

Hysingla[®] ER (hydrocodone bitartrate) extended-release tablets

Formulary Submission Dossier

Prepared for:

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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 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving Hysingla ER and any CYP3A4 inhibitor or inducer [see *Warnings and Precautions (5.11), Drug Interactions (7.1), and Clinical Pharmacology (12.3)*].

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1. EXECUTIVE SUMMARY – CLINICAL AND ECONOMIC VALUE OF THE PRODUCT

1.1. Clinical Benefits

Hysingla ER is the first and only, extended-release (ER), oral formulation of single-entity hydrocodone bitartrate approved for every-24-hour (once daily) dosing 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. Hysingla ER is formulated with abuse-deterrent properties.

Hysingla ER incorporates a proprietary extended-release abuse deterrent technology that provides physicochemical attributes that are intended to make the tablets more difficult to manipulate for the purpose of misuse and abuse by various routes of administration or inadvertent medication error. Hysingla ER has physicochemical properties that confer resistance to crushing, dissolving and breaking – manipulations often required or preferred for abuse through intravenous and intranasal routes. Hysingla ER has two of the four tiers of Food and Drug Administration (FDA) abuse-deterrent labeling claims approved – a Tier 1 claim, indicating that the product is formulated with physicochemical barriers to abuse, and a Tier 3 claim, indicating the product is expected to result in a meaningful reduction in abuse. Furthermore, the Hysingla ER formulation is not susceptible to dose dumping in alcohol, based on *in vitro* ethanol sensitivity tests.

Dosed once-daily, Hysingla ER offers patients the advantage of a convenient dosing regimen that can decrease night awakenings to take scheduled chronic pain medication and can help to reduce patients' pill burden. Furthermore, as a single-entity hydrocodone formulation, Hysingla ER is not limited by toxicities of non-opioid components, such as acetaminophen, which has the potential to cause hepatotoxicity when the patient exceeds the maximum recommended dosage of 4 g/day.

Clinical Development Program Overview

The Hysingla ER clinical development program consisted of 16 studies in which 2476 subjects were exposed to at least one dose of Hysingla ER and 364 subjects had exposure to Hysingla ER for at least 12 months. These studies designed to evaluate the pharmacology, efficacy, safety, and abuse potential of Hysingla ER included two Phase 3 studies (1 placebo-controlled and 1 open-label), 11 pharmacokinetic (PK) studies, and three abuse potential studies. The Phase 3 studies have demonstrated a consistent pattern of pain reduction, or continuing maintenance of pain control in patients with chronic, non-malignant and non-neuropathic pain. Additionally, as a once-daily formulation, Hysingla ER provides a 24-hour pharmacokinetic profile that maintains consistent blood levels and pain relief over the 24-hour dosing interval.

Highlights of results from the Hysingla ER clinical study program are summarized below.

Efficacy / Effectiveness Studies

Efficacy of once daily Hysingla ER 20 mg to 120 mg, in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain was superior to placebo, with significantly lower “average pain over the last 24 hours” pain scores than placebo at week 12 compared with baseline ([HYD3002](#)). Sensitivity analyses of the primary efficacy variable showed a consistent significant treatment difference in favor of Hysingla ER compared with placebo ($P < .05$). The primary efficacy conclusion was robust, regardless of method of imputation used (Data on file, HYD3002).

Results of treatment effectiveness outcomes of the long-term study ([HYD3003](#)) demonstrated consistent effectiveness of Hysingla ER over 52 weeks and continued during a 24-week extension period (HYD3003S). The treatment effects of Hysingla ER, as measured by “average pain over the last 24 hours” scores, were obtained early, with the full extent of these effects established when a stable Hysingla ER dose was achieved, with improvements maintained during the long-term treatment (Data on file, HYD3003).

- As measured by “pain right now” scores, no loss in analgesia was observed immediately prior to each daily dosing, and the same level of pain relief was maintained over the 24-hour dosing interval (Data on file, HYD3003).
- During the maintenance period, approximately 66% and 40% of patients achieved at least 30% reduction and at least 50% reduction in pain, respectively, from screening and maintained the same levels of pain relief throughout the period (Data on file, HYD3003).
- During both the 52-week maintenance period and the 24-week extension period, treatment effectiveness was maintained without the continued requirement for dose increases (Data on file, HYD3003).
- During the maintenance period, the majority (86.5%) either stayed on the same starting Hysingla ER dose or had 1 dose level increase from the end of post-titration period; few (4.3%) subjects required more than 1 dose level increase (Data on file, HYD3003).

Both the pivotal and long-term studies evaluated additional secondary and exploratory efficacy endpoints, which support the primary efficacy analysis or suggest additional potential benefits of Hysingla ER (Data on file, HYD3002; Data on file, HYD3003). These are described further in section 3.0.

Safety

Hysingla ER contains a boxed warning on the risks of addiction, abuse, and misuse, life-threatening respiratory depression, accidental ingestion, neonatal opioid withdrawal syndrome, and cytochrome P450 3A4 interactions. This risk information must be considered when prescribing Hysingla ER.

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. There were more opioid-experienced patients (1017 [56%] patients) than opioid-naïve patients (810 [44%] patients). Overall, the mean (SD) age of subjects receiving Hysingla ER was 50.0 (13.1) years; 241 (13%) were age 65 and older (including those age 75 and older), while 42 (2%) were age 75 and older.

The overall adverse reaction profile of Hysingla ER is consistent with that of other approved oral mu-opioid analgesics and no unusual safety concerns have been identified. The most common adverse reactions ($\geq 5\%$) reported by patients treated with Hysingla ER in the chronic pain clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence. Furthermore, in clinical trials, no unexpected adverse reactions were seen in the elderly patients who received Hysingla ER when initiated and titrated appropriately. Overall, the first instance of adverse events (AEs) tended to occur in the first 30 days of treatment, and a similar time dependence pattern was observed for individual opioid-related AEs such as nausea, constipation, dizziness, and somnolence.

Furthermore, while cases of hearing impairment or permanent hearing loss have been reported for hydrocodone/acetaminophen combination formulations, predominantly in patients with chronic overdose, comprehensive audiologic assessments conducted to evaluate the potential impact of Hysingla ER treatment on patients' hearing functions in controlled and uncontrolled clinical trials up to 12 months with Hysingla ER, found no signal of ototoxicity (Data on file, HYD3002; Data on file, HYD3003).

Abuse-Deterrence Studies

A comprehensive *in vitro* and *in vivo* premarket assessment of the abuse-deterrent properties of Hysingla ER demonstrated that Hysingla ER has physicochemical properties that confer resistance to physical and chemical manipulations, and showed reduced “drug liking” in oral and intranasal human abuse potential studies, all of which should translate to a reduced potential for abuse and misuse and their consequences (addiction, overdose, and death) in the real-world setting.

Overall, the physicochemical properties of the Hysingla ER formulation make it more difficult to chew or crush for the purposes of oral and intranasal administration, and the formulation retains a proportion of its extended-release properties even when manipulated for the purposes of abuse. A survey of abusers also suggests that the physical properties of Hysingla ER are likely to serve as discouragement from deciding to choose Hysingla ER as a drug to abuse.

1.2. Economic Benefits

Chronic pain has a profound impact on all areas of patients' lives and has a huge economic burden on society (Porreca et al. 2006). Chronic pain adversely affects quality of life, including job performance, social relationships, normal daily activities, and emotional well-being (McCarberg et al. 2008). In a survey of working adults, it was determined that lost productive time (due to absenteeism and to reduced performance while at work or —presenteeism) from pain due to conditions such as headache, arthritis, back pain and other musculoskeletal conditions costs an estimated \$61.2 billion per year. The majority (76.6%) of lost productive time was explained by reduced work performance, not absenteeism (Stewart et al. 2003). Another study evaluating arthritis pain exacerbations in U.S. workers found that the estimated lost productive work time from arthritis in the U.S. workforce was \$7.11 billion, with 65.7% of this cost attributed to the 38% of workers with pain exacerbations (Ricci et al. 2005).

Direct medical costs from uncontrolled pain are attributed to more frequent medical service utilization, including physician office visits, emergency department visits, and unscheduled hospitalizations (Grant et al. 1995). Costs of uncontrolled pain also include impairments in health-related quality of life (HRQL) such as decreased sleep, decreased physical functioning, decreased enjoyment of life, decreased ability to perform normal work, and decreased activity (Galer et al. 2000; Briggs et al. 1999).

A budget impact model was developed to estimate the impact on a managed care organization's budget of including Hysingla ER as a treatment option for patients with chronic pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Key uncertainties for payers are how many patients will use Hysingla ER and for how long. The budget impact model is based on a detailed analysis of longitudinal claims data to understand the likely economic impact of Hysingla ER for different subpopulations. Key components of the model include an understanding of treatment patterns for patients prescribed immediate-release (IR) hydrocodone, and, based upon those treatment patterns, a projection of the impact on pharmacy budgets. The model can be customized to payers' specific formularies.

While a large number of patients (~11.9 million commercial patients) are prescribed IR hydrocodone, the majority (88.8%) are prescribed it for a short period of time (< 60 days) and have little continued use (on average < 2 months in the subsequent year). Patients who have used IR hydrocodone for at least 60 days have a longer duration of therapy in the following year (8.8 months, on average). Even among this group, however, opioid spend represents < 3% of total medical expenditures. This group is more likely to initiate use of an ER/LA opioid and has substantially greater average monthly prescription of IR hydrocodone (~50% with at least 120 pills/month compared to < 6% among all IR hydrocodone patients).

Taken together and based upon market uptake assumptions, these characteristics lead to a self-limiting budget impact (incremental cost Per Patient Per Month [PMPM] of < \$0.01 in this population and in the overall IR hydrocodone population).

1.3. Conclusions

Chronic pain is a major health problem that affects millions of people in the United States and results in personal suffering, reduced functionality, and reduced productivity. The direct and indirect costs of chronic pain are vast. The development of opioid formulations that have abuse-deterrent properties is of significant

importance in providing a societal benefit in helping to curtail the serious public health problem of opioid drug abuse and misuse, while continuing to allow access for patients who require opioid analgesics.

Hysingla ER, as an extended-release, oral formulation of single-entity hydrocodone bitartrate approved for every-24-hour (once daily) dosing, helps to fill the unmet need for safe, effective, and convenient therapies to treat chronic pain. Hysingla ER has abuse-deterrent properties that have resulted in FDA-approved Tier 1 and Tier 3 abuse deterrent labeling claims – a Tier 1 claim, indicating that the product is formulated with physicochemical barriers to abuse, and a Tier 3 claim, indicating the product is expected to result in a meaningful reduction in abuse. Results from the robust Hysingla ER clinical development program provide evidence that Hysingla ER at the studied doses is effective and tolerated for pain management in opioid naïve and opioid tolerant patients with different levels of moderate to severe chronic pain. These studies have demonstrated a consistent pattern of pain reduction or continuing maintenance of pain control in patients with chronic, non-malignant and non-neuropathic pain.

For patients with chronic pain, compliance with administration of analgesics is essential to prevent gaps in pain relief. As a once-daily formulation, Hysingla ER decreases pill burden, may decrease the need to awaken at night to take another dose of pain medication, and provides a convenient and simplified dosing regimen for the patient. Furthermore, as a single-entity hydrocodone formulation, Hysingla ER is not subject to the potential toxicities of non-opioid components, such as acetaminophen, when taken at doses exceeding the maximum recommended dose.

2. PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1. Product Description

2.1.a. Generic Name, Brand Name, and Therapeutic Class

Brand Name: Hysingla™ ER

Generic Name: hydrocodone bitartrate extended-release tablets

Therapeutic Class: opioid analgesic

2.1.b.-2.1.d. Dosage form, Strength, Package Size, NDC Number, and WAC

Table 1. Hysingla ER Description, How Supplied, NDC Number, and WAC

Product Description	How Supplied	NDC Number	WAC (\$)
Hysingla ER (hydrocodone bitartrate) extended-release tablets 20 mg are round, green-colored, bi-convex tablets printed with "HYD 20"	Child-resistant closure, opaque plastic bottles of 60	59011-271-60	394.20
Hysingla ER (hydrocodone bitartrate) extended-release tablets 30 mg are round, yellow-colored, bi-convex tablets printed with "HYD 30"	Child-resistant closure, opaque plastic bottles of 60	59011-272-60	575.40
Hysingla ER (hydrocodone bitartrate) extended-release tablets 40 mg are round, grey-colored, bi-convex tablets printed with "HYD 40"	Child-resistant closure, opaque plastic bottles of 60	59011-273-60	775.20
Hysingla ER (hydrocodone bitartrate) extended-release tablets 60 mg are round, beige-colored, bi-convex tablets printed with "HYD 60"	Child-resistant closure, opaque plastic bottles of 60	50911-274-60	1,073.40
Hysingla ER (hydrocodone bitartrate) extended-release tablets 80 mg are round, pink-colored, bi-convex tablets printed with "HYD 80"	Child-resistant closure, opaque plastic bottles of 60	50911-275-60	1,447.20
Hysingla ER (hydrocodone bitartrate) extended-release tablets 100 mg are round, blue-colored, bi-convex tablets printed with "HYD 100"	Child-resistant closure, opaque plastic bottles of 60	50911-276-60	1,841.40
Hysingla ER (hydrocodone bitartrate) extended-release tablets 120 mg are round, white-colored, bi-convex tablets printed with "HYD 120"	Child-resistant closure, opaque plastic bottles of 60	50911-277-60	2,040.60

Hysingla ER Delivery System

Hysingla ER tablets provide delivery of hydrocodone bitartrate over a 24-hour period, allowing for once-daily dosing (once every 24 hours).

Hysingla ER utilizes a matrix drug delivery system with a colored, cosmetic, film coat. This cosmetic coat does not affect drug delivery – its only purpose is to differentiate tablet strengths. In matrix-type drug delivery systems, the active pharmaceutical ingredient and excipient(s) that control the rate of release of the active ingredient are distributed throughout the dosage form (Langer 1993). Hysingla ER tablets do not contain an immediate-release component nor do they behave pharmacokinetically as though they do.

Hysingla ER must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Crushing, chewing, or dissolving Hysingla ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death.

Hysingla ER is formulated with RESISTEC™ technology. RESISTEC is Purdue Pharma's proprietary extended-release solid oral dosage formulation platform. RESISTEC uses a unique combination of polymer

and processing that (1) confers tablet hardness (2) imparts viscosity when dissolved in aqueous solutions and (3) resists increased drug release rate when mixed with alcoholic beverages, *in vitro* (Data on file, NDA – Quality Overall Summary).

Abuse-deterrent Technology

The physicochemical attributes of Hysingla ER are intended to make the tablets more difficult to manipulate for the purpose of misuse and abuse by various routes of administration and to reduce the likelihood of certain inadvertent medication errors. Hysingla ER has physicochemical properties that confer resistance to crushing, dissolving and breaking – manipulations often required or preferred for abuse through intravenous and intranasal routes, and it maintains some extended-release characteristics even if the tablet is physically compromised.

In addition to tablet size and shape, the rate of release of hydrocodone from each Hysingla ER tablet is controlled by the polyethylene oxide excipient (in this case, a retardant). When subjected to an aqueous environment, polyethylene oxide gradually swells and forms a viscous hydrogel. This hydrogel controls the rate of drug release from the dosage form. After treatment via a specific manufacturing process, it is also the polyethylene oxide excipient that imparts hardness to the tablet (Data on file, NDA – Quality Overall Summary).

This technology is not expected to have an impact on the ability for nonmedical use by swallowing a single or multiple intact tablets. It should be noted that not all opioid formulations that incorporate abuse-deterrent technologies possess equivalent degrees of abuse deterrence; a comprehensive *in vitro* and *in vivo* research program is required to determine if a given product meets FDA standards for abuse-deterrent properties.

Subsection 9.2, Abuse, of the Hysingla ER Full Prescribing information describes results from abuse-deterrence studies, summarizes them, and specifies certain abuse-deterrent properties (labeling claims) of Hysingla ER. Hysingla ER has two FDA-approved abuse-deterrent labeling claims – a Tier 1 claim, indicating that the product is formulated with physicochemical barriers to abuse, and a Tier 3 claim, indicating the product is expected to result in a meaningful reduction in abuse (FDA 2013). However, abuse of Hysingla ER by the intravenous, intranasal, and oral routes is still possible.

Furthermore, the Hysingla ER formulation is not susceptible to dose dumping in the presence of alcoholic beverages, based on required *in vitro* tests in various concentrations of ethanol and simulated gastric fluid (Data on file, NDA – Quality Overall Summary). Dose dumping is the unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified-release dosage form (Meyer et al. 2005). Alcohol-induced dose dumping does not occur when Hysingla ER tablets are in the presence of ethanol, as its extended-release properties are maintained (Data on file, NDA – Quality Overall Summary). However, as stated in the WARNINGS AND PRECAUTIONS section of the enclosed Full Prescribing Information, 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).

2.1.e. AHFS Classification

Opiate Agonists: 28:08.08

2.1.f. FDA approved indication(s) and the date approval was granted

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.

Date of Approval:

11/20/2014

2.1.g. Pharmacology

Please refer to section 12 of the Full Prescribing Information for clinical pharmacology.

Additional Information Not Contained In Full Prescribing Information

Opioid analgesics can be categorized by their pharmacologic activity at specific opioid receptor(s). Mu (μ), delta (δ), and kappa (κ) are the three major opioid receptor classes that mediate analgesia and the other effects of opioid analgesics. The mu-opioid receptor is the prototypic opioid receptor and remains the most important in the clinical management of pain (Cherny et al. 1996; Gourlay et al. 2005; Inturrisi et al. 2002; Pasternak et al. 2004). Agonism at the mu receptor is associated with effects such as analgesia, respiratory depression, sedation, miosis, euphoria, and reduced gastrointestinal motility (Cherny et al. 1996; Gourlay et al. 2005).

Hydrocodone is a semisynthetic mu receptor agonist opioid. Mu opioids work at multiple levels to produce analgesic activity. All μ -opioid agonists (non-selective opioids of the morphine type) appear to work the same way, modifying the transmission of pain impulses in the nerves and spinal cord, altering the processing of pain stimuli in the brain stem, and modifying the appreciation of pain by the individual. The relative analgesic potency of hydrocodone is believed to be equivalent to that of oxycodone and two times that of oral morphine.

Although hydromorphone, the O-demethylated metabolite of hydrocodone, has a greater affinity for the μ -opioid receptor than does hydrocodone, the conversion of hydrocodone to hydromorphone is not an essential step in the production of an analgesic response to hydrocodone (Tomkins et al. 1997; Lelas et al. 1999; Navani et al. 2013).

2.1.h. Pharmacokinetics/Pharmacodynamics

Please refer to sections 12.2 and 12.3 of the Full Prescribing Information for pharmacodynamics and pharmacokinetics, respectively.

Additional Information Not Contained In Full Prescribing Information

Dose Proportionality and Bioequivalence

Steady State (Data on file, HYD1002)

An open-label, once-daily, multiple dose pharmacokinetic study of Hysingla ER 120 mg administered once daily for 5 days in 27 healthy subjects under naltrexone blockade, demonstrated that hydrocodone pharmacokinetic profiles were similar on day 1 and day 5 (steady state). Steady-state systemic exposure of hydrocodone was achieved by the second dose. The minimum observed plasma hydrocodone concentrations at the end of each dosing interval (concentrations at 24, 48, 72, and 96 hours after the first dose) were generally similar. Mean accumulation ratios for AUC_{tau} , C_{max} , and C_{min} were 1.3, 1.1, and 1.1, respectively. This

minimal accumulation at steady state was consistent with once-daily dosing of Hysingla ER with a $t_{1/2}$ of hydrocodone from 5 to 9 hours.

Dose Proportionality and Single-Dose Pharmacokinetics (Data on file, HYD1004)

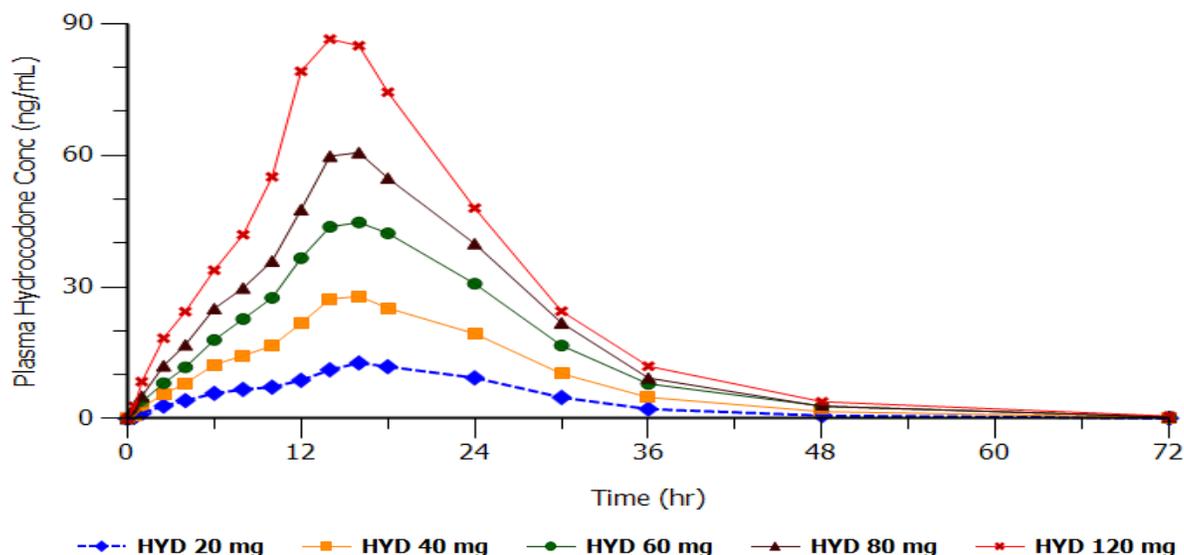
Dose proportionality and single-dose pharmacokinetics of Hysingla ER was evaluated across the dosage range of 20 to 120 mg with naltrexone blockade. This study was a randomized, open-label, single-dose, 5-treatment, 4-period, crossover, incomplete block design in 40 healthy adult subjects. A minimum washout of seven days separated dose administrations, and blood samples were obtained pre-dose and at additional time points through 72 hours post-dose.

