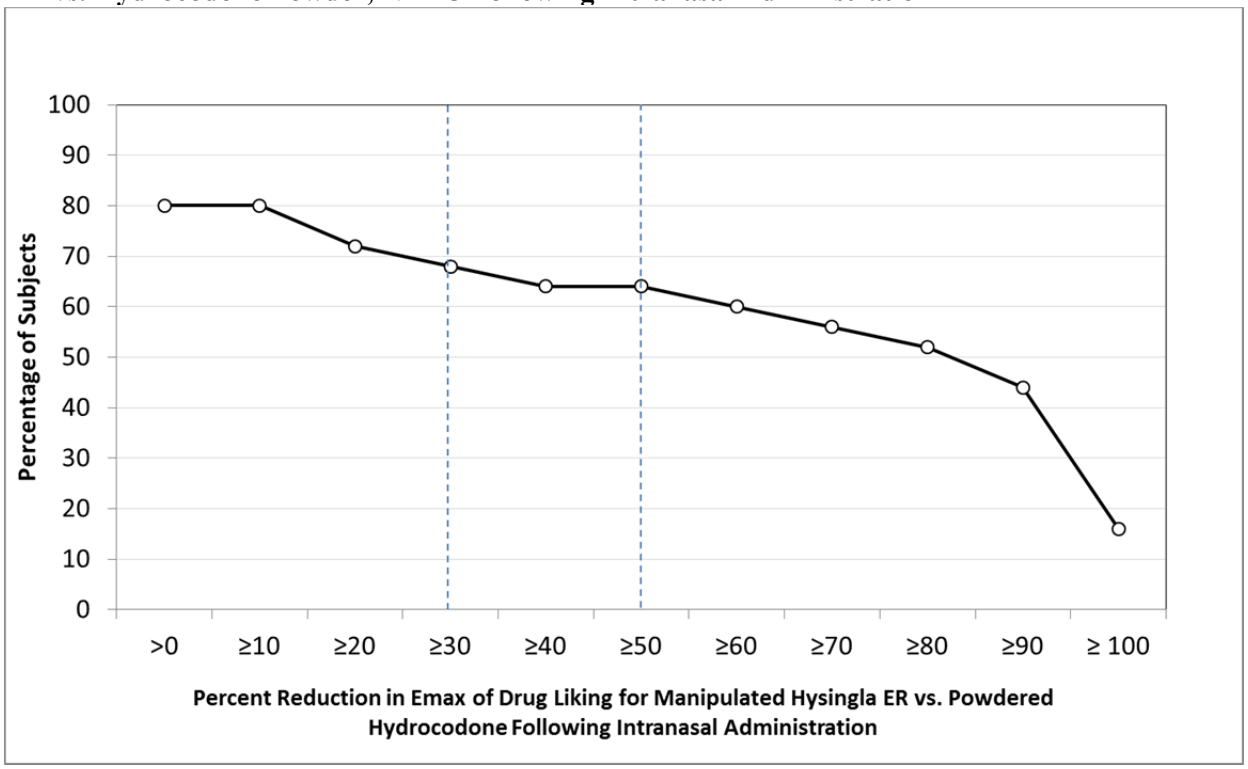
VAS Scale (100 point) *Intranasal (n=25)*	HYSINGLA ER Manipulated	Hydrocodone Powder
Drug Liking*		
Mean (SE)	65.4 (3.7)	90.4 (2.6)
Median (Range)	56 (50–100)	100 (51–100)
Take Drug Again**		
Mean (SE)	36.4 (8.2)	85.2 (5.0)
Median (Range)	14 (0-100)	100 (1-100)

*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)
** Unipolar scale (0=maximum negative response, 100=maximum positive response)

Figure 1 demonstrates a comparison of peak drug liking scores for tampered HYSINGLA ER compared with powdered hydrocodone in subjects (n = 25) who received both treatments intranasally. The Y-axis represents the percent of subjects attaining a percent reduction in peak drug liking scores for tampered HYSINGLA ER vs. hydrocodone powder greater than or equal to the value on the X-axis.

Approximately 80% (n = 20) of subjects had some reduction in drug liking with tampered HYSINGLA ER relative to hydrocodone powder. Sixty-eight percent (n = 17) of subjects had a reduction of at least 30% in drug liking with tampered HYSINGLA ER compared with hydrocodone powder, and approximately 64% (n = 16) of subjects had a reduction of at least 50% in drug liking with tampered HYSINGLA ER compared with hydrocodone powder. Approximately 20% (n = 5) of subjects had no reduction in liking with tampered HYSINGLA ER relative to hydrocodone powder.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for Manipulated HYSINGLA ER vs. Hydrocodone Powder, N = 25 Following Intranasal Administration



Oral Abuse Potential Study

In the oral abuse potential study, 40 subjects were dosed and 35 subjects completed the study. Treatments studied included oral administrations of chewed HYSINGLA ER 60 mg tablets, intact HYSINGLA ER 60 mg tablets, 60 mg aqueous hydrocodone bitartrate solution, and placebo.

The oral administration of chewed and intact HYSINGLA ER was associated with statistically lower mean and median scores on scales that measure drug liking and desire to take drug again (P<0.001), compared to hydrocodone solution as summarized in Table 4.

Table 4. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again VAS Following Oral Administration of HYSINGLA ER and Hydrocodone Solution in Non-dependent Recreational Opioid Users

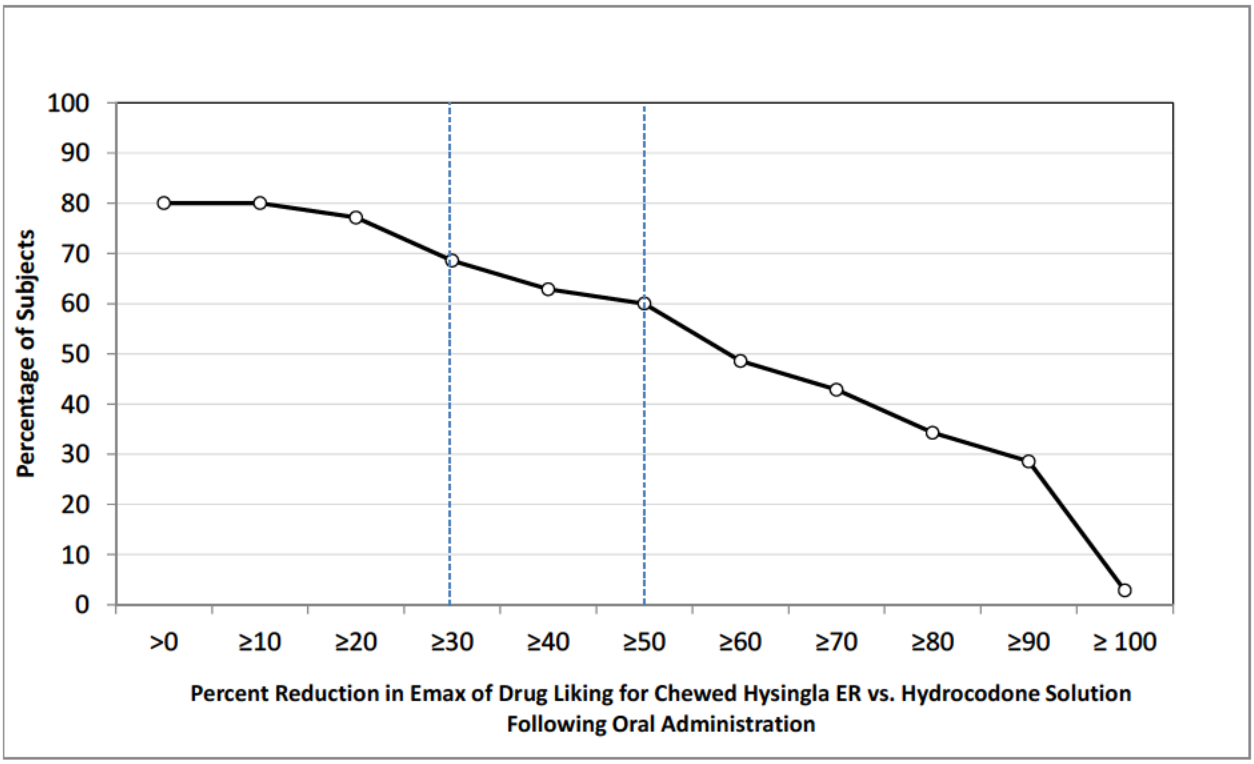
VAS Scale (100 point)	HYSINGLA ER		Hydrocodone
Oral (n=35)	**Intact**	**Chewed**	**Solution**
Drug Liking*			
Mean (SE)	63.3 (2.7)	69.0 (3.0)	94.0 (1.7)
Median (Range)	58 (50–100)	66 (50–100)	100 (51–100)
Take Drug Again**			
Mean (SE)	34.3 (6.1)	44.3 (6.9)	89.7 (3.6)
Median (Range)	24 (0-100)	55 (0-100)	100 (1-100)

*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)
** Unipolar scale (0=maximum negative response, 100=maximum positive response)

Figure 2 demonstrates a comparison of peak drug liking scores for chewed HYSINGLA ER compared with hydrocodone solution in subjects who received both treatments orally. The Y-axis represents the percent of subjects attaining a percent reduction in peak drug liking scores for chewed HYSINGLA ER vs. hydrocodone solution greater than or equal to the value on the X-axis.

Approximately 80% (n = 28) of subjects had some reduction in drug liking with chewed HYSINGLA ER relative to hydrocodone solution. Approximately 69% (n = 24) of subjects had a reduction of at least 30% in drug liking with chewed HYSINGLA ER compared with hydrocodone solution, and approximately 60% (n = 21) of subjects had a reduction of at least 50% in drug liking with chewed HYSINGLA ER compared with hydrocodone solution. Approximately 20% (n = 7) of subjects had no reduction in drug liking with chewed HYSINGLA ER relative to hydrocodone solution.