Systemic exposure (AUC and C_{max}) increased linearly with doses from 20 to 120 mg (**Figure 1**). Plasma levels remained detectable for more than 72 hours postdose in most subjects at the dose level of 40 mg and above. The mean terminal half-life ($t_{1/2}$) was similar for all Hysingla ER dose strengths ranging from 7 to 9 hour.

Dose proportionality was assessed by clinical and statistical review of the descriptive data for Hysingla ER. The power model approach was used as a sensitivity method for assessment of dose proportionality. A mixed-model approach was used to estimate the magnitude of β (slope parameter of interest) and to derive the confidence interval (CI) around the slope. Dose proportionality was concluded when the 90% CIs for β were completely contained within the critical range of (0.875, 1.125) (see **Table 2**).

The 90% confidence intervals associated with dose-proportionality slope estimates for C_{max} and AUC_{inf} showed minimal deviation from defined critical ranges for the dose levels of 20, 40, 60, 80, and 120 mg (see **Table 2**).

Figure 1. Plasma Hydrocodone Concentrations Following Single Doses of Hysingla ER Tablets



*HYD = Hysingla ER

Table 2. Dose Proportionality Statistical Results Across Studies

Hysingla ER Doses	Pharmacokinetic Parameters	Slope Estimate	90% Confidence Interval	Critical Range ^a
20 mg, 40 mg, 60 mg, 80 mg, 120 mg	AUC _{0-inf} (ng·hr/mL)	1.11	[1.02 – 1.20]	[0.88 – 1.12]
	C _{max} (ng/mL)	1.16	[1.08 – 1.24]	

^aA mixed model was used to estimate the slope and its associated 90% confidence interval. Dose proportionality was achieved when the 90% CI lies entirely within the critical range determined from the acceptance interval for the ratio of dose-normalized geometric mean values and the maximal dose ratio used in the study (Smith BP et al. 2000).

24-hour pharmacokinetic profile of Hysingla ER versus Vicoprofen at Steady-State (Data on file, HYD1016)

In a single-center, randomized, open-label, 2-treatment, 2-period, multiple-dose, cross over study in 24 healthy subjects, the bioavailability of hydrocodone after administration of Hysingla ER was compared to an equivalent daily hydrocodone dose as the listed drug, Vicoprofen® (hydrocodone bitartrate/ ibuprofen) over a 24-hour dosing period.

Subjects received naltrexone blockade in both periods and blood samples were obtained pre-dose and at additional time points during the two periods through 72 hours post-dose. **Figure 2** depicts the steady-state plasma hydrocodone concentrations following administration for 3 days of Hysingla ER 30 mg every 24 hours and (hydrocodone bitartrate, 7.5 mg /ibuprofen, 200 mg) every 6 hours (for a total daily hydrocodone dose of 30 mg). The systemic exposure ($AUC_{24,ss}$) and average plasma concentration ($C_{avg,ss}$) of hydrocodone at steady state (after 3 days) after once-daily administration of Hysingla ER was equivalent to that after every 6-hour administration of hydrocodone/ibuprofen (**Table 3**). Once-daily administration of Hysingla ER also diminished the percent fluctuation between peak and trough concentrations observed with the immediate-release (IR) tablets administered every 6 hours (61% vs 96%). These results demonstrate that patients receiving IR hydrocodone combination formulations may be converted to Hysingla ER by administering the same total daily hydrocodone dose.

Figure 2. Mean Steady State Hydrocodone Plasma Concentration Versus Time Profiles

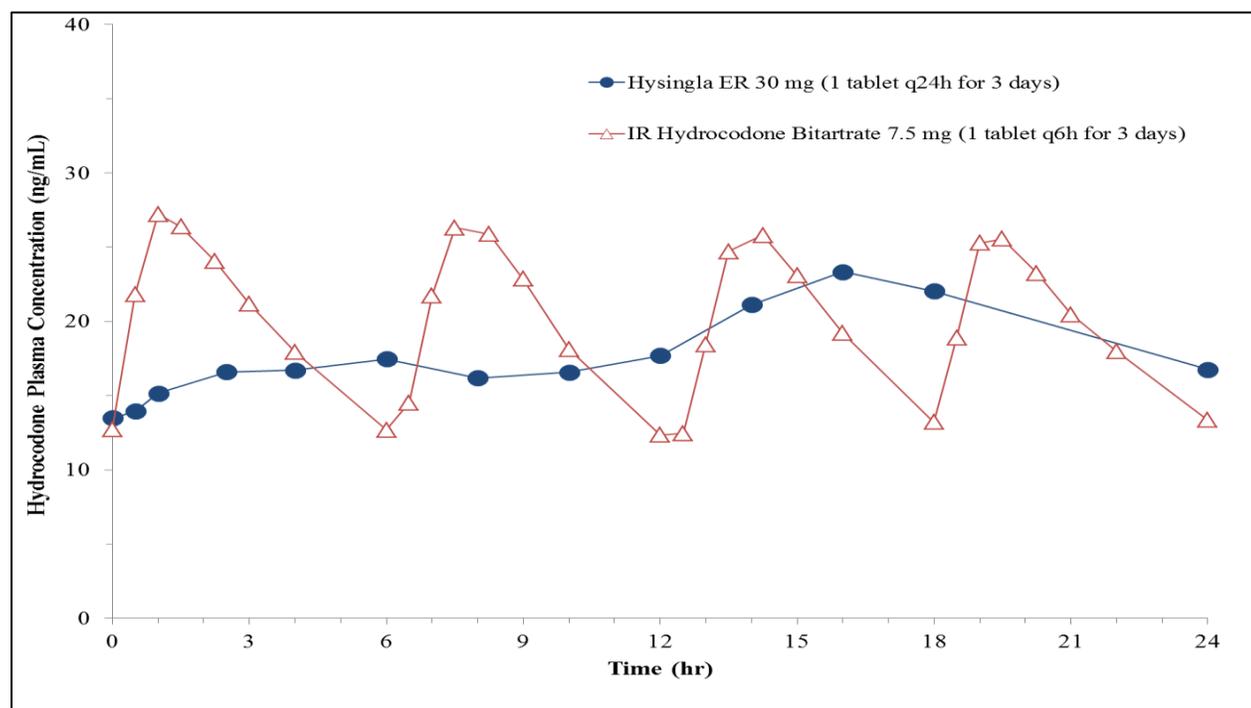


Table 3. Mean (\pm SD) Hydrocodone Pharmacokinetic Parameters

Metric (Unit)	Hysingla ER (30 mg q24h) n = 22	IR Hydrocodone Bitartrate 7.5 mg/ Ibuprofen 200 mg (1 tablet q6h) n = 23
AUC_{24,ss} (ng·h/mL)	443 \pm 128	470 \pm 111
C_{avg,ss} (ng/mL)	18.5 \pm 5.3	19.6 \pm 4.6

Effect of Alcohol on Hysingla ER Dissolution Profile (Giordano et al. 2014; Data on file, NDA – Clinical Overview)

An in vitro study evaluating the effects of varying concentrations of ethanol on the dissolution of Hysingla ER tablets was conducted. The dissolution profiles of the lowest and highest strengths (ie, 20 mg and 120 mg) of Hysingla ER tablets in the absence (0%) and presence of 4%, 10%, 20%, and 40% (v/v) ethanol in simulated gastric fluid (SGF) were evaluated at 1, 2, 4, 8, 12, 18 and 24 hours.

The dissolution profiles for Hysingla ER 20 and 120 mg tablets showed that the rate at which hydrocodone was released (dissolution rate) decreased with increasing ethanol concentration. The presence of ethanol at 10%, 20%, and 40% concentrations in SGF decreased the dissolution rate of hydrocodone consistently over 24 hours for both tablet strengths. The magnitude of the decrease in dissolution rate was greater for the higher ethanol concentrations. At the lowest ethanol concentration tested (4% ethanol in SGF), release profiles over 24 hours were similar to those in SGF alone (0% ethanol).

There was no evidence of an increase in the rate of hydrocodone release from Hysingla ER tablets in the presence of ethanol up to 40% (v/v) in the dissolution media in vitro. Therefore, formulation dependent dose dumping should not occur if Hysingla ER tablets were to be taken concomitantly with alcoholic drinks. The in

vitro test results for alcohol sensitivity demonstrated no evidence of dose dumping across various ethanol concentrations. Based upon these results, an in vivo study to assess the effects of alcohol on hydrocodone release from Hysingla ER tablets in human subjects was not needed and therefore was not requested by the FDA.

These *in vitro* findings regarding the effect of ethyl alcohol on hydrocodone release from Hysingla ER Tablets do not in any way lessen the importance of the statements in the Hysingla ER Full Prescribing Information about the dangers of alcohol consumption during treatment with Hysingla ER due to the potential for additive central nervous system depression. The concomitant use of Hysingla ER tablets and alcohol can increase the risk of respiratory depression, profound sedation, coma, and death.

Pharmacokinetics in Hepatic Impairment (Data on file, HYD1007; Cipriano et al. 2013)

A phase 1, open-label, parallel-group study assessed the effect of hepatic impairment on the single-dose pharmacokinetics and safety of Hysingla ER 20 mg tablet. Study enrolled 32 adult subjects ranging in age from 37 to 64 years (mean: 54.2 years) with normal hepatic function, mild hepatic impairment, moderate hepatic impairment, and severe hepatic impairment based on Child-Pugh classification. Blood samples for pharmacokinetic analysis of hydrocodone, norhydrocodone, and hydromorphone concentrations were collected before dosing and through 168 hours after study drug dosing.

The summary of mean and Least Squares (LS) geometric mean plasma pharmacokinetic metrics of hydrocodone following a single 20 mg oral dose of Hysingla ER are presented in **Table 4**. The mean AUC_{inf} values of hydrocodone were 342, 310, 390, and 415 ng·h/mL in subjects with normal hepatic function and mild, moderate, and severe hepatic impairment, respectively. The corresponding mean hydrocodone C_{max} values were 16, 15, 17, and 18 ng/mL, respectively. Median T_{max} of hydrocodone ranged from 14 to 18 hours and mean half-life ranged from 7.8 to 11.9 hours across subjects with normal hepatic function and hepatic impairment. Compared to subjects with normal hepatic function, the LS geometric mean AUC_{inf} values were 14% lower, 13% higher, and 4% higher in patients with mild, moderate, and severe hepatic impairment, respectively. The corresponding LS geometric mean C_{max} values were 6% lower, 5% higher, and 5% higher, respectively.

Table 4. Summary of Mean (\pm SD) and LS Geometric Mean Plasma Pharmacokinetic Metrics of Hydrocodone

Metric (Unit)		Normal Hepatic Function n = 8	Mild Hepatic Impairment n = 8	Moderate Hepatic Impairment n = 8	Severe Hepatic Impairment n = 8
AUC_{inf} (ng·h/mL)	Mean (\pm SD)	342 \pm 36.8	310 \pm 124 ^a	390 \pm 70.9	415 \pm 200
	LS Geometric Mean	340	294	384	353
C_{max} (ng/mL)	Mean (\pm SD)	16.0 \pm 5.0	15.3 \pm 5.6	17.0 \pm 5.9	18.4 \pm 9.1
	LS Geometric Mean	15.3	14.4	16.1	16.0

^an = 7

For norhydrocodone, subjects with mild hepatic impairment had similar systemic exposures as compared to subjects with normal hepatic function. Arithmetic mean AUC_{inf} of norhydrocodone decreased by 46% and 41% in subjects with moderate or severe hepatic impairment, respectively, compared with normal hepatic function. The corresponding arithmetic mean C_{max} values decreased by 51% and 53%, respectively.

The AUC and C_{max} of hydromorphone, which is a minor (representing up to 3% systemic exposure of hydrocodone) active metabolite, were low and variable across all hepatic function groups.

The mean plasma protein binding of hydrocodone in patients with normal hepatic function and mild, moderate, and severe hepatic impairment was low and similar at 36%, 37%, 33%, and 34%, respectively.

Overall, 17 adverse events were reported and 11 of 32 subjects (34%) experienced at least 1 adverse event. The number of adverse events were similar across the groups: normal hepatic function (2 events), mild hepatic function (5 events), moderate hepatic function (3 events), and severe hepatic function (2 events). The only adverse event that was reported in at least 2 subjects in any hepatic function group was headache. There were no serious adverse events or early discontinuations due to adverse events.

2.1.i. Contraindications, Warnings, Precautions, and Adverse Reactions

Please refer to the Boxed Warning and sections 4, 5, and 6 of the Full Prescribing Information

Effects on QT/QTc

Please refer to section 5.14 and section 12.2 of the Hysingla ER Full Prescribing Information for QTc Interval Prolongation and Effects on Cardiac Electrophysiology

Study to Evaluate the Effect of Hysingla ER at Doses Up To 160 mg on QT/QTc Intervals in Healthy Adult Volunteers (Data on file, HYD1009)

The effects of multiple doses (once daily for 3 days) of Hysingla ER 80, 120 and 160 mg were evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin 400 mg), 3-treatment parallel-group, dose-escalating study in 208 healthy male and female subjects aged 18 to 50 years. Treatment groups were: Hysingla ER (20, 40, 80, 120, and 160 mg), placebo (placebo control), and moxifloxacin (positive control).

For subjects randomized to Hysingla ER, the dose-escalation sequence was Hysingla ER 20 mg daily for 3 days, Hysingla ER 40 mg for 3 days, Hysingla ER 80 mg for 3 days, Hysingla ER 120 mg for 3 days, and Hysingla 160 mg (given as one Hysingla ER 120 mg and one Hysingla ER 40 mg) for 3 days. This was followed by a down titration (taper) of Hysingla ER 80 mg for 3 days, then Hysingla ER 20 mg for 3 days. Subjects randomized to the positive control group received a single active dose of moxifloxacin 400 mg on days 9, 12, and 15. The QTc evaluation for Hysingla ER was performed over a 24-hour period during the third day of 80, 120 and 160 mg Hysingla ER dosing, when the plasma concentrations of hydrocodone and its metabolites, hydromorphone and norhydrocodone were at steady state. The QTc effects of placebo and moxifloxacin treatments were evaluated at each of the corresponding time points over the same 24-hour periods. A pharmacokinetic/ pharmacodynamic analysis was also conducted to explore the relationship between placebo-corrected (placebo-adjusted) change from baseline in QTc intervals^a and plasma concentrations of hydrocodone, norhydrocodone, and hydromorphone.

There was no clinically meaningful effect on mean QTc at either 80 or 120 mg Hysingla ER doses administered once daily for 3 days; however, the maximum tested dose of 160 mg Hysingla ER administered once daily for 3 days prolonged the time-matched, placebo-corrected change from baseline estimate for QTcI by a maximum of 9.85 (2-sided 90% CI: 6.73 - 12.97) milliseconds (msec) across 14 assessment time points (**Table 5**). The magnitude of QTcI prolongation at Hysingla ER 160 mg was similar to the prolongation following each of the three successive moxifloxacin evaluations in the study.

^a individual correction [QTcI], Bazett's correction [QTcB], and Fridericia's correction [QTcF]

Table 5. Placebo-Corrected Change from Baseline Estimates for QTcI for Hysingla ER and Moxifloxacin

Treatment	Data-Based Time Averaged (msec)	Model-Based Time Averaged (90% CI) (msec)	Time-Matched Maximum (90%CI) (msec)
Hysingla ER 80 mg (Day 9)	3.9	3.72 (1.52, 5.91)	6.25 (3.35, 9.14)
Hysingla ER 120 mg (Day 12)	5.0	4.75 (2.19, 7.31)	7.55 (4.41, 10.70)
Hysingla ER 160 mg (Day 15)	7.7	6.93 (4.58, 9.27)	9.85 (6.73, 12.97)
Moxifloxacin 400 mg (Day 9)	7.2	7.69 (5.4, 9.98)	12.64 (9.59, 15.7)
Moxifloxacin 400 mg (Day 12)	6.5	7.05 (4.42, 9.67)	11.57 (8.22, 14.91)
Moxifloxacin 400 mg (Day 15)	5.2	5.48 (3.08, 7.88)	9.6 (6.57, 12.64)

There was no clear relationship between hydrocodone plasma concentrations and QTcI. The upper confidence values for QTcI at C_{max} for hydrocodone, norhydrocodone, and hydromorphone were 7.3, 8.2, and 8.6 msec, respectively.

Once-daily dosing of Hysingla ER up to 160 mg for three days had no effect on heart rate, AV conduction, wave morphology, or cardiac depolarization as measured by PR and QRS interval durations. Additionally, a gender analysis showed that there was no relevant gender effect on the effects of Hysingla ER on cardiac repolarization.

Ten subjects (4.8%), including 7 subjects in the Hysingla ER group, discontinued from the study due to adverse events. Treatment-emergent adverse events reported by subjects given Hysingla ER with an incidence of $\geq 10\%$ were: infrequent bowel movements, nausea, vomiting, abdominal pain, dry mouth, headache, dizziness, somnolence, application site irritation, pruritus, muscle spasms, and hiccups.

Adverse Events which can Signal Potential Proarrhythmic Effects from Hysingla ER Clinical Studies

Although drug-induced prolongation of the QT/QTc interval is usually asymptomatic, an increased rate of certain AEs in patients taking an investigational agent can signal potential proarrhythmic effects. The ICH E14 guidance suggests that the rates of the following clinical events should be compared in the treated and control patients, particularly when there is evidence of an effect on the QT/QTc interval: torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures. (FDA Guidance for Industry. 2005)

Adverse events related to QT prolongation or cardiac repolarization in Hysingla ER-treated subjects (N = 1827) in the pooled chronic pain studies were low (< 1%) with syncope and electrocardiogram QT prolonged reported in 4 and 3 patients, respectively. (Data on file, NDA – Integrated Summary of Safety)

Hysingla ER and Potential Effects on Hearing (Data on file, Audiology Report; Campbell et al, 2014)

Reports have been published in the literature describing sensorineural hearing impairment in patients with a history of hydrocodone/acetaminophen use. Therefore, comprehensive audiology assessments were conducted to evaluate the potential effect of Hysingla ER (20, 40, 60, 80, and 120 mg) on hearing function in

two phase III clinical studies ([HYD3002](#) and [HYD3003](#)) by licensed audiologists. Two patient populations were analyzed. The integrated analysis population (N = 1207) consisted of Hysingla ER treated patients in the open-label, long-term (12-month) safety study and in the double-blind, placebo-controlled study. The randomized population consisted of Hysingla ER (n = 296) or placebo (n = 292) patients in the double-blind, placebo-controlled study. Comprehensive audiologic evaluations, including air-conduction pure-tone audiometry in conventional frequency range (250 to 8,000 Hz) and ultra-high frequency range (10,000 to 16,000 Hz), bone-conduction pure-tone audiometry, immittance audiometry (tympanometry), speech reception threshold, and word recognition were performed at baseline, at various time points during each study (air-conduction pure-tone audiometry assessments only), and at the end of treatment. Additional assessments, such as the Dizziness Handicap Inventory (DHI) and Tinnitus Handicap Inventory (THI), were performed at each clinic visit.

The primary audiology analysis, based on air-conduction pure-tone audiometry at conventional frequencies, evaluated patients with potential hearing loss vs. potential hearing improvement by American Speech-Language Hearing Association (ASHA) criteria. ASHA criteria for early detection of ototoxicity were defined as: a threshold shift of ≥ 20 decibels (dB) from baseline at one frequency, a threshold shift of ≥ 10 dB from baseline at 2 adjacent frequencies, and/or loss of response in 3 or more adjacent frequencies where responses were present at baseline. The other audiology assessments performed were classified as supportive or supplemental analyses.

The majority of patients in the integrated analysis population were female (58%), < 65 years old (88%), and white (74%), and a similar proportion of patients were opioid-naïve and opioid-experienced (47% and 53%, respectively). Similar baseline results were observed for the randomized population. Among the integrated analysis population, 187 (15%) and 144 (12%) patients received Hysingla ER maintenance treatment for ≥ 6 and ≥ 12 months, respectively. The mean (SD) cumulative length of exposure was 95.2 (120.36) days and the mean (SD) average daily dose of Hysingla ER was 48.7 (27.04) mg. For the randomized population, the mean (SD) cumulative length of exposure to Hysingla ER was 69.7 (25.22) days for patients in the Hysingla ER group (n = 296) and 66.5 (27.56) days for patients in the placebo group (n = 292). The mean (SD) average daily dose of Hysingla ER was 56.9 (31.76) mg for patients in the Hysingla ER group.

The majority of patients in the integrated analysis population had exposure to potential ototoxic medications 30 days prior to and during the studies. Of the patients who took potential ototoxic medications, the majority of the patients took medications that belong to the Non-Steroidal Anti-Inflammatory Drug (NSAID) and acetaminophen categories. For the randomized population, the proportions of patients who took potential ototoxic medications prior to study entry were similar for the Hysingla ER and placebo groups. As the double-blind placebo-controlled study prohibited the use of non-study pain medications during the study, the proportions of patients in the randomized population who received potential ototoxic medications was smaller than those in the integrated analysis population.

In the primary analysis, a similar number of patients (71 patients; 8%) had decreased hearing sensitivity (defined as an ASHA event) compared to the number of patients (99 patients; 11%) who had improvement in hearing sensitivity for the integrated analysis population. Mean changes from baseline to the end of Hysingla ER exposure were generally small, bidirectional, and not clinically notable. The results showed large variability and the variability increased as the test frequency increased. For the randomized population, similar proportions of patients in the Hysingla ER and placebo groups had potential hearing loss and potential hearing improvement by ASHA criteria. Additionally, of the subjects with ASHA events who had a subsequent audiology assessment, all either no longer met ASHA criteria or were stabilized. No subjects were identified to have progressive hearing loss.

No dose-response relationship was observed between the Hysingla ER dose levels and incidences of potential hearing loss and potential hearing improvement by ASHA criteria. Increased duration of Hysingla ER exposure was not associated with increased incidences of changes in hearing status.

Incidence of the worst (highest) Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade for patients meeting ASHA criteria was also analyzed. Few ASHA events (2 patients; < 1%) were classified as CTCAE toxicity grade 2 or 3, while no subjects had CTCAE grade 4 ASHA events.