Figure 2. Percent Reduction Profiles for E_{max} of Drug Liking VAS for Chewed HYSINGLA ER vs. Hydrocodone Solution, N = 35 Following Oral Administration



The results of a similar analysis of drug liking for intact HYSINGLA ER relative to hydrocodone solution were comparable to the results of chewed HYSINGLA ER relative to hydrocodone solution. Approximately 83% (n = 29) of subjects had some reduction in drug liking with intact HYSINGLA ER relative to hydrocodone solution. Eighty-three percent (n = 29) of subjects had a reduction of at least 30% in peak drug liking scores with intact HYSINGLA ER compared to hydrocodone solution, and approximately 74% (n = 26) of subjects had a reduction of at least 50% in peak drug liking scores with intact HYSINGLA ER compared with hydrocodone solution. Approximately 17% (n = 6) had no reduction in drug liking with intact HYSINGLA ER relative to hydrocodone solution.

Summary

The *in vitro* data demonstrate that HYSINGLA ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the *in vitro* data, also indicate that HYSINGLA ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of HYSINGLA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

HYSINGLA ER contains hydrocodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, addiction, and criminal diversion *[See Warnings and Precautions (5.1) and Drug Abuse and Dependence (9)]*.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

HYSINGLA ER should be discontinued by a gradual downward titration *[see Dosage and Administration (2.6)]*. If HYSINGLA ER is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.3)]*.

10 OVERDOSAGE

10.1 Symptoms

Acute overdosage with opioids is often characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

10.2 Treatment

In the treatment of HYSINGLA ER overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation.

Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

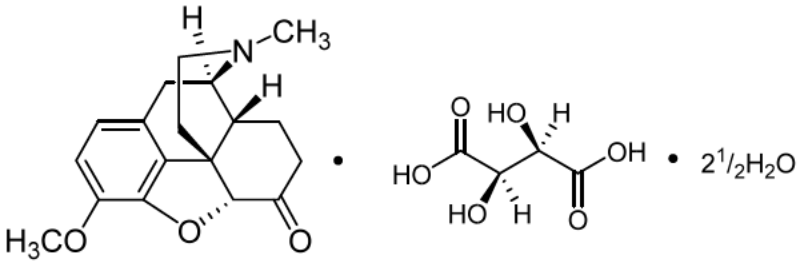
The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from opioid overdosage. Nalmefene is an alternative opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of HYSINGLA ER may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling, as needed, to maintain adequate respiration.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on HYSINGLA ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

HYSINGLA™ ER (hydrocodone bitartrate) extended-release tablets are supplied in 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg and 120 mg film-coated tablets for oral administration. The tablet strengths describe the amount of hydrocodone per tablet as the bitartrate salt.

Hydrocodone bitartrate is an opioid agonist. Its chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). Its structural formula is:



Empirical formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$; Molecular weight: 494.49.

Hydrocodone bitartrate exists as fine white crystals or a crystalline powder. It is affected by light. It is soluble in water, slightly soluble in alcohol, and insoluble in ether and chloroform.

The 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg and 120 mg tablets contain the following inactive ingredients: Butylated Hydroxytoluene (BHT, an additive in Polyethylene Oxide), Hydroxypropyl Cellulose, Macrogol/PEG 3350, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Oxide, Polysorbate 80, Polyvinyl Alcohol, Talc, Titanium Dioxide, and Black Ink.

The 20 mg tablets also contain Iron Oxide Yellow and FD&C Blue #2 Aluminum Lake/Indigo Carmine Aluminum Lake.

The 30 mg tablets also contain Iron Oxide Yellow.

The 40 mg tablets also contain Iron Oxide Yellow, Iron Oxide Red, and Iron Oxide Black.

The 60 mg tablets also contain Iron Oxide Yellow and Iron Oxide Red.

The 80 mg tablets also contain Iron Oxide Red.

The 100 mg tablets also contain FD&C Blue #2 Aluminum Lake.

Black Ink Contains: Shellac Glaze (in Ethanol), Isopropyl Alcohol, Iron Oxide Black, N-Butyl Alcohol, Propylene Glycol and Ammonium Hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydrocodone is a semi-synthetic opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. Hydrocodone acts as an agonist binding to and activating opioid receptors in the brain and spinal cord, which are coupled to G-protein complexes and modulate synaptic transmission through adenylate cyclase. The pharmacological effects of hydrocodone including analgesia, euphoria, respiratory depression and physiological dependence are believed to be primarily mediated via μ opioid receptors.

12.2 Pharmacodynamics

Cardiac Electrophysiology
QTc interval prolongation was studied in a double-blind, placebo- and positive-controlled 3-treatment parallel-group, dose-escalating study of HYSINGLA ER in 196 healthy subjects. QTc interval prolongation was observed following HYSINGLA ER 160 mg per day. The maximum mean (90% upper confidence bound) difference in the QTc interval between HYSINGLA ER and placebo (after baseline-correction) at steady state was 6 (9) milliseconds, 7 (10) milliseconds, and 10 (13) milliseconds at HYSINGLA ER doses of 80 mg, 120 mg and 160mg respectively. For clinical implications of the prolonged QTc interval, see Warnings and Precautions (5.14).

Central Nervous System
The principal therapeutic action of hydrocodone is analgesia. In common with other opioids, hydrocodone causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Opioids depress the cough reflex by direct effect on the cough center in the medulla.

Hydrocodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Overdosage (10.1)]*. In addition to analgesia, the widely diverse effects of hydrocodone include drowsiness, changes in mood, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system *[see Clinical Pharmacology (12.2)]*.

Gastrointestinal Tract and Other Smooth Muscle
Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System
Hydrocodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

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

Concentration/Exposure—Adverse Experience Relationships
There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. As with all opioids, the dose of HYSINGLA ER must be individualized *[see Dosage and Administration (2.1, 2.2)]*. The effective analgesic dose for some patients will be too high to be tolerated by other patients.

12.3 Pharmacokinetics

Absorption
HYSINGLA ER is a single-entity extended-release formulation of hydrocodone that yields a gradual increase in plasma hydrocodone concentrations with a median T_{max} of 14 – 16 hours noted for different dose strengths. Peak plasma levels may occur in the range of 6 -30 hours after single dose HYSINGLA ER administration.

Systemic exposure (AUC and C_{max}) increased linearly with doses from 20 to 120 mg. Both C_{max} and AUC increased slightly more than dose proportionally (Table 5). The mean terminal half-life ($t_{1/2}$) was similar for all HYSINGLA ER dose strengths ranging from 7 to 9 hours.

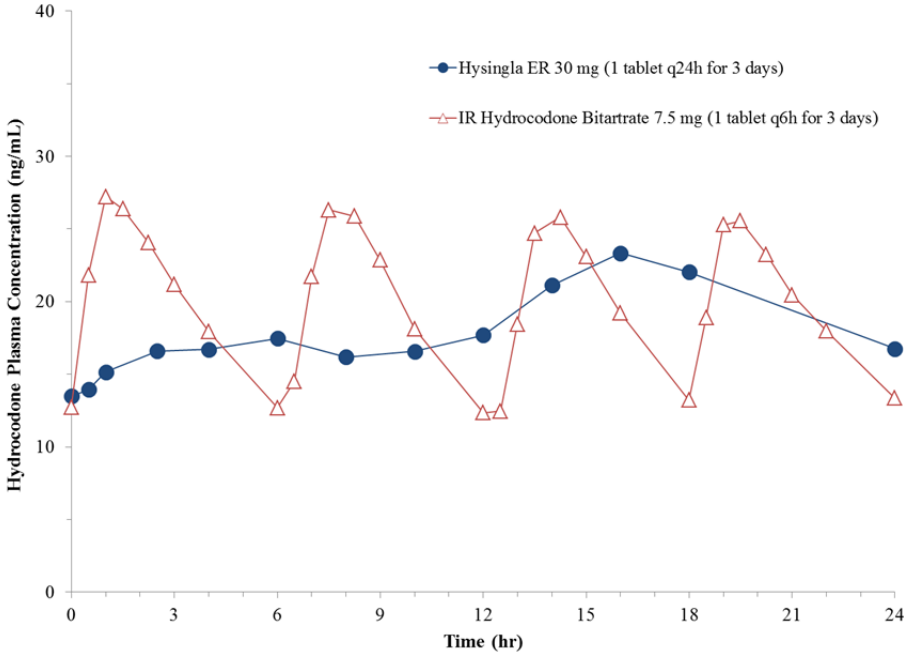
Table 5 Mean (SD) Single-Dose Pharmacokinetic Parameters of HYSINGLA ER

Dose Strength (mg)	AUCinf (ng•h/mL)	C_{max} (ng/mL)	T_{max}* (h)
20	284 (128)	14.6 (5.5)	16 (6, 24)
40	622 (252)	33.9 (11.8)	16 (6, 24)
60	1009 (294)	53.6 (15.4)	14 (10, 30)
80	1304 (375)	69.1 (17.2)	16 (10, 24)
120	1787 (679)	110 (44.1)	14 (6, 30)

* median (minimum, maximum)

As compared to an immediate-release hydrocodone combination product, HYSINGLA ER at the same daily dose results in similar bioavailability but with lower maximum concentrations at steady state. (Figure 3).

Figure 3. Mean Steady-State Plasma Hydrocodone Concentration Profile



Steady-state plasma hydrocodone concentrations were confirmed on day 3 of once-daily dosing of HYSINGLA ER. The extent of accumulation of systemic exposure was 1.3 and 1.1 fold with respect to AUC and C_{max} at steady-state. The mean terminal half-life ($t_{1/2}$) at steady state was 7 hours. Median T_{max} values were 14 hours (range: 12 to 24 hours) on both Day 1 and Day 5 following once daily administration of HYSINGLA ER for five days. Daily fluctuation in peak to trough plasma levels of hydrocodone were higher at 80 mg and 120 mg doses of HYSINGLA ER compared to 30 mg dose (Table 6).

Table 6 Mean (SD) Steady-State Hydrocodone Pharmacokinetic Parameters

Regimen	AUC24,ss (ng•h/mL)	C_{max},ss (ng/mL)	C_{min},ss (ng/mL)	%Fluctuation*
HYSINGLA ER				
30 mg q24h	443 (128)	26.4 (7.4)	16.7 (5.2)	61 (6.4,113)
80 mg q24h	1252 (352)	82.6 (25.7)	28.2 (12)	105 (36,214)
120 mg q24h	1938 (729)	135 (50)	63.6 (29)	97.9 (32, 250)

* Mean (minimum, maximum); Percentage fluctuation in plasma concentration is derived as (C_{max},ss – C_{min}, ss)*100/Cavg,ss.