Data patterns from the additional analyses in speech reception threshold, bone-conduction pure-tone audiometry, word recognition, immittance audiometry, THI, and DHI did not suggest ototoxicity with Hysingla ER and supported the primary analysis conclusions.

In addition, specific adverse events (AEs) identified as pertaining to hearing impairment and vestibular disorders were evaluated. There were 1827 subjects exposed to Hysingla ER in the safety population, including 798 (44%), 500 (27%), and 364 (20%) patients with exposure \geq 3 months, \geq 6 months, and \geq 12 months, respectively. The incidence of hearing impairment and vestibular disorder-related events was low. Overall, 59 patients (3%) in the safety population experienced a treatment-emergent adverse event (TEAE) related to hearing impairment and vestibular disorders. Most frequently occurring events were tinnitus (37 patients; 2%) dizziness (13 patients; 1%;), and vertigo (4 patients; < 1%). These data did not suggest an increased risk for hearing impairment or vestibular disorders with Hysingla ER.

2.1.j. Drug Interactions

Please refer to section 7 of the Full Prescribing Information for drug interactions.

2.1.k. Dosage and Administration

Please refer to section 2 of the Full Prescribing Information for dosage and administration.

Hysingla ER 24-hour Analgesia (Data on file, HYD3002; Data on file, HYD3003; Data on file, NDA – Summary of Clinical Efficacy; Data on file, HYD3003 post-hoc pain score analysis; Wen et al. PainWeek 2014 [#146])

Hysingla ER is a matrix delivery system that provides systemic delivery of hydrocodone for 24 hours. The clinical efficacy of Hysingla ER, dosed once daily, was demonstrated in the pivotal clinical study, 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 ([HYD3002](#)). Additionally, an open-label, 52-week study evaluating persistence of analgesia and long-term safety of Hysingla ER in patients with chronic, moderate to severe, nonmalignant and nonneuropathic pain support the efficacy of Hysingla ER dosed every 24 hours ([HYD3003](#)). Maintenance of analgesia at the end of the dosing interval and the effectiveness of extended-release analgesic medications throughout their dosing interval were assessed by evaluating pain score trends as described below.

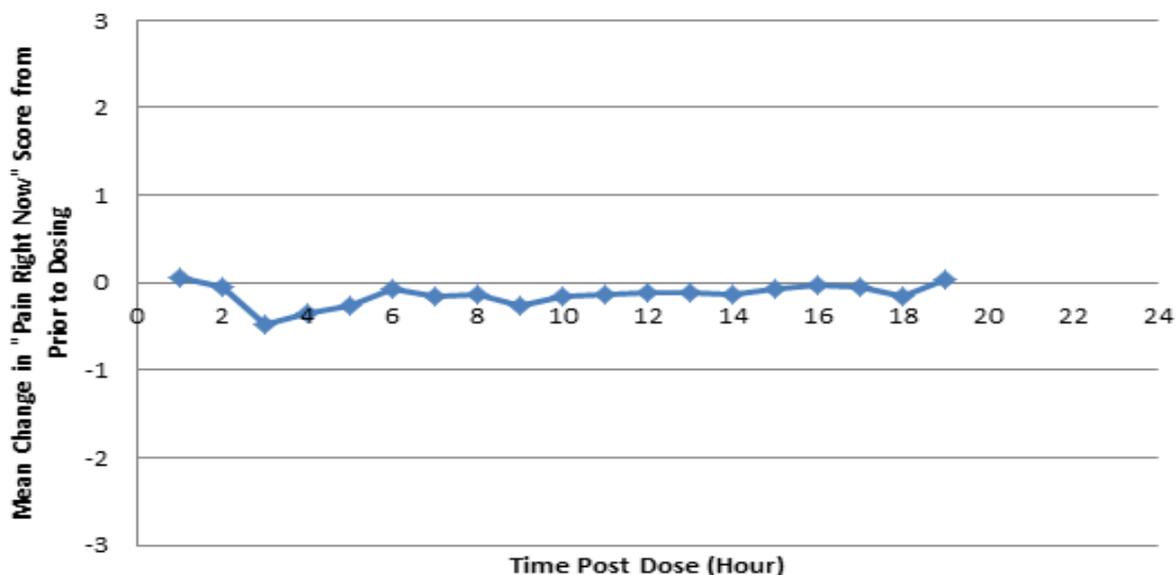
The primary efficacy variable in the 12-week clinical trial was the weekly mean pain intensity score calculated using the daily diary “average pain over the last 24 hours” scores for chronic low back pain (on an 11-point scale: 0 = no pain to 10 = pain as bad as you can imagine) recorded by the patient during the double-blind period. Hysingla ER dosed every 24 hours was shown to be superior to placebo for the primary endpoint, week 12 mean pain intensity score using daily diary scores for “average pain over the last 24 hours” (4.23 v 3.70; $P = .0016$) (Data on file, HYD 3002; Wen et al. PainWeek 2014 [#146]).

In the persistence of analgesia and long-term safety study of Hysingla ER, following a dose titration period, patients who attained a stabilized Hysingla ER dose continued in a 52-week maintenance treatment period. Analgesic efficacy was assessed from the daily “pain right now” scores for nonmalignant and nonneuropathic pain (measured on an 11-point NRS, where 0 = no pain and 10 = pain as bad as you can imagine). Analgesia was evaluated twice each day for 3 months, once just prior to dosing and again at approximately 8 pm, representing various time points post-dose during the dose titration period and during the first 12 weeks of the maintenance period. Also collected at 8 pm each day was the “average pain over the last 24 hour” scores (Data on file, HYD3003).

The mean (SD) “pain right now” predose score, coinciding with “trough” hydrocodone systemic exposure following Hysingla ER dosing, was 3.6 (1.92) (n = 725 patients) in the maintenance period. This score is similar to the “pain right now” score recorded at 12 hours post-dose, which was 3.4 (1.93) (n = 592 patients) in the maintenance period. In addition, the mean “pain right now” predose score was similar to the mean “average pain over the last 24 hour” score [3.5 (1.80) (n = 726 patients)]. This analysis showed that pain relief was not compromised at the end of the 24-hour dosing interval (Data on file, NDA - Summary of Clinical Efficacy).

An additional analysis evaluated the mean change in “pain right now” scores from immediately prior to each daily Hysingla ER dose to various time points post-dose during the maintenance period (**Figure 3**). Up to 19 hours post-dose (where sufficient data were recorded, n = 15 to 587 patients), the mean “pain right now” scores recorded at post dose time points did not differ from that recorded immediately prior to each daily dosing, indicating that persistent pain control was maintained during the dosing interval (Data on file, HYD3003 post-hoc pain score analysis).

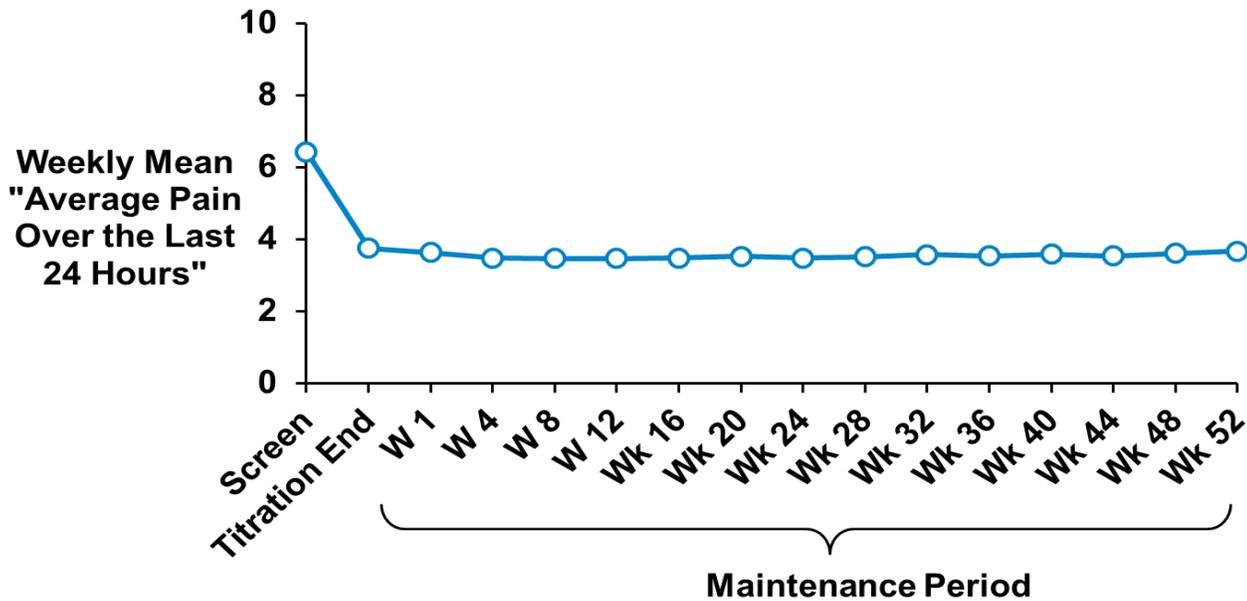
Figure 3. Mean Change in “Pain Right Now” Scores From Immediately Prior to Each Daily Dose To Various Time Points Post-dose During the Maintenance Period



Persistence of analgesia (Data on file, HYD3003; Wen et al. APS 2014)

In the open-label study evaluating persistence of analgesia and long-term safety of Hysingla ER ([HYD3003](#)), treatment with Hysingla ER improved the mean pain intensity scores (as assessed by changes from baseline in daily “average pain over the last 24 hours” scores) plotted every 4 weeks. The weekly mean standard deviation (SD) pain intensity score based on daily “average pain over the last 24 hours” scores decreased from 6.43 (1.602) at baseline to 3.75 (1.862) at the end of dose titration for patients who entered the maintenance period. This improvement was sustained throughout the maintenance period, indicating adequate pain control was maintained with long-term Hysingla ER treatment (**Figure 4**).

Figure 4. Hysingla ER Weekly Mean "Average Pain Over the Last 24 Hours" Scores up to 52 weeks



The average daily dose of Hysingla ER was 65 mg and remained relatively stable during the 52 week maintenance period. The average daily dose for patients with at least 6 months exposure and at least 12 months exposure were similar (64.84 mg and 63.60 mg, respectively). Most patients stayed on their stabilized dose during the maintenance period. Overall, 4.3% of patients had their Hysingla ER dose increased > 1 dose level at the end of the maintenance period, while 9.1% patients decreased their dose.

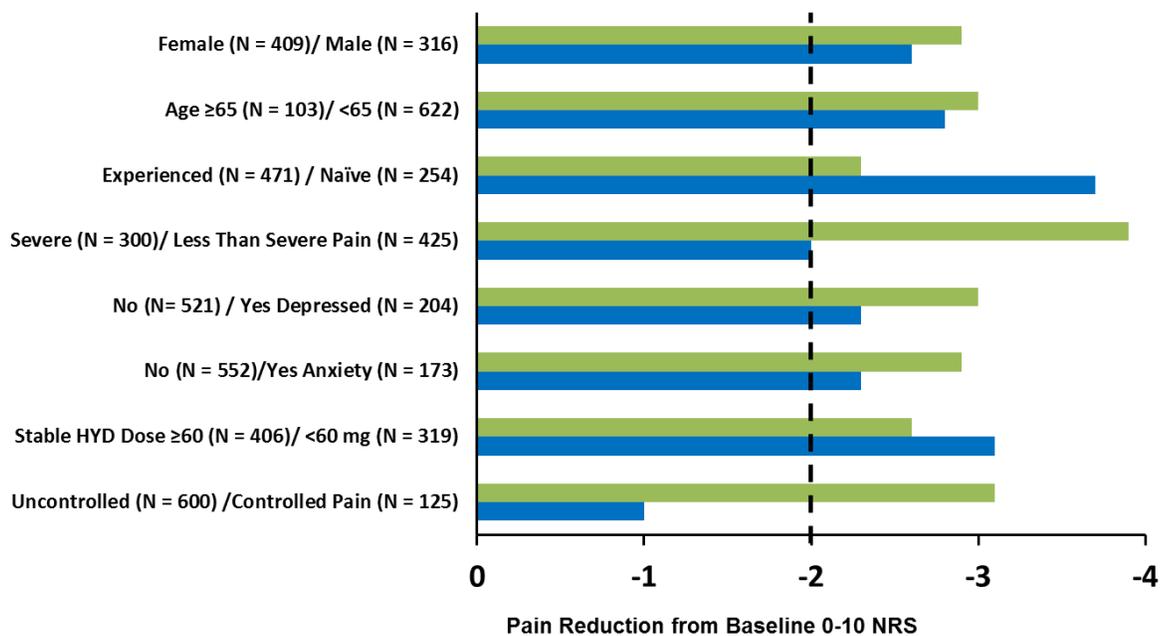
Patient Subgroup Analysis (Data on file, HYD3003; Wen et al. PainWeek 2014 [#147])

A post-hoc analysis of the 52-week study evaluating persistence of analgesia and long-term safety of Hysingla ER (HYD 3003) evaluated the treatment effectiveness and tolerability of single-entity, once-daily Hysingla ER 20 mg to 120 mg tablets in different patient subgroups with moderate to severe chronic pain. Patients were analyzed by subgroup according to data collected at screening: sex, age, opioid experience, pain severity (less than severe pain = pain < 7, severe pain = pain score ≥ 7), baseline pain control, depression status, and anxiety status. In addition, patients were analysed by whether their stable Hysingla ER daily dose was less than 60 mg at the end of dose titration.

In general, most demographic and baseline characteristics were similar within subgroups. Differences in the proportion of opioid experienced patients were observed in the subgroups defined by baseline pain severity, controlled pain, Hysingla ER dose levels by the end of the open-label titration period, depression, and anxiety. Differences in the proportion of women were observed in the subgroups defined by pain severity, depression, and anxiety. Opioid-naïve patients achieved lower stable Hysingla ER doses than opioid-experienced patients; patients with depression or anxiety had higher stable Hysingla ER doses than their counterparts because both groups comprised a larger proportion of opioid-experienced patients. Patients younger than 65 years had higher stable Hysingla doses than older patients.

Among patients who entered the maintenance period, the mean reduction in pain from baseline was clinically important (2 points or greater) across all subgroups, with the exception of patients who had controlled pain (Figure 5). Even among patients with controlled pain, mean reductions in pain were greater than 1 point. The largest reductions were seen in patients with severe pain and opioid-naïve patients. As the Hysingla ER dose was individually titrated, a similar extent of pain reduction was seen in both those on a stable Hysingla ER dose of < 60 mg/day and those ≥ 60 mg/day.

Figure 5. Reduction in Pain from Baseline, Maintenance Population



All subgroups showed a reduction from baseline (improvement) in pain interference with activities of daily living. Among patients with controlled pain, reductions of greater than 1 point in pain interference were seen. Similar improvements were seen in sleep and physical function as measured with the MOS Sleep-R and the SF-36. All treatment effects were maintained throughout the 12-month maintenance treatment period.

In general, the odds ratios for opioid-related, treatment-emergent adverse events (TEAEs) $\geq 5\%$ were balanced within subgroups (ie, TEAEs were not found to occur more frequently in one half of a subgroup than in the other). The largest differences (largest odds ratios) were seen in the subgroups defined by opioid experience and by age.

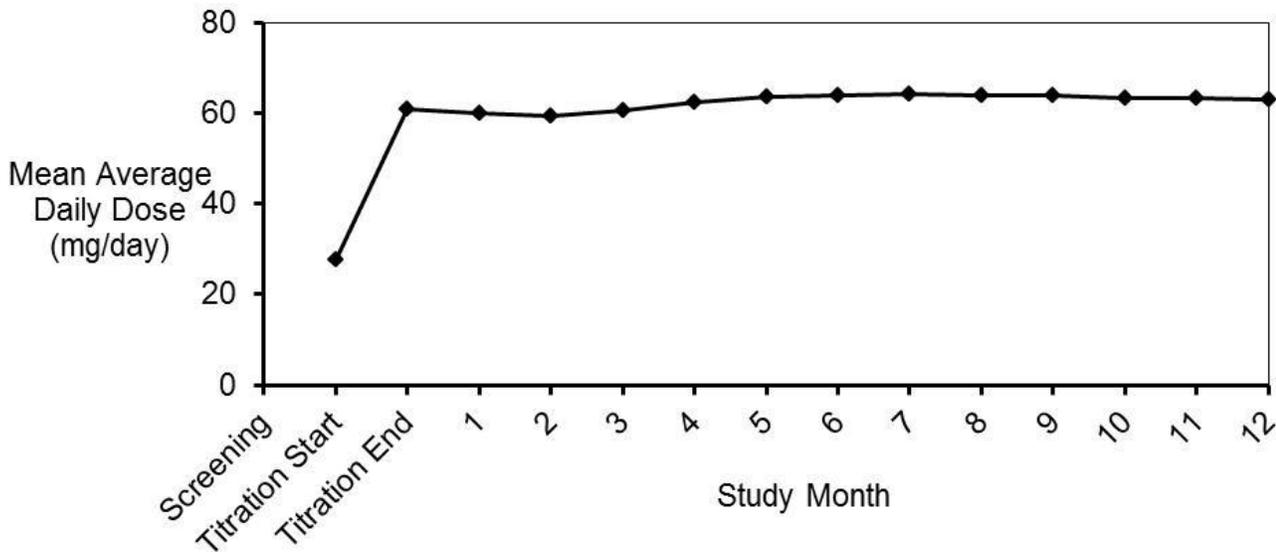
Analysis Evaluating the Conversion from Hydrocodone/Acetaminophen to Hysingla ER (Wen et al. PainWeek 2014 [#148])

A post-hoc analysis used data from the two phase III Hysingla ER studies ([HYD3002](#) and [HYD3003](#)) to evaluate the analgesic efficacy and safety of Hysingla ER in patients with moderate to severe chronic pain who transitioned from hydrocodone/acetaminophen (HCD/APAP) combination analgesics.

Consistent with the primary results of the randomized, placebo-controlled study, this post-hoc efficacy analysis of HCD/APAP users (n = 129) who transitioned to Hysingla ER (n = 62) showed statistically significant pain reduction with Hysingla ER treatment compared with placebo (n = 67) (average pain score at week 12, 4.8 for placebo vs. 4.2 for Hysingla ER, $P = .0357$).

Among patients in the long-term study who had previously used HCD/APAP (n = 269), a favorable change from baseline in pain relief was achieved with Hysingla ER treatment and maintained throughout 12-month treatment period. The average daily dose of Hysingla ER remained relatively stable during the during the 12-month maintenance period (**Figure 6**). Over 80% of HCD/APAP users who transitioned to Hysingla ER required either no dose adjustment or a 1 level dose increase for the duration of the maintenance period.

Figure 6. Average Daily Dose of Hysingla ER Over 12 Months



Among HCD/APAP users who transitioned to Hysingla ER, the most frequent TEAEs were consistent with those associated with opioid analgesics.

2.1.i. Access

Hysingla ER is a schedule II controlled substance approved 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. It must be dispensed with the Hysingla ER Medication Guide.

2.1.m. Co-Prescribed / Concomitant Therapies

Guideline Recommendations on the Use of Supplemental Analgesia

The American Pain Society (APS) in their *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain* recommends the use of supplemental analgesia with extended-release opioids. Patients prescribed extended-release opioid preparations should also be provided supplementary doses of immediate-release opioid equivalent to about 5-15% of the total 24-hour dose, to be given every 2 hours as needed (APS 2008).

According to the Veterans Health Administration, Department of Defense (VA/DoD), supplemental opioids may be considered if a patient is experiencing rescue, breakthrough pain, and incident pain. If a short-acting pure agonist opioid, either alone or in combination with a non-opioid analgesic, is used for supplemental therapy, the dose should be equivalent to about 10-15% of the total 24-hour dose, the every four hourly equivalent, or 1/6th of the total 24-hour opioid dose, as needed (VA/DoD 2010).

Please see section 2.2 Titration and Maintenance of Therapy of the Hysingla ER Full Prescribing Information. Patients who experience breakthrough pain during maintenance therapy may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid or non-opioid analgesic. Individually titrate Hysingla ER to a dose that provides adequate analgesia and minimizes adverse reactions.

Hysingla ER Clinical Trials and Supplemental Opioid Analgesic Use

A phase 3, multicenter, enriched-enrollment, randomized-withdrawal design, double-blind, placebo-controlled study compared once-daily Hysingla ER with placebo for the treatment of moderate to severe chronic low back pain ([HYD3002](#)).

Immediate-release (IR) oxycodone was permitted throughout the run-in and double-blind periods. During the run-in period (up to 45 days), subjects were permitted to take a maximum daily dose of up to IR oxycodone 10 mg, while in the double-blind period (12 weeks), the maximum daily IR oxycodone dose allowed was determined by the subject's double-blind study medication dose level as shown in **Table 6**.

Table 6. Amount of IR Oxycodone Permitted Daily during the Double-blind Period

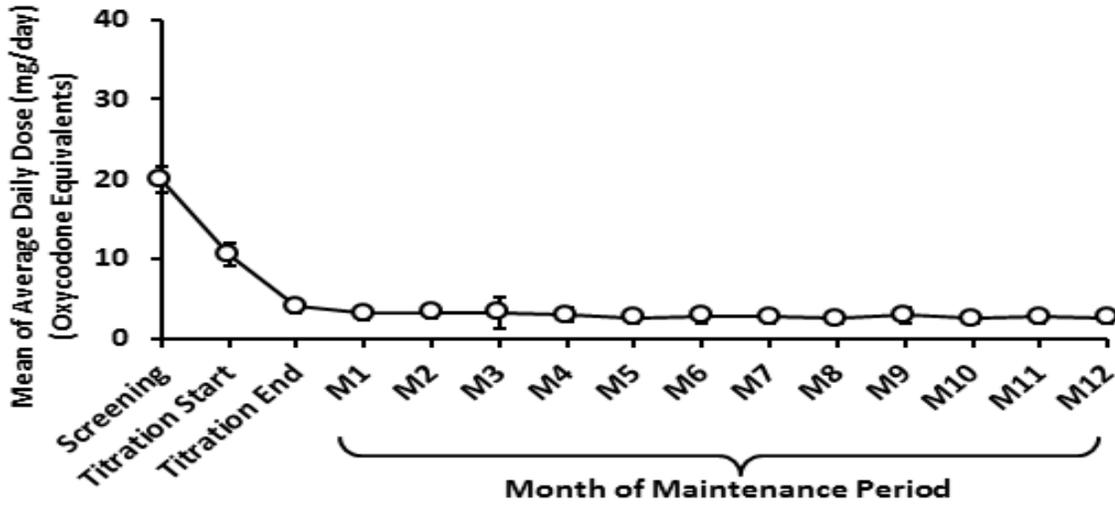
Hysingla ER/Placebo Dose Level	Maximum Immediate-release Oxycodone Daily Dose*
20 mg	10 mg
40 mg	10 mg
60 mg	15 mg
80 mg	20 mg
120 mg	30 mg

*Immediate-release oxycodone could have been administered as 5 to 10 mg/dose, as needed, with a minimum dosing interval of 4 to 6 hours.

The proportion of subjects requiring supplemental IR oxycodone was similar between treatment arms (83% (242/292 patients), placebo vs. 78% (232/296 patients), Hysingla ER). The mean daily number of IR oxycodone 5 mg tablets taken during the run-in period was 0.52 tablets for the randomized population. During the double-blind period, the overall mean use of IR oxycodone was slightly higher in the placebo group (0.90 tablets) compared to the Hysingla ER group (0.67 tablets). The use of rescue was higher in subjects randomized to higher dose strengths.

In a 12-month, phase 3, open-label, multicenter study assessing the long-term safety and effectiveness of Hysingla ER once daily (20 to 120 mg) in opioid-naïve and opioid-experienced subjects with moderate to severe nonmalignant and nonneuropathic chronic pain ([HYD3003](#)), patients could receive supplemental pain medication, including short-acting opioids (but not extended-release/long-acting opioids), as deemed appropriate by the investigator. During the 52-week maintenance period, the most frequently used concomitant opioid medications (by $\geq 5\%$ of patients) were Vicodin (32%), Oxycocet (8%), tramadol (6%), oxycodone (5%), and morphine (5%). The use of short-acting opioids was substantially reduced upon conversion to Hysingla ER therapy, and remained at this reduced level through 12 months of Hysingla ER treatment (**Figure 7**) (Wen et al. PainWeek 2014 [#461]).

Figure 7. Requirement for Prescribed Non-study Short-acting Opioids



2.1.n. Hysingla ER and Comparator Products (Prescribing Information)

The following tables (**Tables 7.1-7.7**) provide a comparison of selected prescribing information for Hysingla ER and its primary comparator opioid analgesics.

Tables 7.1 - 7.7. Comparison of Hysingla ER and Opioid Analgesic Products

(Reference: Information in Tables 7.1-7.7 is obtained from each individual product's Full Prescribing Information)

Table 7.1. Comparison of Hysingla ER and Opioid Analgesic Products

Product	Indications and Usage	Mechanism of Action	Dosing Interval and Administration	Titration	Maximum Dose	Food Effect	Alcohol Pharmacokinetic Effect	Abuse-Deterrence Labeling Claims
REFERENCE DRUG: Hysingla™ ER (hydrocodone bitartrate), CII	<p>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.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> 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. 	<p>Hydrocodone is an orally active semi-synthetic opioid agonist derived from two naturally occurring opiates, codeine and thebaine. Hydrocodone is a relatively selective μ-opioid receptor agonist compared to other opioids. 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.</p>	<ul style="list-style-type: none"> Every 24 hours Daily doses of Hysingla ER greater than 80 mg are only for use in opioid tolerant patients 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. Crushing, chewing, or dissolving Hysingla ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death 	<ul style="list-style-type: none"> Every 3–5 days 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Can be administered without regard to food 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 	<ul style="list-style-type: none"> No 	<ul style="list-style-type: none"> Yes
Butrans® (buprenorphine) Transdermal System, CIII	<p>For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.</p> <p><u>Limitations of Use</u></p>	<p>Buprenorphine is a partial agonist at μ opioid receptors. Buprenorphine is also an antagonist at kappa opioid receptors, an agonist at delta opioid receptors, and a partial agonist at ORL-1</p>	<ul style="list-style-type: none"> Every 7 days Intended for transdermal use only Apply to the upper outer arm, upper chest, upper back or the side of the chest. Rotate among the 8 described skin sites. After 	<ul style="list-style-type: none"> Every 72 hours 	<ul style="list-style-type: none"> The maximum Butrans dose is 20 mcg/hr Do not exceed a dose of one 20 mcg/hr Butrans 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> No 	<ul style="list-style-type: none"> No

	<ul style="list-style-type: none"> 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 Butrans 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. Butrans is not indicated as an as-needed (prn) analgesic 	<p>(nociceptin) receptors. The contributions of these actions to its analgesic profile are unclear.</p> <p>Its clinical actions result from binding to the opioid receptors.</p>	<p>Butrans removal, wait a minimum of 21 days before reapplying to the same skin site.</p> <ul style="list-style-type: none"> Apply to a hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaven. Do not apply to irritated skin. If the application site must be cleaned, clean the site with water only. Do not use soaps, alcohol, oils, lotions, or abrasive devices. Allow the skin to dry before applying butrans. 		system due to the risk of QTc interval prolongation			
Tylenol® #3 (codeine phosphate/APAP), CIII	For the relief of mild to moderately severe pain	<ul style="list-style-type: none"> Codeine: Centrally-acting analgesic APAP: Peripherally acting, non-opiate, non-salicylate analgesic and antipyretic 	<ul style="list-style-type: none"> 5-60 mg codeine every 4 hours 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Not to exceed 360 mg codeine or 4000 mg APAP/24 hours 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> No 	<ul style="list-style-type: none"> No
Duragesic® (fentanyl transdermal system), CII	<p>For the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.</p> <p>Patients considered opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> Because of the risks of addiction, abuse, and 	<p>Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system.</p>	<ul style="list-style-type: none"> Every 72 hours Intended for transdermal use only Apply patch to intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. The next patch is applied to a different skin site after removal of the previous transdermal system. Avoid exposing application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and 	<ul style="list-style-type: none"> Every 3 days 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> No 	<ul style="list-style-type: none"> No

	<p>misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Duragesic 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.</p>		<p>heated water beds, while wearing the system</p>					
<p>Vicodin[®] (hydrocodone bitartrate/APAP), CII</p>	<p>For the relief of moderate to moderately severe pain</p>	<ul style="list-style-type: none"> Hydrocodone: semi-synthetic narcotic analgesic and antitussive (opioid receptors) APAP: Antipyretic activity is mediated through hypothalamic heat regulating centers; inhibits prostaglandin synthetase. 	<ul style="list-style-type: none"> Every 4 to 6 hours as needed for pain 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> 5 mg/300 mg: total daily dosage should not exceed 8 tablets 7.5 mg/300 mg: total daily dosage should not exceed 6 tablets 10 mg/300 mg: total daily dosage should not exceed 6 tablets 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> No 	<ul style="list-style-type: none"> No
<p>Zohydro[®] ER (hydrocodone bitartrate), CII</p>	<p>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.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> 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 	<p>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 a full agonist, binding to and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular gray matter, the ventromedial medulla and the spinal cord to produce analgesia, as well as the</p>	<ul style="list-style-type: none"> Every 12 hours Must be taken whole, one capsule at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Crushing, chewing, or dissolving capsules will result in uncontrolled delivery of hydrocodone and can lead to overdose or death 	<ul style="list-style-type: none"> Every 3-7 days 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Food has no significant effect on the extent of absorption of hydrocodone from Zohydro ER. Although there was no evidence of dose dumping associated with this formulation under fasted and fed 	<ul style="list-style-type: none"> Yes; co-ingestion with alcohol may result in increased plasma levels and a potentially fatal overdose of hydrocodone 	<ul style="list-style-type: none"> No

	<p>Zohydro 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.</p> <ul style="list-style-type: none"> • Zohydro ER is not indicated as an as-needed (prn) analgesic. 	<p>euphorant, respiratory depressant and physiologic dependence properties of agonist opioids like hydrocodone, result principally from agonist action at the μ receptors.</p>				<p>conditions, peak plasma concentration of hydrocodone increased by 27% when a Zohydro ER 20 mg capsule was administered with a high-fat meal.</p>		
<p>Exalgo[®] (hydromorphone HCl), CII</p>	<p>For the management of pain in <u>opioid-tolerant</u> patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.</p> <p>Patients considered opioid tolerant are those who are taking for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • 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 Exalgo 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 	<p>Hydromorphone, a semi-synthetic morphine derivative, is a hydrogenated ketone of morphine. Hydromorphone is principally an agonist of mu-receptors, showing a weak affinity for kappa receptors. As an opioid agonist, the principle therapeutic action of hydromorphone is analgesia. The precise mechanism of action of opioid analgesics is not known but the effects are thought to be mediated through opioid-specific receptors located predominantly in the central nervous system.</p>	<ul style="list-style-type: none"> • Every 24 hours • Swallow tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of hydromorphone 	<ul style="list-style-type: none"> • Every 3-4 days 	<ul style="list-style-type: none"> • There is no intrinsic limit to the analgesic effect of hydromorphone. • Clinically, however, dosage limitations are imposed by the adverse effects, primarily respiratory depression, sedation, nausea, and vomiting, which can result from high doses. 	<ul style="list-style-type: none"> • Can be administered without regard to food 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • No

	<p>provide sufficient management of pain.</p> <ul style="list-style-type: none"> Exalgo is not indicated as an as-needed (prn) analgesic. 							
<p>Dolophine® (methadone HCl), CII</p>	<p>Indicated for:</p> <ul style="list-style-type: none"> Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. <p><u>Limitations of Use:</u></p> <ul style="list-style-type: none"> 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 long-acting opioids, reserve Dolophine 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. Dolophine is not indicated as an as-needed (prn) analgesic. Detoxification treatment of opioid addiction (heroin or other morphine-like drugs). Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services. 	<p>Methadone hydrochloride is a mu-agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid addiction.</p> <p>Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.</p>	<ul style="list-style-type: none"> Every 8 to 12 hours May exhibit cumulative effects with repeated dosing. 	<ul style="list-style-type: none"> Every 1-2 days 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> No 	<ul style="list-style-type: none"> No

<p>Avinza[®] (morphine sulfate ER), CII</p>	<p>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.</p> <p><u>Limitations of Use:</u></p> <ul style="list-style-type: none"> 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 Avinza 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. Avinza is not indicated as an as-needed (prn) analgesic, and persist for an extended period of time. 	<p>Morphine sulfate, a pure opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine include dysphoria, euphoria, somnolence, respiratory depression, diminished gastrointestinal motility, altered circulatory dynamics, histamine release, physical dependence, and alterations of the endocrine and autonomic nervous systems.</p> <p>Morphine produces both its therapeutic and its adverse effects by interaction with one or more classes of specific opioid receptors located throughout the body. Morphine acts as a full agonist, binding with and activating opioid receptors at sites in the peri-aqueductal and peri-ventricular grey matter, the ventro-medial medulla and the spinal cord to produce analgesia.</p>	<ul style="list-style-type: none"> Every 24 hours Avinza capsules must be taken whole. Crushing, chewing, or dissolving the pellets in Avinza will result in uncontrolled delivery of morphine and can lead to overdose or death Contents of the capsules (pellets) may be sprinkled over applesauce and then swallowed if patient is able to reliably swallow the applesauce without chewing. Do not administer Avinza pellets through a nasogastric or gastric tubes. Avinza 90 mg and 120 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. 	<ul style="list-style-type: none"> Every 3-4 days (in increments not greater than 30 mg) 	<ul style="list-style-type: none"> The daily dose of Avinza must be limited to a maximum of 1600 mg/day. Avinza doses of over 1600 mg/day contain a quantity of fumaric acid that has not been demonstrated to be safe, and which may result in serious renal toxicity. 	<ul style="list-style-type: none"> Can be administered without regard to food 	<ul style="list-style-type: none"> Yes; co-ingestion with alcohol can result in fatal plasma morphine levels 	<ul style="list-style-type: none"> No
<p>Embeda[®] (morphine sulfate/ naltrexone HCl ER), CII</p>	<p>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.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, 		<ul style="list-style-type: none"> Every 12 or 24 hours Swallow capsules intact. The pellets in the capsules are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of morphine and release of sufficient dose of naltrexone to precipitate withdrawal 	<ul style="list-style-type: none"> Every 1-2 days 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Can be taken with or without food 	<ul style="list-style-type: none"> Yes; co-ingestion with alcohol may result in increased plasma levels and a potentially fatal overdose of morphine 	<ul style="list-style-type: none"> Yes

	<p>and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Embeda 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.</p> <ul style="list-style-type: none"> • Embeda is not indicated as an as-needed (prn) analgesic. 		<p>in opioid-dependent individuals</p> <ul style="list-style-type: none"> • Contents of the capsules (pellets) may be sprinkled over applesauce and then swallowed if patient is able to reliably swallow the applesauce without chewing. • Do not administer Embeda pellets through a nasogastric or gastric tubes • Embeda 100 mg/4 mg capsules are only for patients in whom tolerance to an opioid of comparable potency is established. 					
<p>Kadian® (morphine sulfate ER), CII</p>	<p>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.</p> <p><u>Limitations of Use:</u></p> <ul style="list-style-type: none"> • 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 Kadian 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. • Kadian is not indicated as an as-needed (prn) analgesic. 		<ul style="list-style-type: none"> • A frequency of either once daily (every 24 hours) or twice daily (every 12 hours) • Kadian capsules must be taken whole. Crushing, chewing, or dissolving the pellets in KADIAN capsules will result in uncontrolled delivery of morphine and can lead to overdose or death • Contents of the capsules (pellets) may be sprinkled over applesauce and then swallowed if patient is able to reliably swallow the applesauce without chewing • Contents of the capsules (pellets) may be administered through a 16 French gastrostomy tube. • Do not administer Kadian pellets through a nasogastric tube 	<ul style="list-style-type: none"> • Every 1-2 days 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • No

<p>MS Contin[®] (morphine sulfate ER), CII</p>	<p>For the management pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • 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 MS Contin 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. • MS Contin is not indicated as an as-needed (prn) analgesic. 		<ul style="list-style-type: none"> • Every 8 or 12 hours • MS Contin tablets must be taken whole. Crushing, chewing, or dissolving tablets will result in uncontrolled delivery of morphine and can lead to overdose or death 	<ul style="list-style-type: none"> • Every 1-2 days 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • No significant differences in C_{max} and AUC when taken while fasting or with a high-fat breakfast 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • No
<p>OxyContin[®] (oxycodone HCl ER), CII</p>	<p>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.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • 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 formulations, reserve OxyContin for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, 	<p>The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.</p>	<ul style="list-style-type: none"> • Every 12 hours • Swallow tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of oxycodone • Take OxyContin one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth • OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid 	<ul style="list-style-type: none"> • Every 1-2 days 	<ul style="list-style-type: none"> • Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. • Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression. 	<ul style="list-style-type: none"> • Food has no significant effect on the extent of absorption of oxycodone from OxyContin 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • Yes

	<p>or would be otherwise inadequate to provide sufficient management of pain.</p> <ul style="list-style-type: none"> • OxyContin is not indicated as an as-needed (prn) analgesic. 		<p>of comparable potency has been established.</p>					
<p>Percocet® (oxycodone HCl/APAP), CII</p>	<p>For the relief of moderate to moderately severe pain.</p>	<p>Oxycodone: semisynthetic pure opioid agonist whose principal therapeutic action is analgesia.</p> <p>APAP: non-opiate, non-salicylate analgesic and antipyretic. The site and mechanism for the analgesic effect of APAP has not been determined.</p>	<ul style="list-style-type: none"> • Every 6 hours as needed for pain 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • The total daily dose of APAP should not exceed 4 grams. 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • No
<p>Opana® ER (oxymorphone HCl), CII</p>	<p>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.</p> <p><u>Limitations of Use</u></p> <ul style="list-style-type: none"> • 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 OPANA 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. • OPANA ER is not indicated as an as-needed (prn) analgesic. 	<p>Oxymorphone, an opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. The precise mechanism of analgesia, the principal therapeutic action of oxymorphone, is unknown. Specific central nervous system opioid receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. In addition, opioid receptors have also been identified within the peripheral nervous system. The role that these receptors play in these drugs' analgesic effects is unknown.</p>	<ul style="list-style-type: none"> • Every 12 hours • Swallow tablets intact. The tablets are not to be crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of oxymorphone • Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth • Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating 	<ul style="list-style-type: none"> • 3-7 days 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • C_{max} was increased by ~ 50% in fed subjects compared to fasted subjects. • AUC increased by ~18% in a study in fed subjects following the administration of oxymorphone hydrochloride extended-release tablets • After single PO dose of 40 mg, a peak plasma level of 2.8 ng/ml is achieved at 1 hour in fasted subjects and a peak of 4.25 ng/ml is achieved at 2 hours in fed 	<ul style="list-style-type: none"> • Yes; co-ingestion with alcohol can result in fatal plasma oxymorphone levels 	<ul style="list-style-type: none"> • No

						<p>subjects with very little difference in the curves thereafter</p> <ul style="list-style-type: none"> • Administer on an empty stomach, at least one hour prior to or two hours after eating 		
<p>Nucynta® ER (tapentadol ER), CII</p>	<p>For the management of</p> <ul style="list-style-type: none"> • pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate • neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. <p><u>Limitations of Use:</u></p> <ul style="list-style-type: none"> • 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 Nucynta ER for use in 	<p>Centrally-acting synthetic analgesic. The exact mechanism of action is unknown. Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI). Analgesia in animal models is derived from both of these properties.</p>	<ul style="list-style-type: none"> • Every 12 hours • Swallow tablets whole. The tablets are not to be cut, crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of tapentadol • Tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth 	<ul style="list-style-type: none"> • Every 3 days (in increments of no more than 50 mg twice daily) 	<ul style="list-style-type: none"> • Maximum total daily dose of Nucynta ER is 500 mg 	<ul style="list-style-type: none"> • AUC and C_{max} increased by 6% and 17%, respectively, when administered after a high-fat, high-calorie breakfast • May be given with or without food 	<ul style="list-style-type: none"> • Yes; co-ingestion with alcohol can result in fatal plasma tapentadol levels 	<ul style="list-style-type: none"> • No

	<p>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.</p> <ul style="list-style-type: none"> • Nucynta ER is not indicated as an as-needed (prn) analgesic. 							
<p>Ultracet[®] (tramadol hydrochloride / APAP), CIV</p>	<p>For the short term (5 days or less) management of acute pain</p>	<p>Tramadol: centrally-acting synthetic opioid analgesic; mu-opioid receptor binding and inhibition of reuptake of norepinephrine and serotonin</p> <p>APAP: Non-opiate, non-salicylate analgesic</p>	<ul style="list-style-type: none"> • 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • Maximum of 8 tablets per day 	<ul style="list-style-type: none"> • When taken with food, the T_{max} was delayed and the C_{max} and AUC were unchanged • Clinical significance unknown. 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • No
<p>Ultram[®] (tramadol hydrochloride), CIV</p>	<p>For the management of moderate to moderately severe pain in adults</p>	<p>Tramadol: centrally-acting synthetic opioid analgesic; mu-opioid receptor binding and inhibition of reuptake of norepinephrine and serotonin</p> <p>APAP: Non-opiate, non-salicylate analgesic</p>	<ul style="list-style-type: none"> • Not requiring rapid onset: Start at 25 mg/day qAM, titrate in 25 mg increments as separate doses every 3 days up to 100 mg/day (25 mg qid), thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg qid) After titration: 50 - 100mg can be administered PRN every 4 to 6 hours, not to exceed 400 mg/day. • Rapid onset needed: 50- 100 mg as needed for pain every 4 to 6 hours, not to exceed 400 mg/day 	<ul style="list-style-type: none"> • Not requiring rapid onset: every 3 days 	<ul style="list-style-type: none"> • Do not exceed 400 mg/day 	<ul style="list-style-type: none"> • No significant effect on rate or extent of absorption • Administer without regard to food 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • No

Ultram[®] ER (tramadol HCl ER), CIV	For the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time	Tramadol: centrally-acting synthetic opioid analgesic; mu-opioid receptor binding and inhibition of reuptake of norepinephrine and serotonin APAP: Non-opiate, non-salicylate analgesic	<ul style="list-style-type: none"> • Initiate at a dose of 100 mg once daily and titrate up as necessary by 100 mg increments every 5 days to relief of pain and depending on tolerability • Not to exceed 300 mg/day 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • Do not exceed 300 mg/day 	With high fat meal C _{max} and AUC decreased by 28% and 16%, respectively, T _{max} increased by 3 hours <ul style="list-style-type: none"> • Take consistently in relation to meals 	<ul style="list-style-type: none"> • No 	<ul style="list-style-type: none"> • No
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Table 7.2. Contraindications