Food Effects

C_{max} and AUC of HYSINGLA ER 120 mg tablets were similar under low fat conditions relative to fasting conditions (17% and 9% higher, respectively). C_{max} was higher (54%) under high fat conditions relative to fasting conditions; however, AUC of HYSINGLA ER 120 mg tablets was only 20% higher when co-administered with a high fat meal. HYSINGLA ER may be administered without regard to meals.

Distribution

Following administration of HYSINGLA ER, the typical (70 kg adult) value of apparent volume of distribution (V/F) is 402 L, suggesting extensive tissue distribution. The extent of *in vivo* binding of hydrocodone to human plasma proteins was minimal with a mean % bound at 36%.

Elimination

Metabolism

Hydrocodone exhibits a complex pattern of metabolism, including *N*-demethylation, *O*-demethylation, and 6-keto reduction to the corresponding 6-α-and 6-β-hydroxy metabolites. CYP3A4 mediated *N*-demethylation to inactive norhydrocodone is the primary metabolic pathway of hydrocodone with a lower contribution from CYP2B6 and CYP2C19. The minor metabolite hydromorphone (<3% of the circulating parent hydrocodone) was mainly formed by CYP2D6 mediated *O*-demethylation with a smaller contribution by CYP2B6 and CYP2C19. Hydromorphone may contribute to the total analgesic effect of hydrocodone.

Excretion

Hydrocodone and its metabolites are cleared primarily by renal excretion. The percent of administered dose excreted unchanged as hydrocodone in urine was 6.5% in subjects with normal renal function, and 5.0%, 4.8%, and 2.3% in subjects with mild, moderate, and severe renal impairment, respectively. Renal clearance (CLr) of hydrocodone in healthy subjects was small (5.3 L/h) compared to apparent oral clearance (CL/F, 83 L/h); suggesting that non-renal clearance is the main elimination route. Ninety-nine percent of the administered dose is eliminated within 72 hours. The mean terminal half-life ($t_{1/2}$) was similar for all HYSINGLA ER dose strengths ranging from approximately 7 to 9 hours across the range of doses.

Specific Populations

Elderly (≥ 65 years)

Following administration of 40 mg HYSINGLA ER, the pharmacokinetics of hydrocodone in healthy elderly subjects (65 to 77 years) are similar to the pharmacokinetics in healthy younger subjects (20 to 45 years). There were no clinically meaningful increase in C_{max} (16%) and AUC (15%) of hydrocodone in elderly as compared with younger adult subjects *[see Use in Specific Populations (8.5)]*.

Gender

Systemic exposure of hydrocodone (C_{max} and AUC) was similar between males and females.

Hepatic Impairment

After a single dose of 20 mg HYSINGLA ER in subjects (8 each) with normal hepatic function, mild, moderate or severe hepatic impairment based on Child-Pugh classifications, mean hydrocodone C_{max} values were 16, 15, 17, and 18 ng/mL, respectively. Mean hydrocodone AUC values were 342, 310, 390, and 415 ng.hr/mL for subjects with normal hepatic function, mild, moderate or severe hepatic impairment, respectively. Mean hydrocodone C_{max} values were -6%, 5%, and 5% and AUC values were -14%, 13%, and 4% in patients with mild, moderate or severe hepatic impairment, respectively.

The mean *in vivo* plasma protein binding of hydrocodone across the groups was similar, ranging from 33% to 37% *[see Use in Specific Populations (8.6)]*.

Renal Impairment

After a single dose of 60 mg HYSINGLA ER in subjects (8 each) with normal renal function, mild, moderate, or severe renal impairment based on Cockcroft-Gault criteria and end stage renal disease patients, mean hydrocodone C_{max} values were 40, 50, 51, 46, and 38 ng/mL, respectively. Mean hydrocodone AUC values were 754, 942, 1222, 1220, and 932 ng.hr/mL for subjects with normal renal function, mild, moderate or severe renal impairment and ESRD, respectively. Hydrocodone C_{max} values were 14%, 23%, 11% and -13% and AUC values were 13%, 61%, 57% and 4% higher in patients with

mild, moderate or severe renal impairment or end stage renal disease, respectively *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

CYP3A4

Co-administration of HYSINGLA ER (20 mg single dose) and CYP3A4 inhibitor ketoconazole (200 mg BID for 6 days) increased mean hydrocodone AUC and C_{max} by 135% and 78%, respectively *[see Warnings and Precautions (5.11) and Drug Interactions (7.1)]*.

CYP2D6

The 90% confidence interval (CI) of the geometric means for hydrocodone AUC_{inf} (98 to 115%), AUC_t (98 to 115%), and C_{max} (93 to 121%) values were within the range of 80 to 125% when a single dose of HYSINGLA ER 20 mg was co-administered with CYP2D6 inhibitor paroxetine (20 mg treatment each morning for 12 days). No differences in systemic exposure of hydrocodone were observed in the presence of paroxetine.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Hydrocodone was evaluated for carcinogenic potential in rats and mice.