Product	Contraindications	
REFERENCE DRUG: Hysingla™ ER (hydrocodone bitartrate), CII	<ul style="list-style-type: none"> Significant respiratory depression Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment 	<ul style="list-style-type: none"> Known or suspected paralytic ileus and GI obstruction Hypersensitivity to any components of Hysingla ER or the active ingredient, hydrocodone bitartrate
Butrans® (buprenorphine) Transdermal System, CIII	<ul style="list-style-type: none"> Patients with significant respiratory depression Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment 	<ul style="list-style-type: none"> Patients with known or suspected paralytic ileus Patients with hypersensitivity (e.g., anaphylaxis) to buprenorphine
Tylenol® #3 (codeine phosphate/ APAP), CIII	<ul style="list-style-type: none"> Hypersensitivity to codeine or acetaminophen 	
Duragesic® (fentanyl transdermal system), CII	<ul style="list-style-type: none"> Patients who are not opioid tolerant Management of acute pain or intermittent pain, or in patients who require opioid analgesia for a short period of time Management of post-operative pain, including use after out-patient or day surgeries, (e.g., tonsillectomies) Management of mild pain Management of intermittent pain 	<ul style="list-style-type: none"> Patient with significant respiratory compromise, especially if adequate monitoring and resuscitative equipment are not readily available Patients who have acute or severe bronchial asthma Patients who have or who are suspected of having paralytic ileus Hyper-sensitivity to fentanyl or any component of the transdermal system. Severe hypersensitivity reactions, including anaphylaxis have been observed with Duragesic
Vicodin® (hydrocodone bitartrate/APAP), CIII	<ul style="list-style-type: none"> Patients with hypersensitivity (e.g., anaphylaxis) to hydrocodone or acetaminophen 	<ul style="list-style-type: none"> Cross-sensitivity may occur in patients hypersensitive to other opioids
Zohydro® ER (hydrocodone bitartrate), CII	<ul style="list-style-type: none"> Patients with significant respiratory depression Patients with known or suspected paralytic ileus 	<ul style="list-style-type: none"> Patients with acute or severe bronchial asthma or hypercarbia Patients with hypersensitivity to hydrocodone bitartrate or any other ingredients in Zohydro ER
Exalgo® (hydromorphone HCl), CII	<ul style="list-style-type: none"> Opioid non-tolerant patients. Fatal respiratory depression could occur in patients who are not opioid tolerant. Patients with significant respiratory depression Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment Patients with known or suspected paralytic ileus 	<ul style="list-style-type: none"> Patients who have had surgical procedures and/or underlying disease resulting in narrowing of the narrowing of the gastrointestinal tract, or have “blind loops” of the gastrointestinal tract or gastrointestinal obstruction Patients with hypersensitivity (e.g., anaphylaxis) to hydromorphone or sulfite-containing medications
Dolophine® (methadone HCl), CII	<ul style="list-style-type: none"> Patients with significant respiratory depression Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment 	<ul style="list-style-type: none"> Patient with known or suspected paralytic ileus Patients with hypersensitivity (e.g., anaphylaxis) to methadone
Avinza® (morphine sulfate ER), CII	<ul style="list-style-type: none"> Patients with significant respiratory depression Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment Patients with known or suspected paralytic ileus Patients with hypersensitivity (e.g., anaphylaxis) to morphine (or naltrexone, Embeda only) 	
Kadian® (morphine sulfate ER), CII		
MS Contin® (morphine sulfate ER), CII		
Embeda® (morphine sulfate/ naltrexone HCl ER), CII		
OxyContin® (oxycodone HCl ER), CII	<ul style="list-style-type: none"> Patients with significant respiratory depression Patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment 	<ul style="list-style-type: none"> Patients with known or suspected paralytic ileus and gastrointestinal obstruction Patients with hypersensitivity (e.g., anaphylaxis) to oxycodone
Percocet®	<ul style="list-style-type: none"> Patients with known hypersensitivity to oxycodone, acetaminophen, or any other 	<ul style="list-style-type: none"> Patients with acute or severe bronchial asthma or hypercarbia

Product	Contraindications	
(oxycodone HCl/APAP), CII	<ul style="list-style-type: none"> component of this product Patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment) 	<ul style="list-style-type: none"> Suspected or known paralytic ileus
Opana[®] ER (oxymorphone HCl), CII	<ul style="list-style-type: none"> Patients with significant respiratory depression Patients with acute or severe bronchial asthma or hypercarbia Patients with known or suspected paralytic ileus 	<ul style="list-style-type: none"> Moderate or severe hepatic impairment Patients with known hypersensitivity to oxymorphone, any other ingredients in Opana ER, or to morphine analogs such as codeine
Nucynta[®] ER (tapentadol), CII	<ul style="list-style-type: none"> Patients with significant respiratory depression Patients with acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment Patients with known or suspected paralytic ileus 	<ul style="list-style-type: none"> Patients with hypersensitivity (e.g. anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product Patients who are receiving monoamine oxidase inhibitors (MAOI) or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events
Ultracet[®] (tramadol hydrochloride / APAP), CIV	<ul style="list-style-type: none"> Hypersensitivity to tramadol, any component of product, or opioids (or acetaminophen, Ultracet only) 	<ul style="list-style-type: none"> Any situation where opioids are contraindicated including acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids, or psychotropic drugs
Ultram[®] (tramadol hydrochloride), CIV		
Ultram[®] ER (tramadol HCl ER), CIV		

Table 7.3. Warnings and Precautions

Product	Warnings and Precautions	
REFERENCE DRUG: Hysingla™ ER (hydrocodone bitartrate), CII	<ul style="list-style-type: none"> • Addiction, Abuse, and Misuse • Life-Threatening Respiratory Depression • Neonatal Opioid Withdrawal Syndrome • Interactions with Central Nervous System Depressants • Use in Elderly, Cachectic, and Debilitated Patients • Use in Patients with Chronic Pulmonary Disease • Use in Patients with Head Injury and Increased Intracranial Pressure 	<ul style="list-style-type: none"> • Hypotensive Effect • GI Obstruction, Dysphagia, and Choking • Decreased Bowel Motility • Cytochrome P450 CYP3A4 Inhibitors and Inducers • Driving and Operating Machinery • Interaction with Mixed Agonist/Antagonist Opioid Analgesics • QTc Interval Prolongation
Butrans® (buprenorphine) transdermal System, CIII	<ul style="list-style-type: none"> • Addiction, Abuse, and Misuse • Life-Threatening Respiratory Depression • Neonatal Opioid Withdrawal Syndrome • Interactions with Alcohol, CNS Depressants, and Illicit Drugs • Use in Elderly, Cachectic, and Debilitated Patients • Use in Patients with Chronic Pulmonary Disease • QTc Prolongation • Hypotensive Effects • Use in Patients with Head Injury or Increased Intracranial Pressure 	<ul style="list-style-type: none"> • Hepatotoxicity • Application Site Skin Reactions • Anaphylactic/Allergic Reactions • Application of External Heat • Patients with Fever • Use in Patients with Gastrointestinal Conditions • Use in Patients with Convulsive or Seizure Disorders • Driving and Operating Machinery • Use in Addiction Treatment
Tylenol® #3 (codeine phosphate/ APAP), CIII	<ul style="list-style-type: none"> • Hepatotoxicity • Hypersensitivity / Anaphylaxis • Head Injuries • Acute Abdominal Conditions 	<ul style="list-style-type: none"> • Abuse Potential • Sulfite Sensitivity • Use with CNS Depressants • Drug/Laboratory Test Interactions
Duragesic® (fentanyl transdermal system), CII	<ul style="list-style-type: none"> • Addiction, Abuse, and Misuse • Life-Threatening Respiratory Depression • Accidental Exposure • Neonatal Opioid Withdrawal Syndrome • Interactions with Central Nervous System Depressants • Use in Elderly, Cachectic, and Debilitated Patients • Chronic Pulmonary Disease • Head Injuries and Increased Intracranial Pressure • Hypotensive Effects 	<ul style="list-style-type: none"> • Interactions with CYP3A4 Inhibitors and Inducers • Application of External Heat • Patients with Fever • Cardiac Disease • Hepatic Impairment • Renal Impairment • Use in Pancreatic/Biliary Tract Disease • Avoidance of Withdrawal • Driving and Operating Machinery
Vicodin® (hydrocodone bitartrate/APAP), CIII	<ul style="list-style-type: none"> • Hepatotoxicity • Serious Skin Reactions • Hypersensitivity/anaphylaxis • Respiratory Depression • Head Injury and Increased Intracranial Pressure • Acute Abdominal Conditions • Cough Reflex 	<ul style="list-style-type: none"> • Special Risk Populations: Elderly/debilitated patients, severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture • Severe Hepatic or Renal Disease • Use with Other CNS Depressants, MAO Inhibitors, Tricyclic Antidepressants • Drug/Laboratory Test Interactions
Zohydro® ER (hydrocodone bitartrate), CII	<ul style="list-style-type: none"> • Addiction, Abuse, and Misuse • Life-Threatening Respiratory Depression • Neonatal Opioid Withdrawal Syndrome • Interactions with CNS Depressants • Elderly, Cachectic, Debilitated Patients • Use in Patients with Chronic Pulmonary Disease • Hypotensive Effect 	<ul style="list-style-type: none"> • Patients with Head Injury or Increased Intracranial Pressure • Use in Patients with Gastrointestinal Conditions • Use in Patients with Convulsive or Seizure Disorders • Avoidance of Withdrawal • Driving and Operating Machinery • Cytochrome P450 CYP3A4 Inhibitors and Inducers

Exalgo[®] (hydromorphone HCl), CII	<ul style="list-style-type: none"> Addiction, Abuse, and Misuse Life-threatening Respiratory Depression Neonatal Opioid Withdrawal Syndrome Interactions with CNS Depressants Use in Elderly, Cachectic, and Debilitated Patients Use in Patients with Chronic Pulmonary Disease Hypotensive Effects 	<ul style="list-style-type: none"> Use in Patients with Head Injury and Increased Intracranial Pressure Use in Patients with Gastrointestinal Conditions Sulfites Use in Patients with Convulsive or Seizure Disorders Avoidance of Withdrawal Driving and Operating Machinery
Dolophine[®] (methadone HCl), CII	<ul style="list-style-type: none"> Addiction, Abuse, and Misuse Life-Threatening Respiratory Depression Life-Threatening QT Prolongation Neonatal Opioid Withdrawal Syndrome Interactions with CNS Depressants Use in Elderly, Cachectic, and Debilitated Patients Use in Patients with Chronic Pulmonary Disease 	<ul style="list-style-type: none"> Hypotensive effect Use in Patients with Head Injury and Increased Intracranial Pressure Use in Patients with Gastrointestinal Conditions Use in Patients with Convulsive or Seizure Disorders Avoidance of Withdrawal Driving and Operating Machinery
Avinza[®] (morphine sulfate ER), CII	<ul style="list-style-type: none"> Addiction, Abuse, and Misuse Life Threatening Respiratory Depression Neonatal Opioid Withdrawal Syndrome Interaction with CNS Depressants Use in Elderly, Cachectic, and Debilitated Patients Use in Patients with Chronic Pulmonary Disease Interactions with CNS Depressants and Illicit Drugs (Embeda) 	<ul style="list-style-type: none"> Hypotensive Effect Use in Patients with Head Injury and Increased Intracranial Pressure Use in Patients with Gastrointestinal Conditions Use in Patients with Convulsive or Seizure Disorders Avoidance of Withdrawal Driving and Operating Machinery
Embeda[®] (morphine sulfate/ naltrexone HCl ER), CII		
Kadian[®] (morphine sulfate ER), CII		
MS Contin[®] (morphine sulfate ER), CII		
OxyContin[®] (oxycodone HCl ER), CII	<ul style="list-style-type: none"> Addiction, Abuse, and Misuse Life-Threatening Respiratory Depression Neonatal Opioid Withdrawal Syndrome Interactions with CNS Depressants Use in Elderly, Cachectic, and Debilitated Patients Use in Patients with Chronic Pulmonary Disease Hypotensive Effects Use in Patients with Head Injury or Increased Intracranial Pressure 	<ul style="list-style-type: none"> Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen Use in Patients with Gastrointestinal Conditions Use in Patients with Convulsive or Seizure Disorders Avoidance of Withdrawal Driving and Operating Machinery Cytochrome P450 3A4 Inhibitors and Inducers Laboratory Monitoring
Percocet[®] (oxycodone HCl/APAP), CII	<ul style="list-style-type: none"> Misuse, Abuse and Diversion of Opioids Respiratory Depression Head Injury and Increase Intracranial Pressure Hypotensive Effect Hepatotoxicity Serious Skin Reactions Hypersensitivity / anaphylaxis 	<ul style="list-style-type: none"> Interactions with Other CNS Depressants Interactions with Mixed Agonist/Antagonist Opioid Analgesics Ambulatory Surgery and Postoperative Use Use in Pancreatic/Biliary Tract Disease Tolerance and Physical Dependence Laboratory Tests
Opana[®] ER (oxymorphone HCl), CII	<ul style="list-style-type: none"> Addiction, Abuse, and Misuse Life Threatening Respiratory Depression Neonatal Opioid Withdrawal Syndrome Interactions with CNS Depressants Use in Elderly, Cachectic, and Debilitated Patients Use in Patients with Chronic Pulmonary Disease Use in Patients with Hepatic Impairment Hypotensive Effect 	<ul style="list-style-type: none"> Use in Patients with Head Injury or Increased Intracranial Pressure Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen Use in Patients with Gastrointestinal Conditions Use in Patients with Convulsive or Seizure Disorders Avoidance of Withdrawal Driving and Operating Machinery

Nucynta[®] ER (tapentadol), CII	<ul style="list-style-type: none"> • Addiction, Abuse, and Misuse • Life-Threatening Respiratory Depression • Neonatal Opioid Withdrawal Syndrome • Interactions with CNS Depressants • Use in Elderly, Cachectic, and Debilitated Patients • Use in Patients with Chronic Pulmonary Disease • Hypotensive Effect • Use in Patients with Head Injury or Increased Intracranial Pressure 	<ul style="list-style-type: none"> • Seizures • Serotonin Syndrome Risk • Use in Patients with Gastrointestinal Conditions • Avoidance of Withdrawal • Driving and Operating Heavy Machinery • Hepatic Impairment • Renal Impairment
Ultracet[®] (tramadol hydrochloride / APAP), CIV	<ul style="list-style-type: none"> • Hepatotoxicity • Serious Skin Reactions • Seizure Risk • Suicide Risk • Serotonin Syndrome Risk • Hypersensitivity / anaphylaxis • Respiratory Depression • Interaction with CNS Depressants 	<ul style="list-style-type: none"> • Interactions with Alcohol and Drugs of Abuse • Increased Intracranial Pressure or Head Trauma • Use in Ambulatory Patients • Use with MAOIs and Serotonin Re-uptake Inhibitors • Use with Alcohol • Use with other APAP containing products • Misuse, Abuse, and Diversion • Risk of Overdosage • Withdrawal
Ultram[®] (tramadol hydrochloride), CIV Ultram[®] ER (tramadol HCl ER), CIV	<ul style="list-style-type: none"> • Seizure Risk • Suicide Risk • Serotonin Syndrome Risk • Anaphylactoid Reactions • Respiratory Depression • Interactions with CNS Depressants • Increased Intracranial Pressure or Head Trauma • Use in Ambulatory Patients 	<ul style="list-style-type: none"> • Use with MAOIs and Serotonin Re-uptake Inhibitors • Withdrawal • Misuse, Abuse, and Diversion of Opioids • Interaction with Alcohol and Drugs of Abuse • Acute Abdominal Condition • Use in Renal and Hepatic Disease • Use in Drug and Alcohol Addiction (Ultram ER only) • Risk of Overdosage (Ultram only)

Table 7.4. Adverse Reactions

Product	Adverse Reactions
REFERENCE DRUG: Hysingla™ ER (hydrocodone bitartrate), CII	Most common treatment-emergent adverse events (≥ 5%) are constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence
Butrans® (buprenorphine) Transdermal System, CIII	Most common adverse reactions (≥ 5%) include: nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash. The most common serious adverse drug reactions (all <0.1%) occurring during clinical trials with Butrans were: chest pain, abdominal pain, vomiting, dehydration, and hypertension/blood pressure increased.
Tylenol® #3 (Codeine phosphate/ APAP), CIII	The most frequently observed adverse reactions include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting. Others include: allergic reactions, euphoria, dysphoria, constipation, abdominal pain, pruritus, rash, thrombocytopenia, agranulocytosis
Duragesic® (fentanyl transdermal system), CII	The most common adverse reactions (≥5%) in a double-blind, randomized, placebo-controlled clinical trial in patients with severe pain were nausea, vomiting, somnolence, dizziness, insomnia, constipation, hyperhidrosis, fatigue, feeling cold, and anorexia. Other common adverse reactions (≥5%) reported in clinical trials in patients with chronic malignant or nonmalignant pain were headache and diarrhea.
Vicodin® (hydrocodone bitartrate/APAP), CIII	The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis, Stevens-Johnson syndrome, toxic epidermal necrolysis.
Zohydro® ER (hydrocodone bitartrate), CII	Most common adverse reactions (≥2%) include: constipation, nausea, somnolence, fatigue, headache, dizziness, dry mouth, vomiting, pruritus, abdominal pain, edema peripheral, upper respiratory tract infection, muscle spasms, urinary tract infection, back pain and tremor.
Exalgo® (hydromorphone HCl), CII	Most common adverse reactions (>10%) are: constipation, nausea, vomiting, somnolence, headache, and dizziness. The most common treatment-related serious adverse reactions from controlled and uncontrolled chronic pain studies were drug withdrawal syndrome, overdose, confusional state, and constipation.
Dolophine® (methadone HCl), CII	Most common adverse reactions are: lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.
Avinza® (morphine sulfate ER), CII	Most common adverse reactions (≥10%) are constipation, nausea, somnolence, vomiting and headache. The most common serious adverse events reported with administration of Avinza were vomiting, nausea, death in patients with underlying malignancy, dehydration, dyspnea, and sepsis.
Embeda® (morphine sulfate/ naltrexone HCl ER), CII Kadian® (morphine sulfate ER), CII	Most common adverse reactions (>10%): constipation, nausea, and somnolence.
MS Contin® (morphine sulfate ER), CII	In clinical trials, the most common adverse reactions with MS Contin were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoric mood, MS Contin may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock
OxyContin® (oxycodone HCl ER), CII	Most common adverse reactions (>5%) are constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. OxyContin may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock
Percocet® (oxycodone HCl/APAP), CII	The most frequently observed non-serious adverse reactions include lightheadedness, dizziness, drowsiness or sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include euphoria, dysphoria, constipation, and pruritus. Serious adverse reactions that may be associated with Percocet tablet use include respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and shock. Rare cases of agranulocytosis has likewise been associated with acetaminophen use. In high doses, the most serious adverse effect is a dose-dependent, potentially fatal hepatic necrosis. Renal tubular necrosis and hypoglycemic coma also may occur. .
Opana® ER (oxymorphone HCl), CII	Adverse reactions in ≥2% of patients in placebo-controlled trials: nausea, constipation, dizziness (excluding vertigo), somnolence, vomiting, pruritus, headache, sweating increased, dry mouth, sedation, diarrhea, insomnia, fatigue, appetite decreased, and abdominal pain. The most common serious adverse events reported with administration of oxymorphone hydrochloride extended-release tablets were chest pain, pneumonia and vomiting.
Nucynta® ER	The most common (≥10%) adverse reactions were nausea, constipation, dizziness, headache, and somnolence.

Product	Adverse Reactions
(tapentadol ER), CII	
Ultracet[®] (tramadol hydrochloride / APAP), CIV	Treatment-emergent adverse events (≥2%) included: constipation, diarrhea, nausea, dry mouth, somnolence, anorexia, insomnia, dizziness, increased sweating, pruritus, prostatic disorder
Ultram[®] (tramadol hydrochloride), CIV	Most frequent adverse reactions (≥5%) are dizziness / vertigo, nausea, constipation, headache, somnolence, vomiting, pruritus, CNS stimulation, asthenia, sweating, dyspepsia, dry mouth, diarrhea
Ultram[®] ER (tramadol HCl ER), CIV	Adverse events (≥5%) included: dizziness (not vertigo), nausea, constipation, headache, somnolence, flushing, pruritus, vomiting, insomnia, dry mouth, diarrhea, asthenia, postural hypotension, sweating increased, anorexia

Table 7.5. Drug Interactions

Product	Drug Interactions	
REFERENCE DRUG: Hysingla™ ER (hydrocodone bitartrate), CII	<ul style="list-style-type: none"> • Drugs Affecting Cytochrome P450 Isoenzymes • Central Nervous System Depressants • Interactions with Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics 	<ul style="list-style-type: none"> • MAO Inhibitors • Anticholinergics • Strong Laxatives
Butrans® (buprenorphine) Transdermal System, CIII	<ul style="list-style-type: none"> • Benzodiazepines • CNS Depressants • Drugs Affecting Cytochrome P450 Isoenzymes 	<ul style="list-style-type: none"> • Skeletal Muscle Relaxants • Anticholinergics
Tylenol® #3 (codeine phosphate/ APAP), CIII	<ul style="list-style-type: none"> • Narcotic analgesics • Alcohol • General anesthetics 	<ul style="list-style-type: none"> • Tranquilizers • Sedative-hypnotics • CNS Depressants
Duragesic® (fentanyl transdermal system), CII	<ul style="list-style-type: none"> • Central Nervous System Depressants • Drugs Affecting Cytochrome P450 3A4 Isoenzymes 	<ul style="list-style-type: none"> • MAO Inhibitors • Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics • Anticholinergics
Vicodin® (hydrocodone bitartrate/APAP), CIII	<ul style="list-style-type: none"> • Central Nervous System Depressants • MAO Inhibitors 	<ul style="list-style-type: none"> • Tricyclic Antidepressants
Zohydro® ER (hydrocodone bitartrate), CII	<ul style="list-style-type: none"> • Alcohol • CNS Depressants • Drugs Affecting Cytochrome P450 Isoenzymes 	<ul style="list-style-type: none"> • Interactions with Mixed Agonist/Antagonist Opioid Analgesics • MAO Inhibitors • Anticholinergics
Exalgo® (hydromorphone HCl), CII	<ul style="list-style-type: none"> • CNS Depressants • Mixed Agonist/Antagonist Opioid Analgesics 	<ul style="list-style-type: none"> • Monoamine Oxidase Inhibitors (MAOI) • Anticholinergics
Dolophine® (methadone HCl), CII	<ul style="list-style-type: none"> • CNS Depressants • Drugs Affecting Cytochrome P450 Isoenzymes • Potentially Arrhythmogenic Agents 	<ul style="list-style-type: none"> • Mixed Agonists/Antagonist and Partial Agonist Opioid Analgesics • Antidepressants • Anticholinergics • Laboratory Test Interactions
Avinza® (morphine sulfate ER), CII	<ul style="list-style-type: none"> • Alcohol (Avinza, Embeda, Kadian only) • CNS Depressants • Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics • Muscle Relaxants • Monoamine Oxidase Inhibitors (MAOIs) 	<ul style="list-style-type: none"> • Cimetidine • Diuretics • Anticholinergics • P-Glycoprotein (PGP) Inhibitors
Embeda® (morphine sulfate/ naltrexone HCl ER), CII		
Kadian® (morphine sulfate ER), CII		
MS Contin® (morphine sulfate ER), CII		
OxyContin® (oxycodone HCl ER), CII	<ul style="list-style-type: none"> • CNS Depressants • Muscle Relaxants • Drugs Affecting Cytochrome P450 Isoenzymes 	<ul style="list-style-type: none"> • Mixed Agonist/ Antagonist and Partial Agonist Opioid Analgesics • Diuretics • Anticholinergics

Percocet® (oxycodone HCl/APAP), CII	<ul style="list-style-type: none"> • Skeletal Muscle Relaxants • CNS Depressants • Agonist/Antagonist Analgesics • Alcohol • Anticholinergics • Oral Contraceptives 	<ul style="list-style-type: none"> • Activated Charcoal • Beta-Blockers • Loop Diuretics • Lamotrigine • Probenecid • Zidovudine
Opana® ER (oxymorphone HCl), CII	<ul style="list-style-type: none"> • Alcohol • CNS Depressants • Interactions with Mixed Agonist/ Antagonist and Partial Agonist Opioid Analgesics 	<ul style="list-style-type: none"> • Muscle Relaxants • Cimetidine • Anticholinergics
Nucynta® ER (tapentadol), CII	<ul style="list-style-type: none"> • Alcohol • Monoamine Oxidase Inhibitors • CNS Depressants • Serotonergic Drugs 	<ul style="list-style-type: none"> • Muscle Relaxants • Mixed Agonist/Antagonist Opioid Analgesics • Anticholinergics
Ultracet® (tramadol hydrochloride / APAP), CIV	<ul style="list-style-type: none"> • CYP2D6 and CYP3A4 inhibitors • Serotonergic drugs • Triptans 	<ul style="list-style-type: none"> • Warfarin • MAOIs and Serotonin Re-uptake Inhibitors • Tricyclic antidepressants
Ultram® (tramadol hydrochloride), CIV	<ul style="list-style-type: none"> • Carbamazepine • Quinidine • Cimetidine 	<ul style="list-style-type: none"> • Neuroleptics • Drugs that reduce seizure threshold • CNS Depressants
Ultram® ER (tramadol HCl ER), CIV	<ul style="list-style-type: none"> • Digoxin 	<ul style="list-style-type: none"> • Alcohol and drugs of abuse

Table 7.6. Use in Specific Populations

Product	Use in Specific Populations
<p>REFERENCE DRUG: Hysingla™ ER (hydrocodone bitartrate), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – There are no adequate and well-controlled studies of hydrocodone use during pregnancy. Based on limited human data in the literature, hydrocodone does not appear to increase the risk of congenital malformations. In animal reproduction and developmental toxicology studies, no embryotoxicity or teratogenicity was observed. Reduced fetal/pup body weights were observed at maternally toxic doses. • Labor and Delivery: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Hydrocodone 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. • Nursing: Hydrocodone has shown to be secreted in milk from both animal studies and clinical studies. The concentrations in milk were 5-fold less than in plasma in the peri-/postnatal study. Standard postpartum dosages of hydrocodone appear to be acceptable to use in women nursing newborns. Prolonged use of high dosages is not advisable. • Pediatric Use: safety and effectiveness has not been established in pediatric patients below the age of 18 years. • Geriatric Use: elderly subjects (greater than 65 years) compared to young adults had similar plasma concentrations of hydrocodone. 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. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. • Hepatic Impairment: Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. No adjustment in starting dose with Hysingla ER is required in patients with mild or moderate hepatic impairment. Initiate therapy with ½ the initial dose of Hysingla ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression. • 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 ½ the initial dose of Hysingla ER in these patients and monitor closely for adverse events such as respiratory depression.
<p>Butrans® (buprenorphine) Transdermal System, CIII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – 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 • Labor and Delivery: Butrans is not for use in women immediately prior to and during labor, where use of short-acting analgesics or other analgesic techniques are more appropriate. • Nursing: Buprenorphine is excreted in breast milk. The amount of buprenorphine received by the infant varies depending on the maternal plasma concentration, the amount of milk ingested by the infant, and the extent of first pass metabolism. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of buprenorphine is stopped. • Pediatric Use: The safety and efficacy of Butrans in patients under 18 years of age has not been established. • Geriatric Use: Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, use caution in the elderly population to ensure safe use. • Hepatic Impairment: Butrans has not been evaluated in patients with severe hepatic impairment. As Butrans is intended for 7-day dosing, consider the use of alternate analgesic therapy in patients with severe hepatic impairment.
<p>Tylenol® #3 (codeine phosphate/ APAP), CIII</p>	<ul style="list-style-type: none"> • Pregnancy: Category C <ul style="list-style-type: none"> – There are no adequate and well-controlled studies in pregnant women. TYLENOL® with Codeine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. • Labor and Delivery: Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. • Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effect on nursing infants is not known. Because of the potential for serious adverse reactions in nursing infants from acetaminophen, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Codeine is secreted into human milk. The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and baby. Caution should be exercised when codeine is administered to a nursing woman. • Pediatric: Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine. Codeine-containing products are contradicted for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy.
<p>Duragesic® (fentanyl transdermal system), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – 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 • Labor and Delivery: Fentanyl readily passes across the placenta to the fetus; therefore, Duragesic is not recommended for analgesia during labor and delivery. • Nursing: Fentanyl is excreted in human milk; therefore, Duragesic is not recommended for use in nursing women because of the possibility of effects in their infants.

Product	Use in Specific Populations
	<ul style="list-style-type: none"> • Pediatric Use: The safety and effectiveness of Duragesic in children under 2 years of age have not been established. • Geriatric Use: Clinical studies of Duragesic did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Monitor geriatric patients closely for signs of sedation and respiratory depression, particularly when initiating therapy with Duragesic and when given in conjunction with other drugs that depress respiration. • Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of Duragesic has not been fully evaluated. Avoid use of Duragesic in patients with severe hepatic impairment. • Renal Impairment: The effect of renal impairment on the pharmacokinetics of Duragesic has not been fully evaluated. Avoid use of Duragesic in patients with severe renal impairment.
<p style="text-align: center;">Vicodin® (hydrocodone bitartrate/APAP), CIII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> - There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. • Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. • Nursing: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. • Pediatric Use: Safety and effectiveness in pediatric patients have not been established. • Geriatric Use: Clinical studies of hydrocodone bitartrate and acetaminophen tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
<p style="text-align: center;">Zohydro® ER (hydrocodone bitartrate), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> - 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 • Labor and Delivery: Opioids cross the placenta and may produce respiratory depression in neonates. Zohydro ER is not for use in women during and immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. • Nursing: Low concentrations of hydrocodone and hydromorphone in breast milk of nursing mothers using hydrocodone for postpartum pain control have been reported in published literature; Infants exposed to Zohydro ER through breast milk should be monitored for excess sedation, respiratory depression. • Pediatric Use: The safety and effectiveness in pediatric patients <18 years have not been established. • Geriatric Use: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of the concomitant disease or other drug therapy. • Hepatic Impairment: No adjustment in starting dose with Zohydro ER is required in patients with mild or moderate hepatic impairment; however, in patients with severe hepatic impairment, start with the lowest dose, 10 mg. Monitor these patients closely for adverse events such as respiratory depression. • Renal Impairment: Patients with renal impairment have higher plasma concentrations than those with normal function. Use a low initial dose of Zohydro ER in patients with renal impairment and monitor closely for adverse events such as respiratory depression.

Product	Use in Specific Populations
<p>Exalgo® (hydromorphone HCl), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – 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 • Labor and Delivery: Exalgo is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. • Nursing: Low concentrations of hydromorphone have been detected in human milk in clinical trials. Withdrawal symptoms can occur in breastfeeding infants when maternal administration of an opioid analgesic is stopped. Nursing should not be undertaken while a patient is receiving Exalgo since hydromorphone is excreted in the milk. • Pediatric Use: The safety and effectiveness of Exalgo in patients 17 years of age and younger have not been established. • Geriatric Use: Elderly patients have been shown to be more sensitive to the adverse effects of opioids compared to the younger population. Therefore, closely monitor elderly patients for respiratory and central nervous system depression when prescribing Exalgo, particularly during initiation and titration. • Hepatic Impairment: Start patients with moderate hepatic impairment on 25% of the Exalgo dose that would be used in patients with normal hepatic function. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression during initiation of therapy with Exalgo and during dose titration. The pharmacokinetics of hydromorphone in severe hepatic impairment patients have not been studied. Use of alternative analgesics is recommended. • Renal Impairment: Start patients with moderate renal impairment on 50% and patients with severe renal impairment on 25% of the Exalgo dose that would be prescribed for patients with normal renal function. Closely monitor patients with renal impairment for respiratory and central nervous system depression during initiation of therapy with Exalgo and during dose titration. As Exalgo is only intended for once daily administration, consider use of an alternate analgesic that may permit more flexibility with the dosing interval in patients with severe renal impairment.
<p>Dolophine® (methadone HCl), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – 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 • Labor and Delivery: Dolophine is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. • Nursing: Methadone is secreted into human milk. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone. Cases of sedation and respiratory depression in infants exposed to methadone through breast milk have been reported. Caution should be exercised when methadone is administered to a nursing woman. • Pediatric Use: The safety, effectiveness, and pharmacokinetics of methadone in pediatric patients below the age of 18 years have not been established. • Geriatric Use: Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. In general, start elderly patients at the low end of the dosing range, taking into account the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients. Closely monitor elderly patients for signs of respiratory and central nervous system depression. • Hepatic Impairment: Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways; therefore, patients with liver impairment may be at risk of increased systemic exposure to methadone after multiple dosing. Start these patients on lower doses and titrate slowly while carefully monitoring for signs of respiratory and central nervous system depression. • Renal Impairment: Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Since unmetabolized methadone and its metabolites are excreted in urine to a variable degree, start these patients on lower doses and with longer dosing intervals and titrate slowly while carefully monitoring for signs of respiratory and central nervous system depression.
<p>Avinza® (morphine sulfate ER), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – 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 • Labor and Delivery: Avinza is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. • Nursing: Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. • Pediatric Use: The safety and effectiveness of Avinza in pediatric patients below the age of 18 years have not been established. • Geriatric Use: The pharmacokinetics of Avinza have not been studied in elderly patients. In clinical studies of Avinza, 100 patients who received Avinza were age 65 and over, including 37 patients over the age of 74. No overall differences in safety were observed between these subjects and younger subjects. • Hepatic Impairment: Morphine pharmacokinetics are altered in individuals with cirrhosis. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted. • Renal Impairment: Morphine pharmacokinetics are altered in patients with renal failure. Adequate studies of the pharmacokinetics of morphine in patients with severe

Product	Use in Specific Populations
<p>Embeda® (morphine sulfate/ naltrexone HCl ER), CII</p>	<p>renal impairment have not been conducted.</p> <ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – 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 • Labor and Delivery: Embeda is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. • Nursing: Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. • Pediatric Use: The safety and effectiveness of Embeda in patients less than 18 years have not been established. • Geriatric Use: Clinical studies of Embeda did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Limited data are available on the pharmacokinetics of Embeda in geriatric patients. • Hepatic Impairment: The pharmacokinetics of morphine was found to be significantly altered in individuals with alcoholic cirrhosis. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted. • Renal Impairment: The pharmacokinetics of morphine are altered patients with in renal failure. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.
<p>Kadian® (morphine sulfate ER), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – 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 • Labor and Delivery: Kadian is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. • Nursing: Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. • Pediatric Use: The safety and effectiveness of Kadian in patients less than 18 years have not been established. • Geriatric Use: Clinical studies of Kadian did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. • Hepatic Impairment: The pharmacokinetics of morphine was found to be significantly altered in individuals with alcoholic cirrhosis. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted. • Renal Impairment: The pharmacokinetics of morphine are altered patients with in renal failure. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.
<p>MS Contin® (morphine sulfate ER), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – 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 • Labor and Delivery: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. MS Contin is not recommended for use in women during and immediately prior to labor. • Nursing: Morphine is excreted in breast milk, with a milk to plasma morphine AUC ratio of approximately 2.5:1. • Pediatric Use: The safety and effectiveness in pediatric patients below the age of 18 years have not been established. • Geriatric Use: The pharmacokinetics of MS Contin have not been studied in elderly patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. • Hepatic Impairment: Morphine pharmacokinetics are altered in individuals with cirrhosis. Adequate studies of the pharmacokinetics of morphine in patients with severe hepatic impairment have not been conducted. • Renal Impairment: Morphine pharmacokinetics are altered in patients with renal failure. Adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been conducted.
<p>OxyContin® (oxycodone HCl ER), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> – 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 • Labor and Delivery: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. OxyContin 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. • Nursing: Oxycodone has been detected in breast milk. Instruct patients not to undertake nursing while receiving OxyContin. Do not initiate OxyContin therapy while nursing because of the possibility of sedation or respiratory depression in the infant.

Product	Use in Specific Populations
	<ul style="list-style-type: none"> • Pediatric Use: Safety and effectiveness of OxyContin in pediatric patients below the age of 18 years have not been established. • Geriatric Use: Reduce the starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients. Respiratory depression is the chief risk in elderly or debilitated patients, usually the result of large initial doses in patients who are not tolerant to opioids, or when opioids are given in conjunction with other agents that depress respiration. Titrate the dose of OxyContin cautiously in these patients. • Hepatic Impairment: A study of OxyContin in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function. Therefore, in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration • Renal Impairment: In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation.
<p>Percocet® (oxycodone HCl/ APAP), CII</p>	<ul style="list-style-type: none"> • Pregnancy Category: C <ul style="list-style-type: none"> - Animal reproductive studies have not been conducted with Percocet. It is also not known whether Percocet can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Percocet should not be given to a pregnant woman unless in the judgment of the physician, the potential benefits outweigh the possible hazards. Opioids can cross the placental barrier and have the potential to cause neonatal respiratory depression. • Labor and Delivery: Percocet tablets are not recommended for use in women during and immediately prior to labor and delivery due to its potential effects on respiratory function in the newborn. • Nursing: Ordinarily, nursing should not be undertaken while a patient is receiving Percocet tablets because of the possibility of sedation and/or respiratory depression in the infant. Oxycodone is excreted in breast milk in low concentrations, and there have been rare reports of somnolence and lethargy in babies of nursing mothers taking an oxycodone/acetaminophen product. Acetaminophen is also excreted in breast milk in low concentrations. • Pediatric Use: Safety and effectiveness in pediatric patients have not been established. • Geriatric Use: Special precaution should be given when determining the dosing amount and frequency of Percocet tablets for geriatric patients, since clearance of oxycodone may be slightly reduced in this patient population when compared to younger patients. • Hepatic Impairment: In a pharmacokinetic study of oxycodone in patients with end-stage liver disease, oxycodone plasma clearance decreased and the elimination half-life increased. Care should be exercised when oxycodone is used in patients with hepatic impairment. • Renal Impairment: In a study of patients with end stage renal impairment, mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance. Oxycodone should be used with caution in patients with renal impairment..
<p>Opana® ER (oxymorphone HCl), CII</p>	<ul style="list-style-type: none"> • Pregnancy: Category C <ul style="list-style-type: none"> - 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 • Labor and Delivery: Opana ER is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. • Nursing: It is not known whether oxymorphone is excreted in human milk. Because many drugs, including some opioids, are excreted in human milk, caution should be exercised when Opana ER is administered to a nursing woman. • Pediatric Use: The safety and effectiveness of Opana ER in patients below the age of 18 years have not been established. • Geriatric Use: Initiate dosing with Opana ER in patients > 65 years of age using the 5 mg dose and monitor closely for signs of respiratory and central nervous system depression when initiating and titrating Opana ER. For patients on prior opioid therapy, start at 50% of the starting dose for a younger patient on prior opioids and titrate slowly. • Hepatic Impairment: Patients with mild hepatic impairment have an increase in oxymorphone bioavailability of 1.6-fold. In opioid-naïve patients with mild hepatic impairment, initiate Opana ER using the 5 mg dose and monitor closely for respiratory and central nervous system depression. Opana ER is contraindicated for patients with moderate and severe hepatic impairment. For patients on prior opioid therapy, start at the 50% of the dose for that a patient with normal hepatic function on prior opioids and titrate slowly. • Renal Impairment: Patients with moderate to severe renal impairment were shown to have an increase in oxymorphone bioavailability ranging from 57-65%. Start opioid-naïve patients with the 5 mg dose of Opana ER and titrate slowly while closely monitoring for respiratory and central nervous system depression. For patients on prior opioid therapy, start at 50% of the dose for a patient with normal renal function on prior opioids and titrate slowly
<p>Nucynta® ER (tapentadol ER), CII</p>	<ul style="list-style-type: none"> • Pregnancy: Category C <ul style="list-style-type: none"> - 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 • Labor and Delivery: Nucynta ER is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. • Nursing: There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the breastfeeding child cannot be excluded. Withdrawal symptoms can

Product	Use in Specific Populations
	<p>occur in breast-feeding infants when maternal administration of Nucynta ER is stopped.</p> <ul style="list-style-type: none"> • Pediatric Use: The safety and efficacy of Nucynta ER in pediatric patients less than 18 years of age have not been established. • Geriatric Use: In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses. • Hepatic Impairment: Administration of tapentadol resulted in higher exposures and serum levels of tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The dose of Nucynta ER should be reduced in patients with moderate hepatic impairment (Child-Pugh Score 7 to 9). Use of Nucynta ER is not recommended in severe hepatic impairment (Child Pugh Score 10 to 15). • Renal Impairment: The safety and effectiveness of Nucynta ER has not been established in patients with severe renal impairment (CLCR <30 mL/min). Use of Nucynta ER in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known.
<p>Ultracet® (tramadol hydrochloride / APAP), CIV</p>	<ul style="list-style-type: none"> • Pregnancy: Category C <ul style="list-style-type: none"> - No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/acetaminophen (300/2604 mg/m² or 1.6 times the maximum daily human tramadol/acetaminophen dosage of 185/1591 mg/m²), but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs. • Labor and Delivery: Should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn. • Nursing: Not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. • Pediatric: The pharmacokinetics of Ultracet tablets has not been studied in pediatric patients below 16 years of age. • Geriatric: A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with Ultracet (n=55, 65-75 years of age and n=19, >75 years of age), showed no significant changes in the pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease; and multiple drug therapy. • Hepatic Impairment: The pharmacokinetics and tolerability of Ultracet in patients with impaired hepatic function have not been studied. Since tramadol and acetaminophen are both extensively metabolized by the liver, the use of Ultracet in patients with hepatic impairment is not recommended • Renal Impairment: The pharmacokinetics of Ultracet in patients with renal impairment has not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of Ultracet be increased, not to exceed 2 tablets every 12 hours.
<p>Ultram® (tramadol hydrochloride), CIV</p>	<ul style="list-style-type: none"> • Pregnancy: Category C <ul style="list-style-type: none"> - No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg or 420 mg/m²), rats (up to 80 mg/kg or 480 mg/m²) or rabbits (up to 300 mg/kg or 3600 mg/m²) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg (3600 mg/m²), a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the maximum daily human dosage (246 mg/m²), respectively. • Labor and Delivery: Should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn • Nursing: Not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. • Geriatric Use: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. In patients over 75 years of age, daily dose > 300 mg/day are not recommended. • Hepatic Impairment: Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in both a larger AUC time curve for tramadol and longer tramadol and M1 elimination t_{1/2}. The recommended dose for adult patients with cirrhosis is 50 mg every 12 hours. • Renal Impairment: Impaired renal function results in a decreased rate and extent of excretion of tramadol and M1. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of Ultram be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, dialysis patients can receive their regular dose on the day of dialysis.
<p>Ultram® ER (tramadol HCl ER), CIV</p>	<ul style="list-style-type: none"> • Pregnancy: Category C <ul style="list-style-type: none"> - Tramadol was not teratogenic at oral dose levels up to 50 mg/kg/day (approximately equivalent to MDHD) in rats and 100 mg/kg (approximately 5-fold MDHD) in rabbits during organogenesis. However, embryo-fetal lethality, reductions in fetal weight and skeletal ossification, and increased supernumerary ribs were observed at a maternal toxic dose of 140 mg/kg in mice (approximately 2-fold MDHD), 80 mg/kg in rats (2-fold MDHD) or 300 mg/kg in rabbits (approximately 15-fold MDHD)

Product	Use in Specific Populations
	<ul style="list-style-type: none"> • Labor and Delivery: Should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn. • Nursing: Not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. • Geriatric Use: The effect of age on the absorption of tramadol from Ultram ER in patients over the age of 65 years has not been studied and is unknown. In general, dosing of an elderly patient (over 65 years of age) should be initiated cautiously, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. Administer with even greater caution in patients over 75 years, due to frequency of adverse events. • Hepatic Impairment: The limited availability of dose strengths of Ultram ER does not permit the dosing flexibility required for safe use in patients with severe hepatic impairment. Therefore, Ultram ER should not be used in patients with severe hepatic impairment. • Renal Impairment: The limited availability of dose strengths of Ultram ER does not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, Ultram ER should not be used in patients with severe renal impairment.