In a two-year bioassay in rats, doses up to 25 mg/kg in males and females were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 0.2-fold the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). In a two-year bioassay in mice, doses up to 200 mg/kg in males and 100 mg/kg in females were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 3.5-fold and 3.0-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons).

Mutagenesis

Hydrocodone was genotoxic in the mouse lymphoma assay in the presence of rat S9 metabolic activation but not in the absence of rat metabolic activation. However, hydrocodone was not genotoxic in the mouse lymphoma assay with or without human S9 metabolic activation. There was no evidence of genotoxic potential with hydrocodone in an *in vitro* bacterial reverse mutation assay with Salmonella typhimurium and Escherichia coli with or without metabolic activation or in an *in vivo* mouse bone marrow micronucleus test with or without metabolic activation.

Impairment of Fertility

No effect on fertility or general reproductive performance was seen with oral administration of hydrocodone to male and female rats at doses up to 25 mg/kg/day (approximately 0.06-fold and 0.08-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons).

14 CLINICAL STUDIES

The efficacy and safety of HYSINGLA ER was evaluated in a randomized double-blind, placebo-controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain.

14.1 Moderate to Severe Chronic Lower Back Pain Study

A total of 905 chronic low back pain patients (opioid naive and opioid-experienced) who were not responsive to their prior analgesic therapy entered an open-label conversion and dose- titration period for up to 45 days with HYSINGLA ER. Patients were dosed once daily with HYSINGLA ER (20 to 120 mg). Patients stopped their prior opioid analgesics and/or nonopioid analgesics prior to starting

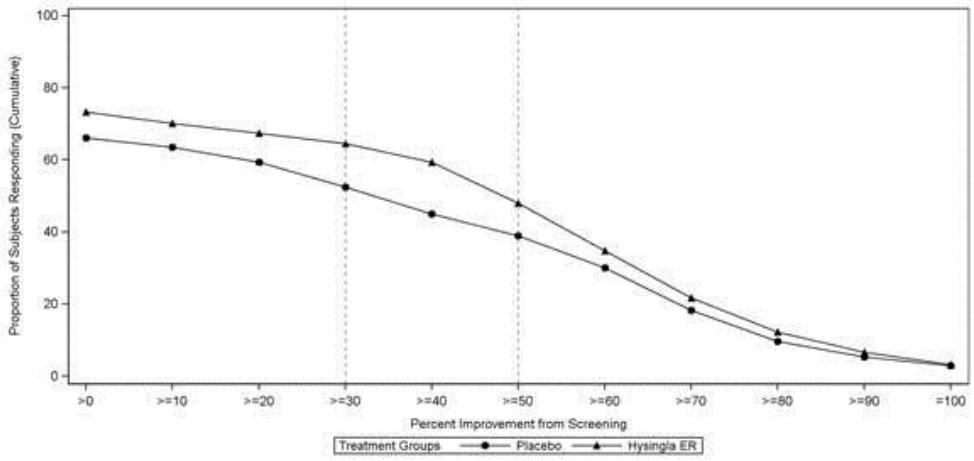
HYSINGLA ER treatment. Optional use of rescue medication (immediate-release oxycodone 5 mg) up to 2 doses (2 tablets) was permitted during the dose titration period. For inadequately controlled pain, HYSINGLA ER dose was allowed to be increased once every 3–5 days until a stabilized and tolerable dose was identified. During the dose-titration period, 65% of the patients achieved a stable HYSINGLA ER dose and entered the double-blind treatment period. The remaining subjects discontinued from the dose-titration period for the following reasons: adverse events (10%); lack of therapeutic effect (5%); confirmed or suspected diversion (3%); subject's choice (5%); lost to follow-up (2%); administrative reasons (2%); and failure to achieve protocol-defined reduction in pain score (7%).

Following the dose titration period, 588 patients (65%) were randomized at a ratio of 1:1 into a 12-week double-blind treatment period with their fixed stabilized dose of HYSINGLA ER (or matching placebo). These patients met the study randomization criteria of adequate analgesia (pain reduction of at least 2 points to a score of 4 or less on a 0-10 numerical rating scale) and acceptable tolerability of HYSINGLA ER. Patients randomized to placebo were given a blinded taper of HYSINGLA ER according to a pre-specified tapering schedule, 3 days on each step-down dose (reduced by 25-50% from the previous dose). Patients were allowed to use rescue medication (immediate-release oxycodone 5 mg) up to 6 doses (6 tablets) per day depending on their randomized HYSINGLA ER dose. During the double-blind period, 229 treated patients (77%) completed the 12-week treatment with HYSINGLA ER and 210 patients (72%) completed on placebo. Overall, 10% of patients discontinued due to lack of therapeutic effect (5% in HYSINGLA patients and 15% in placebo patients); 5% of patients discontinued due to adverse events (6% in HYSINGLA ER treated patients and 3% in placebo patients).

HYSINGLA ER provided greater analgesia compared with placebo. There was a statistically significant difference in the weekly average pain scores at Week 12 between the two groups.