Table 7.7. Pharmacokinetics

Product	Bioavailability	Major Metabolic Pathway(s)	Elimination Half-life
REFERENCE DRUG: Hysingla™ ER (hydrocodone bitartrate ER), CII	<ul style="list-style-type: none"> N/A; Compared to IR hydrocodone combination product, Hysingla ER at the same daily dose results in similar bioavailability but with lower maximum concentrations at steady state 	<ul style="list-style-type: none"> CYP3A4 CYP2D6 	<ul style="list-style-type: none"> ~7 to 9 hours
Butrans® (buprenorphine) Transdermal System, CIII	<ul style="list-style-type: none"> The absolute bioavailability of Butrans relative to IV administration, following a 7-day application, is approximately 15% for all doses (Butrans 5, 10, and 20 mcg/hour). 	<ul style="list-style-type: none"> CYP3A4 UGT-isoenzymes (mainly UGT1A1 and 2B7) 	<ul style="list-style-type: none"> After removal of Butrans, the mean buprenorphine concentrations decrease approximately 50% in 12 hours (range 10-24 hours) with an apparent terminal half-life of approximately 26 hours. Due to this long apparent terminal half-life, patients may require monitoring and treatment for at least 24 hours.
Tylenol® #3 (codeine phosphate/ APAP), CIII	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Conjugation CYP2D6 	<ul style="list-style-type: none"> Codeine = 2.9 hours APAP = 1.25-3 hours
Duragesic® (fentanyl transdermal system), CII	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> CYP3A4 	<ul style="list-style-type: none"> ~20-27 hours
Vicodin® (hydrocodone bitartrate/APAP), CIII	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> O-demethylation N-demethylation 6-keto reduction 	<ul style="list-style-type: none"> 3.8 ± 0.3 hours (hydrocodone)
Zohydro® ER (hydrocodone bitartrate), CII	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> CYP3A4 CYP2D6 	<ul style="list-style-type: none"> ~8 hours
Exalgo® (hydromorphone HCl), CII	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Glucuronidation 	<ul style="list-style-type: none"> ~11 hours (range, 8-15 hours)
Dolophine® (methadone HCl), CII	<ul style="list-style-type: none"> 36-100% 	<ul style="list-style-type: none"> CYP3A4 CYP2B6 CYP2C19 CYP2C9 CYP2D6 <p>} Lesser extent</p>	<ul style="list-style-type: none"> 8-59 hours
Avinza® (morphine sulfate ER), CII	<ul style="list-style-type: none"> <40% 	<ul style="list-style-type: none"> Glucuronidation Sulfation 	<ul style="list-style-type: none"> ~24 hours
Embeda® (morphine sulfate/ naltrexone HCl ER), CII	<ul style="list-style-type: none"> 20-40% 	<ul style="list-style-type: none"> Glucuronidation Sulfation 	<ul style="list-style-type: none"> ~29 hours
Kadian® (morphine sulfate ER), CII	<ul style="list-style-type: none"> 20-40% 	<ul style="list-style-type: none"> Glucuronidation Sulfation 	<ul style="list-style-type: none"> ~11-13 hours
MS Contin® (morphine sulfate ER), CII	<ul style="list-style-type: none"> ~20-40% 	<ul style="list-style-type: none"> Glucuronidation Sulfation 	<ul style="list-style-type: none"> 2-4 hours; in some subjects it is 15 hours
OxyContin® (oxycodone HCl ER), CII	<ul style="list-style-type: none"> 60-87% 	<ul style="list-style-type: none"> CYP3A CYP2D6 	<ul style="list-style-type: none"> 4.5 hours
Percocet® (oxycodone	<ul style="list-style-type: none"> 87% (oxycodone) 	<ul style="list-style-type: none"> CYP2D6 Conjugation 	<ul style="list-style-type: none"> 3.51 ±1.43 hours (oxycodone)

Product	Bioavailability	Major Metabolic Pathway(s)	Elimination Half-life
HCl/APAP), CII			
Opana® ER (oxymorphone HCl), CII	<ul style="list-style-type: none"> • ~10% 	<ul style="list-style-type: none"> • Reduction • Conjugation 	<ul style="list-style-type: none"> • 9.35±2.94-11.30±10.81 hours
Nucynta® ER (tapentadol ER), CII	<ul style="list-style-type: none"> • ~32% 	<ul style="list-style-type: none"> • Conjugation • CYP2C9 and CYP2C19 	<ul style="list-style-type: none"> • 5 hours
Ultracet® (tramadol hydrochloride / APAP), CIV	<ul style="list-style-type: none"> • ~ 75% 	<ul style="list-style-type: none"> • Tramadol: conjugation, CYP2D6, CYP3A4 • APAP: conjugation, CYP2E1, CYP1A2, CYP3A4 	<ul style="list-style-type: none"> • Tramadol = 5-6 hours; M1 = 7 hours • APAP = 2-3 hours
Ultram® (tramadol hydrochloride), CIV	<ul style="list-style-type: none"> • ~ 75% 	<ul style="list-style-type: none"> • CYP2D6 • CYP3A4 • Glucuronidation/sulfation 	<ul style="list-style-type: none"> • Tramadol = 6.3 ± 1.4 hours (increases to ~7 hours upon multiple doses) • M1 = 7.4 ± 1.4 hours
Ultram® ER (tramadol HCl ER), CIV	<ul style="list-style-type: none"> • 85-90% 	<ul style="list-style-type: none"> • CYP2D6 • CYP3A4 • CYP2B6 • Glucuronidation/sulfation 	<ul style="list-style-type: none"> • Tramadol = 7.9 hours • M1 = 8.8 hours

APAP=acetaminophen; AUC=area under the curve; CNS=central nervous system; CYP=cytochrome; ER=extended release; GI=gastrointestinal; HCl=hydrochloride; IV=intravenous; MAO=monoamine oxidase; N/A=not available in Full Prescribing Information for product; PGP=P-glycoprotein

2.2. Place of the Product in Therapy

2.2.1. Chronic Pain Disease Description

a) Epidemiology

Chronic Pain

Approximately 100 million adults in the US experience some type of chronic pain, and prevalence is increasing, due to (Institute of Medicine [IOM] 2011)

- aging of the population, and the concurrent increase in pain-associated diseases (eg, cancer, diabetes, arthritis) (IOM 2011, Cherry et al. 2010)
- increasing obesity, which is also associated with chronic illnesses in which pain is common (eg, diabetes) (IOM 2011)
- improved medical interventions that may save or extend the lives of people who experience catastrophic injury or cancer, and then live with the resulting chronic pain (IOM 2011)
- inadequately treated acute pain after surgery, leading to the development of chronic pain (IOM 2011; Rawal 2007)

Demand for pain treatment is also increasing, due to greater awareness of—and improved treatments for—chronic pain, and improved access to healthcare (IOM 2011).

Risk factors for chronic pain include certain pathophysiologic conditions (eg, degenerative, neurologic, and metabolic conditions; rheumatologic changes; vascular issues), genetics, structural conditions (eg, skeletal malformations, degenerative spine disease, disk herniation), and injury/trauma (Weisberg et al. 1999). Risk factors associated with low back pain in particular are obesity, lack of physical activity, lifting heavy objects, bending and twisting, age, medical conditions such as arthritis and osteoporosis, poor posture, psychological disorders such as stress and depression, and smoking (Chou et al. 2014).

Opioid Abuse and Dependence

After marijuana, pain relievers were the second most frequently abused drug in 2012, with 2.1 million Americans reporting dependence or abuse (Substance Abuse and Mental Health Services Administration [SAMHSA], National Survey on Drug Use and Health [NSDUH] 2012). In 2012, approximately 1.9 million Americans used prescription pain relievers for non-medical reasons for the first time (SAMHSA, NSDUH 2012). The prevalence of opioid abuse has increased approximately 2- to 3-fold over the past decade (SAMHSA, NSDUH 2012; Dufour et al. 2014; Rice et al. 2013). Emergency department (ED) visits for nonmedical use of pharmaceuticals more than doubled (132%) from 2004 to 2011, accounting for approximately 1.25 million visits (SAMHSA, Drug Abuse Warning Network [DAWN] 2013). Involvement of opiates or opioids in these ED visits rose by 183% over the same time period. (SAMHSA, DAWN 2013).

Acetaminophen

The prevalence of acetaminophen usage at dosages >4 g/day is unknown (Blieden et al. 2014) However, database analyses suggest that approximately 20% of patients are prescribed opioid-acetaminophen combination products at an acetaminophen dosage ≥ 4 g/day (Duh et al. 2010; Mort et al. 2011). Patients prescribed combination opioid-acetaminophen treatment are at greater risk for hospitalization due to liver toxicity than those prescribed opioids only, especially at acetaminophen doses ≥ 4 g (Blieden et al. 2014). Approximately 63% of unintentional acetaminophen overdoses have been attributed to the use of opioid-acetaminophen combination products, and just over half of all ED visits due to unintentional acetaminophen overdose were related to opioid-acetaminophen combination products (Michna et al. 2010; Budnitz et al. 2011).

b) Pathophysiology

Pain

Pain is a complex and subjective phenomenon. Biologically, nociceptive pain is the result of the receipt and transmission of noxious stimuli by the nervous system (Schaible et al. 2004). Pain stimuli are translated by nociceptors into electric impulses that are transmitted to the spinal cord and brainstem (Schaible et al. 2004). The pain signal can be modified by interactions among numerous neurotransmitters and receptors (Schaible et al. 2004). These interactions may result in increased sensitivity to pain in and around an injured area, or descending pathways may reduce the perception of pain (Bourne et al. 2014). One such pathway involves endogenous opioids; when these activate the mu opioid receptor, pain transmission is blocked in the brain and descending pathways are activated, reducing the perception of pain (Bourne et al. 2014).

Opioid Abuse and Dependence

Drugs that are liable to be abused, including opioids, substantially increase dopamine levels in the brain and alter the neurobiology of the individual. These changes ultimately lead to behaviors and symptoms typical of addiction, abuse, and dependence, such as drug seeking, reduced interest in normally pleasurable activities of daily life, poor impulse control, compulsive drug-related behaviors, and relapse (Volkow et al. 2004).

Acetaminophen-Induced Hepatotoxicity

Acetaminophen is metabolized by 3 pathways (McGill et al. 2013). The primary and secondary pathways produce metabolites that are then excreted; however, the tertiary pathway produces a toxic active metabolite (McGill et al. 2013). After a therapeutic dose of acetaminophen, this metabolite binds to liver glutathione (GSH) and is excreted (McGill et al. 2013). Upon acetaminophen overdose, however, GSH levels are reduced, and the unbound toxic metabolite binds to cellular proteins, ultimately inducing hepatocellular death and liver necrosis (McGill et al. 2013).

c) Clinical Presentation

Pain is a subjective, unpleasant, sensory and emotional experience (Loeser et al. 2011). Pain may be acute or chronic, lasting longer than several months (IOM 2011; Manchikanti et al. 2012). Chronic nonmalignant nonneuropathic pain refers to pain that is not caused by cancer or neuropathy; it includes muscle pain, inflammatory pain, and mechanical or compressive pain (eg, low back, neck, musculoskeletal) (Hooten et al. 2013; Chou et al. 2014; IOM 2011).

Accurate assessment of chronic pain is needed to tailor treatment appropriately, and should evaluate (Sarzi-Puttini 2012; Hooten et al. 2013; Chou et al. 2014)

- location, intensity, quality, onset, and duration of pain
- functional ability and goals, including issues with work and disability
- mechanism involved (eg, inflammation)
- psychosocial factors (eg, depression, substance abuse)
- other contributing factors or barriers to improvement

A medical history and physical are critical to this evaluation, as are quantitative scales used to characterize chronic pain and assess general health status, the severity of the pain, functioning, disability, and quality of life (Chou et al. 2014; Hooten et al. 2013). Imaging may be useful to identify physical pathologies contributing to the pain (Hooten et al. 2013).

Opioids and acetaminophen are two important classes of pharmacotherapy used in pain management (See [Section 2.2.2](#)). Unfortunately, many opioid therapies are associated with a high risk for abuse, and may be ingested intact, perhaps in higher quantities than prescribed; crushed and swallowed, snorted, or smoked; or

crushed, dissolved, and injected by patients and others, including people with addiction disorders (FDA 2013; Manchikanti et al. 2012; IOM 2011). Substance abuse is associated with problems at home, work, or school, or with family or friends; physical danger; and criminal and legal issues (SAMHSA, NSDUH 2012). Substance dependence is considered more severe than abuse and involves health and emotional problems related to substance use, tolerance, withdrawal, not engaging in other activities in order to engage in substance use, spending a substantial amount of time engaging in substance use, unsuccessful attempts to reduce substance use, and using the substance more than or for longer than intended (SAMHSA, NSDUH 2012).

At dosages >4 g/day, acetaminophen can cause serious hepatotoxicity, and acetaminophen overdose is a serious concern, one which is high on the radar of organizations such as the American Liver Foundation (ALF), American Geriatric Society (AGS), Centers for Medicare and Medicaid Services (CMS), and FDA (Tylenol FPI 2009; ALF 2014; AGS 2009; CMS 2014; FDA Safe Use Initiative 2014). Hepatotoxicity associated with large overdoses of acetaminophen can result in nausea, vomiting, profuse perspiration, malaise, and, if not treated promptly, liver failure and death (McNeil Consumer Healthcare 2009; Vicodin FPI 2014; Zydone FPI 2011; Percocet FPI 2011). Acetaminophen overdose frequently occurs as a result of accidental ingestion by children, or as a result of misdosing by adults (Budnitz 2011). The labeling for combination opioid-acetaminophen products contains hepatotoxicity warnings stating that acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death (Vicodin FPI 2014; Zydone FPI 2011; Percocet FPI 2013). Some epidemiologic evidence also indicates that acetaminophen is an ototoxic agent (Curhan et al. 2010; Curhan et al. 2012).

Because of the risks associated with acetaminophen overdose, in January 2011, FDA requested that manufacturers limit the amount of acetaminophen in each tablet or capsule of combination drug products to ≤325 mg by January 2014. In 2014, FDA instituted proceedings to withdraw from the market any combination products containing >325 mg of acetaminophen (FDA Safety Alert 2014).

d) Societal, Humanistic and/or Economic Burden

Chronic Pain

Family members and friends of those with chronic pain may find themselves taking on new and demanding roles, while at the same time coping with the physical and psychological changes in their loved one (IOM 2011). Over the long term, these negative changes can affect relationships and strain financial resources (IOM 2011). The physical, mental, and social well-being of those who suffer from chronic pain may deteriorate enough to cause depression (Dersh et al. 2002; Arnow et al. 2006; Von Korff et al. 2005).

Healthcare utilization, including ambulatory visits, ED visits, and hospital admissions, is significantly greater among patients with chronic pain than among those without chronic pain (Leider et al. 2011). The estimated annual economic cost of pain in the US, including the costs of health care and lost productivity, is \$560 to \$635 billion (2010 dollars) (IOM 2011). Care for chronic back pain alone costs \$17.5 billion annually (as of 2000) (IOM 2011). A quarter of the cost of health care for pain is born by federal Medicare insurance; in 2008, 14% of Medicare expenditures went towards payments related to chronic pain (\$65.3 billion) (IOM 2011). Other government agencies, such as the VA, also pay substantial amounts to address chronic pain, contributing to a total cost to the federal government of \$99 billion (IOM 2011). Adding to this expense is lost tax revenue resulting from lost productivity (IOM 2011).

The results of a survey conducted from 2000 to 2007 found that, among patients with nonmalignant chronic pain, 99% were prescribed medication for their pain, and of these, 29% were prescribed ≥5 medications. In total, pain medication cost approximately \$17.8 billion annually (2009 dollars) (Rasu et al. 2014). Approximately 114 million prescriptions were written for opioids or opioid-like medications, with an annual cost of approximately \$3.6 billion, or approximately 20% of the total annual cost of pain medication. Combination hydrocodone/acetaminophen was the most frequently prescribed opioid/opioid-like medication (39 million prescriptions from 2000 to 2007, for a total cost of \$4.3 billion) (Rasu et al. 2014).

In 2000, outpatient visits for chronic pain made up approximately 11.3% of all office visits; in 2007, this had increased to approximately 14.3%. This trend is predicted to continue, reaching approximately 16% by 2015 (Rasu et al. 2014).

Opioid Abuse and Dependence

Substance abuse is frequently associated with comorbidities such as psychiatric disorders, pain, and abuse of other substances (McAdam-Marx et al. 2010; Baser et al. 2014).

In 2011, almost a quarter of all drug-related visits to the ED, or approximately 1.2 million visits, were the result of nonmedical use of pharmaceuticals. Approximately half of these ED visits were the result of pharmaceutical abuse or misuse. Pain relievers were the most common type of drug involved in these ED visits, with oxycodone, hydrocodone, and methadone associated with 12.1%, 6.6%, and 5.4%, respectively, of such visits in 2011 (SAMHSA, DAWN 2013).

Subsequent to an ED visit, many patients received further treatment in a hospital or other facility (SAMHSA, DAWN 2013). In 2007, the total costs of prescription opioid abuse were estimated at \$55.7 billion, including \$25.6 billion for lost productivity, \$25.0 billion for health care, and \$5.1 billion for criminal justice costs (Birnbaum 2011). Studies of the Veterans Health Administration, Medicaid, and commercial insurers have also demonstrated significantly higher healthcare utilization and costs for those who abuse opioids, versus those who do not (Baser et al. 2014; Rice et al. 2013; McAdam-Marx et al. 2010; White et al. 2005).

A 2014 analysis of claims data for approximately 9,000 abusers and 395,000 non-abusers (comparison cohort) found that the annual per-patient healthcare excess cost of opioid abuse was \$10,627 (2012 dollars); this figure was largely driven by inpatient costs, followed by ED and rehabilitation costs. The per-member per-month (PMPM) cost of diagnosed opioid abuse was calculated to be \$1.71 (Rice et al. 2014).

Abuse-deterrent technology has the potential to reduce these costs. Using data from the Truven Health Analytics database from 2009 through 2011, it has been estimated that use of reformulated extended-release (ER) oxycodone would result in a savings of \$430 million (2011 dollars) in medical and drug costs among diagnosed and undiagnosed abusers (Rossiter et al. 2014). An extension of this analysis, which assumed that reformulated ER oxycodone would affect both direct and indirect costs to the same extent, estimated a total savings of approximately \$1 billion (2011 dollars), with reductions in criminal justice costs, lost productivity, and medical and drug costs for caregivers making up the additional \$605 million in savings (Kirson et al. 2014).

Acetaminophen Overdose

From 1993 to 2007, acetaminophen overdose was responsible for approximately 750,000 ED visits (average 50,103 per year, or 17.81 visits per 100,000 people per year) (Li et al. 2011). Approximately 33,000 patients were hospitalized annually for acetaminophen overdose from 2000 to 2006 (13.9 hospitalizations per 100,000 people over the 7-year period) (Manthripragada et al. 2011).

2.2.2. Approaches to Treatment

a) Principle Treatment Approaches for Chronic Pain

Pharmacotherapy is the principle element of a comprehensive chronic pain treatment plan. Medications are often used in conjunction with other interventional, surgical, psychological, and rehabilitation treatment modalities. Treatment should be tailored to both the individual and the presenting problem.

There are three broad categories of drugs to treat chronic pain – nonopioid analgesics, opioid analgesics, and adjuvant analgesics. The nonopioid analgesics include NSAIDs and acetaminophen (Portenoy 2000). NSAIDs including aspirin, the non-selective and selective COX-inhibitors, and acetaminophen are commonly used for

mild to moderate chronic nociceptive pain conditions. There is no evidence of their efficacy in treating neuropathic pain.

Opioids are used for pain ranging from moderate to severe depending on the specific opioid. Opioids are generally effective in treating nociceptive pain, but also have efficacy in neuropathic pain in some individuals (Dworkin et al. 2010).

Adjuvant agents or co-analgesics are drugs whose primary or initial indication was not for the treatment of pain, but may be used as analgesics in some chronic pain conditions. These include antidepressants, anticonvulsants, corticosteroids, muscle relaxants, local anesthetics, topical analgesics, and baclofen (Portenoy 2000; APS 2008). Many of these agents such as tricyclic antidepressants, anticonvulsants, and topical agents (eg, capsaicin, lidocaine patches) are effective for treating neuropathic pain.

The World Health Organization (WHO) has promoted the three-step analgesic ladder as a framework for the rational use of analgesic medications in the treatment of cancer pain. Step I specifies the use of non-opioid analgesics. If this does not relieve the pain, step II recommends adding an opioid for mild to moderate pain. Step III comprises the use of an opioid for moderate to severe pain, with or without nonopioids. If needed, adjuvant drugs can be used at each step (WHO 1996). Although this analgesic ladder approach was developed for cancer pain, this approach has been used for the treatment of other types of pain, as well. A more recent guideline for the treatment of cancer pain recommends moving away from the WHO analgesic ladder approach because cancer pain rarely progresses in a step wise fashion. The AGS recommends that all elderly patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy (AGS 2009). Additionally, for elderly patients, sustained-release preparations are recommended as they increase compliance and dosing frequency may be reduced (Pergolizzi et al. 2008).

b) Alternative Treatment Options for Chronic Pain

Chronic pain management can be carried out in many different ways. For many patients a combination of therapies (eg, rehabilitation, pharmacotherapy, interventional therapy, behavioral therapy, surgery) is the most successful approach.

Psychological therapies for chronic pain include individual cognitive behavioral therapy, hypnotic analgesia, and biofeedback treatment. Some interventional approaches to chronic pain management are diagnostic blocks, therapeutic blocks, implanted nerve stimulators, intraspinal drug delivery systems, and neuroablative procedures. Rehabilitation approaches include physical and occupational therapy, exercise, ergonomic modifications, thermal massage, transcutaneous electrical nerve stimulation, and orthotics. Surgery may also be indicated for the treatment of certain chronic pain conditions (eg, spinal disorders, arthritis) (Wisconsin Medical Society Task Force on Pain Management [WMS] 2004).

c) Place of Hysingla ER in Treatment of Chronic Pain

Hysingla ER is the first and only extended-release, oral formulation of single-entity hydrocodone bitartrate approved for every-24-hour (once daily) dosing 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.

Hysingla ER is formulated with abuse-deterrent properties that are intended to make the tablets more difficult to manipulate for the purpose of misuse and abuse by intranasal, intravenous, or oral routes of administration. Further, it has the potential to reduce risk of unintentional misuse and/or inadvertent medication error by patients or caregivers. Additionally, Hysingla ER has FDA-approved Tier 1 and Tier 3 abuse-deterrent labeling claims, which indicate that the product is formulated with physicochemical barriers to abuse and that the product is expected to result in a meaningful reduction in abuse.

Long-acting preparations may be preferred over short-acting agents in patients who require around-the-clock analgesic therapy because they allow less frequent dosing and may potentially decrease pain fluctuations and improve compliance (VA/DoD 2010). Dosed once-daily, Hysingla ER offers patients the advantage of a convenient dosing regimen that can decrease night awakenings to take scheduled chronic pain medication and can reduce patients' pill burden.

Furthermore, as a single-entity hydrocodone formulation, Hysingla ER is not limited by toxicities of non-opioid components, such as acetaminophen, which has the potential to cause hepatotoxicity when the patient exceeds the maximum recommended dosage of 4 g/day.

Guidelines for chronic pain conditions recommend the use of opioids for patients who have not responded to nonopioid analgesics (APS 2008, Chou et al. 2009). The efficacy of Hysingla ER has been demonstrated in both opioid naïve and opioid experienced patients with moderate to severe chronic pain (see [Section 3.0](#)).

d) Chronic Pain Management Intervention Strategies Accompanying Hysingla ER

None.

e) Outcomes of Treatment for Chronic Pain

Patients on chronic opioid therapy should be regularly monitored for documentation of pain intensity and level of functioning, assessment of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapy (Chou et al. 2009). Expected outcomes of treatment for chronic pain include pain reduction, improved physical function, patient satisfaction with and tolerability of therapies.