The percentage of patients (responders) in each group who demonstrated improvement in their weekly average pain scores at Week 12, as compared with screening is shown in Figure 4. The figure is cumulative, so that patients whose change from screening is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were classified as non-responders. Treatment with HYSINGLA ER resulted in a higher proportion of responders, defined as patients with at least a 30% and 50% improvement, as compared with placebo.

Figure 4. **Percent Improvement in Pain Intensity**



16 HOW SUPPLIED/STORAGE AND HANDLING

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 20 mg are round, green-colored, bi-convex tablets printed with “HYD 20” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-271-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 30 mg are round, yellow-colored, bi-convex tablets printed with “HYD 30” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-272-60).

HYSINGLA ER (hydrocodone bitartrate)extended-release tablets 40 mg are round, grey-colored, bi-convex tablets printed with “HYD 40” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-273-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 60 mg are round, beige-colored, bi-convex tablets printed with “HYD 60” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-274-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 80 mg are round, pink-colored, bi-convex tablets printed with “HYD 80” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-275-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 100 mg are round, blue-colored, bi-convex tablets printed with “HYD 100” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-276-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 120 mg are round, white-colored, bi-convex tablets printed with “HYD 120” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-277-60).

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container, as defined by the USP.

CAUTION

DEA FORM REQUIRED

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Addiction, Abuse, and Misuse
Inform patients that the use of HYSINGLA ER, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share HYSINGLA ER with others and to take steps to protect HYSINGLA ER from theft or misuse.

Life-Threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting HYSINGLA ER or when the dose is increased, and that it can occur even at recommended doses *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Consumption

Inform patients that accidental exposure, especially in children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*. Instruct patients to take steps to store HYSINGLA ER securely and to dispose of unused HYSINGLA ER in accordance with local state guidelines and/or regulations.

Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that chronic use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.3)]*.

Interaction with Alcohol and other CNS Depressants
Inform patients that the concomitant use of alcohol with HYSINGLA ER can increase the risk of life-threatening respiratory depression *[see Warnings and Precautions (5.4)]*. Instruct patients not to consume alcoholic beverages, as well as prescription and over-the counter products that contain alcohol, during treatment with HYSINGLA ER. Inform patients that potentially serious additive effects may occur if HYSINGLA ER is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Important Administration Instructions
Instruct patients how to properly take HYSINGLA ER, including the following:

- The tablets must be swallowed whole and must not be chewed, crushed, or dissolved. Taking chewed, crushed or dissolved HYSINGLA ER tablets or contents can lead to rapid release and absorption of a potentially fatal dose of hydrocodone.
- Use HYSINGLA ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression).
- Contact prescriber if pain control is not adequate or if there are adverse reactions occurring during therapy.
- Do not discontinue HYSINGLA ER without first discussing the need for a tapering regimen with the prescriber.
- HYSINGLA ER tablets should be taken one tablet at a time.
- Do not pre-soak, lick or otherwise wet the tablet prior to placing in the mouth which may result in difficulty swallowing HYSINGLA ER tablets.
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth.

Hypotension
Inform patients that HYSINGLA ER may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Driving or Operating Heavy Machinery
Inform patients that HYSINGLA ER may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Blood levels of hydrocodone, in some patients, may be high at the end of 24 hours after repeated dose administration. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention. Instruct patients to monitor their analgesic response following the use of strong laxatives and to contact the prescriber if changes are noted.

QT interval prolongation

Inform patients that QT prolongation has been observed with HYSINGLA ER *[see Clinical Pharmacology (12.2)]*. HYSINGLA ER should be avoided in patients with congenital long QT syndrome. Instruct patients with a history of congestive heart failure or bradyarrhythmias, and patients at risk for electrolyte abnormalities or who are taking other medications known to prolong the QT interval that periodic monitoring of electrocardiograms and electrolytes may be necessary during therapy with HYSINGLA ER.

Anaphylaxis
Inform patients that anaphylaxis has been reported with ingredients contained in HYSINGLA ER. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy
Advise female patients that HYSINGLA ER may cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Nursing Mothers
Advise female patients that HYSINGLA ER passes into human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue drug *[See Use in Specific Populations (8.3)]*

Disposal of unused HYSINGLA ER
Advise patients to dispose of any unused tablets from a prescription as soon as they are no longer needed in accordance with local state guidelines and/or regulations.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

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U.S. Patent Numbers: 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

Medication Guide
HYSINGLA ER (hye-SING-luh)
(hydrocodone bitartrate) extended-release tablets, CII

HYSINGLA ER is:

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

Important information about HYSINGLA ER:

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

Do not take HYSINGLA ER if you have:

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

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

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- heart rhythm problems (long QT syndrome)
- abuse of street or prescription drugs, alcohol addiction, or mental health problems

Tell your healthcare provider if you are:

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

When taking HYSINGLA ER:

- Do not change your dose. Take HYSINGLA ER exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 24 hours, at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time the next day.
- Swallow HYSINGLA ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject HYSINGLA ER because this may cause you to overdose and die.
- HYSINGLA ER should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing it in your mouth to avoid choking on the tablet.

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

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

While taking HYSINGLA ER, DO NOT:

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

The possible side effects of HYSINGLA ER are:

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

Get emergency medical help if you have:

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

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

Manufactured by: Purdue Pharma L.P., Stamford, CT 06901-3431, www.purduepharma.com or call 1-888-726-7535

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Issue: 11/2014

Reference ID: 3661016

S/N 123456789012
LOT NO VARNISH
EXP LOT & EXP

Usual Dosage: Read accompanying prescribing literature.

U.S. Patent Nos. 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

NDC 59011-271-60

Hysingla™ ER

(hydrocodone bitartrate) extended-release tablets

20 mg

Attention Dispenser: Accompanying Medication Guide must be provided to the patient upon dispensing.

60 Tablets ℞ Only

Swallow tablets whole.
Do not cut, break, chew, crush, or dissolve.

Dispe se in a t ght, light-resistant container.
Store at 25°C (77°F); excursions permitted between 15°-30 C (59 86°F).

Purdue Pharma L.P.
Stamford, CT 06901-3431

303512-0B

N 3 59011-271-60 3

S/N 12345678912
LOT NO VARNISH
EXP LOT & EXP

Usual Dosage: Read accompanying prescribing literature.

U.S. Patent Nos. 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

NDC 59011-272-60

Hysingla™ ER

(hydrocodone bitartrate)
extended-release tablets

30 mg

CII

Attention Dispenser: Accompanying Medication Guide must be provided to the patient upon dispensing.

60 Tab ets x Only

Swallow tab ets who e

Do not cut, break, chew, crush, or dissolve.

Dispense in a tight, light-resistant container.
Store at 25°C (77°F); excursions permitted between 15°-30°C (59 86°F).

Purdue Pharma L.P.
Stamf d, CT 06901-3431

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N 3 59011-272-60 0

S/N 12345678901 2
LOT NO VARNISH
EXP LOT & EXP

Usual Dosage: Read accompanying prescribing literature.

U.S. P tent No . 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8 551,520; 8,647,667 and 8,808,740.

NDC 59011-273-60

Hysingla™ ER

(hydrocodone bitartrate)
extended-release tablets

40 mg

CII

Attention Dispenser: Accompanying Medication Guide must be provided to the patient upon dispensing.

60 Tablets R_x Only

Swa low tablets wh l .

Do not cut, break, chew, crush, or dissolve.

Dispense in a tight, light-resistant container.
Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Purdue Pharma L.P.
Stamford, CT 06901-3431

303514-0B

N 3 59011-273-60 7

S/N 12345678901 2
LOT NO VARNISH
EXP LOT & EXP

Usual Dosage: Read accompanying prescribing literature.

U.S. Patent Nos. 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

NDC 59011-274-60

Hysingla™ ER

(hydrocodone bitartrate)
extended-release tablets

60 mg CII

Attention Dispenser: Accompanying Medication Guide must be provided to the patient upon dispensing.

60 Tablets Rx Only

Swallow tablets whole.
Do not cut, break, chew, crush, or dissolve.

Dispense in a tight, light-resistant container.
Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Purdue Pharma L.P.
Stamford, CT 06901-3431
303515-0B

N 3 59011-274-60 4

Reference ID: 3661016

S/N 123456789012
LOT NO VARNISH
EXP LOT & EXP

Usual Dosage: Read accompanying prescribing literature.

U.S. Patent Nos. 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

NDC 59011-275-60

Hysingla™ ER

(hydrocodone bitartrate)
extended-release tablets

80 mg

CII

Attention Dispenser: Accompanying Medication Guide must be provided to the patient upon dispensing.

60 Tablets R_x Only

Swallow tablets whole.

Do not cut, break, chew, crush, or dissolve.

Dispense in a tight, light-resistant container.
Store at 25°C (77°F); excursions permitted between 15°–30°C (59°–86°F).

Purdue Pharma L.P.
Stamford, CT 06901-3431

303516-0B

N 3 59011-275-60 1

S/N 12345678912
LOT NO VARNISH
EXP LOT & EXP

Usual Dosage: Read accompanying prescribing literature.

U.S. Patent Nos. 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

NDC 59011-276-60

Hysingla™ ER

(hydrocodone bitartrate)
extended-release tablets

100 mg CII

Attention Dispenser: Accompanying Medication Guide must be provided to the patient upon dispensing.

60 Tablets R_x Only

Swallow tablets whole.
Do not cut, break, chew, crush, or dissolve.

Dispense in a tight, light-resistant cont ner.
Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Purdue Pharma L.P.
Stamford, CT 06901-3431
303517-0B

N 3 59011-276-60 8

Reference ID: 3661016

S/N 123456789012
LOT NO VARNISH
EXP LOT & EXP

Usual Dosage: Read accompanying prescribing literature.

U.S. Patent Nos. 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

NDC 59011-277-60

Hysingla™ ER

(hydrocodone bitartrate)
extended-release tablets

120 mg CII

Attention Dispenser: Accompanying Medication Guide must be provided to the patient upon dispensing.

60 Tablets R_x Only

Swallow tablets whole.

Do not cut, break, chew, crush, or dissolve.

Dispense in a tight, light-resistant container.
Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Purdue Pharma L.P.
Stamford, CT 06901-3431

303518-0B

N 3 59011-277-60 5