The Hysingla ER clinical development program consisted of 16 studies in which 2476 subjects were exposed to at least one dose of Hysingla ER and 364 subjects had exposure to Hysingla ER for at least 12 months. These studies included two Phase 3 studies (1 placebo-controlled [[HYD3002](#)] and 1 open-label [[HYD3003](#)]), 11 pharmacokinetic (PK) studies, and three [abuse potential](#) studies designed to evaluate the pharmacology, efficacy, safety, and abuse potential of Hysingla ER. The Phase 3 studies have demonstrated a consistent pattern of pain reduction, or continuing maintenance of pain control in patients with chronic, non-malignant and non-neuropathic pain. Additionally, as a once-daily formulation, Hysingla ER provides a 24-hour pharmacokinetic profile that maintains consistent blood levels and pain relief over the 24-hour dosing interval. Highlights of results from the Hysingla ER clinical study program are summarized below.

Efficacy of once daily Hysingla ER 20 mg to 120 mg, in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain was superior to placebo, with significantly lower week 12 “average pain over the last 24 hours” pain scores than placebo at week 12 compared with baseline. Sensitivity analyses of the primary efficacy variable showed a consistent significant treatment difference in favor of Hysingla ER compared with placebo ($P < .05$). The primary efficacy conclusion was robust, regardless of method of imputation used (Data on file, HYD3002).

Results of treatment effectiveness outcomes of the long-term study (HYD3003) demonstrated consistent effectiveness of Hysingla ER over 52 weeks and continued during a 24-week extension period (HYD3003S). The treatment effects of Hysingla ER, as measured by “average pain over the last 24 hours” scores, were obtained early, with the full extent of these effects established when a stable Hysingla ER dose was achieved, with improvements maintained during the long-term treatment (Data on file, HYD3003).

- As measured by “pain right now” scores, no loss in analgesia was observed immediately prior to each daily dosing, and the same level of pain relief was maintained over the 24-hour dosing interval (Data on file, HYD3003).

- During the maintenance period, approximately 66% and 40% of patients achieved at least 30% reduction and at least 50% reduction in pain, respectively, from screening and maintained the same levels of pain relief throughout the period (Data on file, HYD3003).
- During both the 52-week maintenance period and the 24-week extension period, treatment effectiveness was maintained without the continued requirement for dose increases (Data on file, HYD3003).
- During the maintenance period, the majority (86.5%) either stayed on the same starting Hysingla ER dose or had 1 dose level increase at the end of post-titration period; few (4.3%) subjects required more than 1 dose level increase (Data on file, HYD3003).

Both the pivotal and long-term studies evaluated additional secondary and exploratory efficacy endpoints, which support the primary efficacy analysis or suggest additional potential benefits of Hysingla ER (see [Section 3.0](#)).

f) Other Drug Development or Post-Marketing Obligations

Hysingla ER is subject to post-marketing requirements authorized by FDA that include conducting epidemiological studies to evaluate whether the abuse-deterrent properties of Hysingla ER result in significant and meaningful decrease in misuse, abuse, addiction, overdose, and death in the community. Studies will be conducted in accordance with the FDA draft guidance on abuse-deterrent opioids to allow for FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Hysingla ER (FDA 2013).

In addition, as a member of the ER/LA opioid analgesic class, studies assessing the serious risks of misuse, abuse, addiction, overdose, and death, as well as estimating the serious risk for the development of hyperalgesia and tolerance associated with the long-term use of ER opioids, including Hysingla ER, prescribed for the management of chronic pain will be conducted.

Further, Hysingla ER is subject to the requirements of the Extended-Release and Long-Acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS). The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death. The REMS elements include a Medication Guide, Elements to Assure Safe Use, and a timetable for submission of assessments. Additional information can be found at www.ER-LA-opioidREMS.com.

g) Other Key Assumptions

None.

2.2.3. Relevant Treatment Guidelines and Consensus Statement from National and/or International Bodies

There are many chronic pain treatment guidelines for different pain conditions that include recommendations for the use of opioids. Some of the national treatment guidelines are listed with their recommendation in **Table 8**.

Table 8. Treatment Guidelines for Chronic Pain Conditions

Organization/Society	Treatment Guidelines	Recommendation(s)
American Academy of Neurology	Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy. <i>Neurology</i> . 2011;76:1758-1765	<ul style="list-style-type: none"> • Opioids should be considered for the treatment of painful diabetic neuropathy.
	Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. <i>Neurology</i> . 2004;63(6):959-965.	<ul style="list-style-type: none"> • There is class I evidence that long acting oral opioid preparations provide relief in treatment of postherpetic neuralgia.
American College of Occupational and Environmental Medicine (ACOEM)	American College of Occupational and Environmental Medicine. ACOEM guidelines for the chronic use of opioids. 2011.	<ul style="list-style-type: none"> • Opioid analgesics may be appropriate for select patients with chronic persistent pain that is not well-controlled with non-opioid treatment
American College of Physicians and the American Pain Society	Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. <i>Ann Intern Med</i> . 2007;147(7):478-491.	<ul style="list-style-type: none"> • Opioid analgesics are an option when used judiciously in patients with acute or chronic low back pain who have severe, disabling pain that is not controlled (or is unlikely to be controlled) with acetaminophen and NSAIDs.
American College of Rheumatology	Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. <i>Arthritis Care Res</i> . 2012 Apr;64(4):465-74.	<ul style="list-style-type: none"> • Opioids are conditionally recommended in patients who had an inadequate response to initial therapy. • Opioids are strongly recommended in patients with symptomatic osteoarthritis who were unwilling to undergo or are not candidates for total joint arthroplasty after failing medical therapy.
American Geriatric Society	American Geriatric Society. Pharmacological management of persistent pain in older persons. <i>J Am Geriatr Soc</i> . 2009;57(8):1331-1346.	<ul style="list-style-type: none"> • All patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy.
American Pain Society	Chou R, Fanciullo GJ, Fine PG, et al. Opioid treatment guidelines: clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. <i>J Pain</i> . 2009;10(2):113-130. [American Pain Society-and American Academy of Pain Medicine]	<ul style="list-style-type: none"> • Chronic opioid therapy can be an effective therapy for carefully selected and monitored patients with chronic noncancer pain.
	American Pain Society. <i>Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain</i> . 6 th ed. Glenview, IL: American Pain Society; 2008.	<ul style="list-style-type: none"> • Opioid analgesics should be added to nonopioids to manage pain that does not respond to nonopioids alone. • Long duration of action of controlled-release and transdermal opioids lessens severity of end-of-dose pain and often allows patients to sleep through the night.

Organization/Society	Treatment Guidelines	Recommendation(s)
American Society of Anesthesiologists	American Society of Anesthesiologists. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. <i>Anesthesiology</i> . 2010;112(4):810-833.	<ul style="list-style-type: none"> • As part of a multimodal pain management strategy, extended-release oral opioids should be used for neuropathic or back pain patients.
American Society of Interventional Pain Physicians (ASIPP)	Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic noncancer pain: part I – evidence assessment. <i>Pain Physician</i> . 2012;15:S1-S66.	<ul style="list-style-type: none"> • Opioid therapy may improve quality of life parameters.
	Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP): Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain: Part 2 - Guidance. <i>Pain Physician</i> . 2012;15:S67-S116.	<ul style="list-style-type: none"> • Chronic opioid therapy may be continued, with continuous adherence monitoring, modified at any time during this phase, with fair evidence showing effectiveness of opioids in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse effects. • Specific to initiating and maintaining chronic opioid therapy for ≥90 days, clinicians must understand the effectiveness and adverse consequences of long-term opioid therapy in chronic non-cancer pain and its limitations. • For severe pain, first line therapy may include hydrocodone, oxycodone, hydromorphone, or morphine. • In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided.
International Association for the Study of Pain (IASP)	Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. <i>Mayo Clin Proc</i> . 2010;85(3 Suppl):S3-14.	<ul style="list-style-type: none"> • Opioid analgesics have shown efficacy in several high-quality RCTs involving patients with different types of NP. • Opioid analgesics are recommended as second-line treatments that can be considered for first-line use in certain clinical circumstances. • Because the optimal opioid dosage varies substantially from patient to patient, patients must undergo individualized opioid titration, using dosages that have shown efficacy in NP trials and typically using extended-release formulations for long-term treatment.

Organization/Society	Treatment Guidelines	Recommendation(s)
	Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. <i>Clin Infect Dis</i> . 2007;44(Suppl 1):S1-26.	<ul style="list-style-type: none"> • For pain that is moderate to severe in intensity treatment with a strong opioid analgesic is recommended on the basis of the consistent efficacy of this class of medications in patients with inflammatory and neuropathic pain. • Once an effective dosage of a short-acting medication is determined, treatment can be switched to a long-acting medication, which is more convenient for patients and may also provide a more consistent level of pain relief.
National Opioid Use Guideline Group	National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic noncancer pain. Version 5.6. April 2010. Available at: http://nationalpaincentre.mcmaster.ca/opioid/ .	<ul style="list-style-type: none"> • Opioids are more effective than placebo for chronic, noncancer pain and function. • CR formulations are recommended for the elderly for reasons of compliance
Veterans Health Administration, Department of Defense	Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain. May 2010.	<ul style="list-style-type: none"> • Long-acting preparations may be preferred over short-acting agents in patients who require around-the-clock analgesic therapy because they allow less frequent dosing and, potentially, may decrease pain fluctuations and improve compliance. • This guideline supports the use of long-acting opioids in a scheduled manner for chronic pain, rather than the use of supplemental or as-needed (PRN) opioids for exacerbations.

2.3. Evidence for Pharmacogenomic Tests and Drugs

There is no information on the evidence for pharmacogenomic tests and drugs available.

3. SUPPORTING CLINICAL EVIDENCE

3.1. Summarizing Key Clinical Studies

3.1.1. Published and Unpublished Data and Clinical Studies Supporting Labeled Indications

a) Pivotal Safety and Efficacy Study

A randomized double-blind, placebo-controlled, multi-center, 12-week clinical trial to determine the efficacy and safety of Hysingla ER in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain (HYD3002)

Citations / Funding: Wen W, Sitar S, Lynch SY, He E, Ripa SR. Efficacy and Safety of Once-Daily Hydrocodone (Hysingla™ ER) in Chronic Low Back Pain. Poster presented at: PAINWeek, Las Vegas, USA September 2014. Abstract No: Poster 146. / **Funding:** Purdue Pharma LP.

Location / Study Dates: 94 sites in US / Mar-2012 to Sep-2013.

Clinical Trials.gov Identifier: NCT01452529

Objective: The primary objective of this study was to evaluate the analgesic efficacy and safety of Hysingla ER 20 to 120 mg once-daily compared to placebo in patients with moderate to severe chronic low back pain uncontrolled by their current stable analgesic regimen.

Methods: This was a randomized, double-blind, placebo-controlled enriched study in male and female patients aged 18 years or older with low back pain for at least 3 months related to nonmalignant and nonneuropathic conditions and was not adequately controlled by their stable incoming analgesic regimen of nonopioid or opioid ≤ 100 mg per day oxycodone equivalents.

The study consisted of a prerandomization phase, a double-blind period, and a safety follow-up period. The prerandomization phase consisted of a baseline period (up to 14 days) and an open-label dose titration (run-in) period (up to 45 days) designed to assess patients' qualification for randomization. Patients were screened and eligible to enter into the titration period if they had at least 3 of 5 days of "average pain over the last 24 hours" scores ≥ 5 on an 11-point Numeric Rating Scale (NRS) where 0=no pain and 10=pain as bad as you can imagine. Patients discontinued all analgesic medications prior to starting run-in period. Opioid-naïve patients began treatment with Hysingla ER 20 mg, and opioid-experienced patients were converted to a Hysingla ER dose that was 25% to 50% of their incoming opioid total daily dosage. Patients who tolerated Hysingla ER but did not achieve satisfactory analgesia had their Hysingla ER doses up-titrated to the next dose level every 3 to 5 days. Dose up-titration occurred until a stable dose was achieved (maximum daily dose was 120 mg). Supplemental analgesic medication (5 mg immediate-release oxycodone, up to 10 mg daily) was permitted as patients titrated to their stable Hysingla ER dose.

In order to qualify for randomization in the 12-week double-blind period, a patient was to have demonstrated adequate analgesia (pain reduction of at least 2 points to a score of ≤ 4) and acceptable tolerability with Hysingla ER treatment during the run-in period. Patients were stratified by their opioid experience prior to the study (naïve or experienced) and by the stable Hysingla ER dose they received at the end of the run-in period and were randomized 1:1 to either their stabilized Hysingla ER dose or matching placebo. Clinic visits during the double-blind period occurred at weeks 1, 2, 4, 8, and 12. During the first 14 days of the double-blind period, patients who were randomized to the placebo treatment arm were tapered to placebo in a blinded fashion. Subsequent to the 2-week taper period, patients randomized to Hysingla ER 40 mg, 60 mg, 80 mg, or 120 mg or matching placebo were permitted one down-titration if the investigator determined that the patient was not adequately tolerating the treatment, followed by one up-titration back to the randomized dose if tolerating treatment but not achieving adequate analgesia. No other dosage adjustment was permitted.

Patients were allowed immediate-release oxycodone 5-10 mg every 4-6 hours (up to 30 mg per day depending on the patient’s current dose of study drug) as supplemental analgesic medication.

The primary efficacy endpoint was the weekly mean pain intensity score calculated using the daily “average pain over the last 24 hours” scores for chronic low back pain at week 12 recorded by the patient in an electronic diary during the double-blind period. Analysis of the weekly mean pain intensity scores was performed using a mixed effects model with repeated measures (MMRM) incorporating a pattern mixture model (PMM) approach to account for missing values based on the reason for discontinuation. Secondary efficacy endpoints were responder analysis, sleep disturbance as assessed by Medical Outcome Study Sleep Scale - Revised (MOS Sleep-R) at Weeks 4, 8, and 12, and Patient Global Impression of Changes (PGIC) at end of study. Safety assessments included: all adverse events, opioid withdrawal, clinical laboratory results, physical exams, vital signs, ECGs, audiology assessments, and assessment of aberrant drug behavior.

Patient Disposition: Of the 905 patients who qualified for the open-label treatment period, 592 (65%) completed the run-in period and achieved a stable Hysingla ER dose. The remaining patients discontinued from the dose-titration period for the following reasons: adverse events (AEs) (10%); lack of therapeutic effect (5%); confirmed or suspected diversion (3%); patient’s choice (5%); lost to follow-up (2%); administrative reasons (2%); and failure to achieve protocol-defined reduction in pain score (7%).

Of the 588 randomized patients, 439 (75%) patients completed the double-blind treatment period on study drug (210 on Hysingla ER and 229 on placebo). A higher proportion of patients randomized to placebo discontinued due to lack of therapeutic effect (15%) compared with patients randomized to Hysingla ER (5%); a higher proportion of patients randomized to Hysingla ER (6%) discontinued due to AEs compared with patients randomized to placebo (3%).

The demographic and baseline characteristics of the patients randomized to Hysingla ER were similar to those of the patients randomized to placebo except for race, with slightly more African Americans in the Hysingla ER group (23%) vs placebo group (17%). The mean (SD) age of patients who entered the double-blind period was 48 (13.2) years for patients randomized to the placebo group vs 49 (13.5) years for patients randomized to the Hysingla ER group.

Efficacy Results: Results of the primary analysis showed that Hysingla ER was superior to placebo, with statistically significant lower pain scores than placebo at week 12 compared with baseline (**Table 9**).

Table 9. Summary of Primary Efficacy Results for Average Pain Over the Last 24 Hours

Average Pain over Last 24 hours	Placebo (n=292)	Hysingla ER (n=296)	Hysingla ER vs Placebo		
			LS Means Difference (SE)	95% CI	P value
Baseline, mean (SD)	7.4 (1.19)	7.4 (1.13)			
Prerandomization, mean (SD)	2.8 (1.15)	2.8 (1.16)			
Week 12, LS mean (SE)	4.23 (0.126)	3.70 (0.128)	-0.53 (0.180)	-0.882, -0.178	.0016

MMRM with PMM

Responders to treatment were defined as patients with a ≥ 30% reduction in pain and also a ≥ 50% reduction in pain compared with baseline. Statistically significant differences in favor of Hysingla ER were seen between treatment groups for the proportion of patients with a ≥ 30% reduction in pain ($P = .0033$) and a ≥ 50% reduction in pain ($P = .0225$). Sixty-five percent (65%) and 48% of the Hysingla ER patients and 53% and 39% of the placebo patients had a ≥ 30% and ≥ 50% improvement in pain, respectively. The high placebo effect (72% of the placebo patients completed the study) in this study may explain the relatively small difference in the percentages of responders between the 2 treatment groups.

Results of the MOS Sleep-R sleep disturbance subscale analysis showed that, by the end of the run-in period, the sleep disturbance subscale showed improvements in both treatment groups (from 44.72 at baseline to

51.48 at end of run in for placebo and 44.38 at baseline to 50.33 at end of run-in for Hysingla ER); however, there was no significant difference between Hysingla ER and placebo during the double-blind period.

The proportion of patients reporting “very much improved” or “much improved” on the PGIC rating scale was significantly higher (61%) in the Hysingla ER treatment group compared with the placebo group (49%) ($P = .0036$).

Safety Results: Forty-nine percent of the patients were stabilized at and randomized to a dose of 60 mg or higher. The average daily dose of Hysingla ER [mean (SD)] for the Hysingla ER group during the double blind period was 56.9 (31.76), and 43.7 (22.41) for the safety population overall (run-in and double-blind periods) during Hysingla ER exposure.

During the run-in period, the incidence of TEAEs was 431 (48%) of 905 patients. During the double-blind period, the incidence of TEAEs observed in the randomized safety population was 136 (46%) in Hysingla ER patients and 103 (35%) in placebo-treated patients. TEAEs that occurred at an incidence of $\geq 5\%$ during the run-in period included: GI disorders (nausea, vomiting, and constipation); and nervous system disorders (dizziness, headache, and somnolence). TEAEs that occurred at an incidence of $\geq 5\%$ during the double-blind period included GI disorders (nausea and vomiting). The TEAEs that occurred more frequently in patients receiving Hysingla ER than in patients receiving placebo and those with a difference of $\geq 2\%$ included nausea, vomiting, and influenza.

Confirmed diversion or suspected diversion by patients in either the run-in period or double-blind period was reported for 39 patients (4.3%). Few patients ($\leq 1\%$) experienced AEs associated with opioid withdrawal during opioid conversion or during cessation of Hysingla ER treatment.

Conclusions: Hysingla ER was shown to be superior to placebo in pain relief. There were no new safety signals of concern detected during the study. The AEs experienced by patients during the study were those typically associated with mu-opioid analgesics.

b) Long-term Safety and Effectiveness Study

An open-label study evaluating persistence of analgesia and long-term safety of Hysingla ER in patients with chronic, moderate to severe, nonmalignant and nonneuropathic pain (HYD3003 and HYD3003S)

Citations / Funding: Lynch S, Wen W, Taber L, Munera C, Ripa S. Long-term safety and effectiveness of once-daily, single-entity, abuse-deterrent hydrocodone in chronic nonmalignant and nonneuropathic pain: results of a long-term open-label study. *J Pain*. 2014;15(4):S91, abstr 461. / **Funding:** Purdue Pharma LP.

Location / Study Dates: Core Study 88 sites in US / Jul-2011 to Aug-2013; Extension Study 23 sites in US / Apr-2013 to Feb-2014. **Clinical Trials.gov Identifier:** NCT01400139

Objective: The primary objective of this study was to characterize the long-term safety of Hysingla ER 20 to 120 mg once daily in patients with chronic nonmalignant and nonneuropathic pain.

Methods: This was an open-label, multicenter study in male and female patients aged 18 years or older with moderate to severe, chronic nonmalignant and nonneuropathic pain as their predominant pain condition for at least the previous 3 months before screening. Patients had to be on a stable analgesic regimen equivalent to 0 to 120 mg/day of oxycodone for *controlled* pain (with an “average pain over the last 14 days” score ≤ 4 at the screening visit) or 0 to 100 mg/day of oxycodone for *uncontrolled* pain (with an “average pain over the last 14 days” score ≥ 5 at the screening visit) prior to the screening visit, and must have been deemed appropriate candidates for around-the-clock opioid treatment. Opioid-naïve patients could enroll in the study.

The study consisted of a screening period of up to 14 days, a dose titration period of up to 45 days, a maintenance period of 52 weeks, and optional Hysingla ER taper period of up to 14 days. Patients who completed the maintenance period were offered the option to enter a 6 month open-label extension study. During the dose titration period, all patients were converted to an appropriate Hysingla ER dose based on their incoming opioid regimen and opioid naïve patients were initiated on Hysingla ER 20 mg. If adequate analgesia was not achieved, patients were titrated until a stable dose was achieved (maximum daily dose 120 mg). Patients who achieved satisfactory analgesia with tolerable adverse effects entered the maintenance period on the Hysingla ER stabilized dose from the end of the dose titration period followed by unlimited dose adjustments (between 20 mg and 120 mg) at the discretion of the investigator. Patients received supplemental pain medication, as deemed appropriate by the investigator, including nonopioid and short-acting opioid medications. Ongoing nonopioid analgesics could have been continued on a stable regimen throughout the study.

Assessments made in order to assess the treatment effectiveness of Hysingla ER included the following measures: pain assessments (“pain right now” and “average pain over the last 24 hours”) as measured on an 11-point numerical rating scale; key aspects of sleep as measured by the Medical Outcomes Study Sleep Scale - Revised (MOS Sleep-R); functional health and well-being from the patient’s perspective as assessed by the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36); patient’s ability to perform specific activities of daily living, severity of pain, and the interference of pain with daily functions as assessed by the Brief Pain Inventory - Short Form (BPI-SF); patient’s satisfaction with and preference for using the study drug for their pain medication assessed with the Treatment Satisfaction Questionnaire (Part I and Part II); and the Patient’s Global Impression of Change (PGIC) rating score. Safety was assessed using adverse events (AEs), clinical laboratory results, vital sign measurements, ECGs, and various other assessments.

During the dose titration and maintenance periods, patients recorded in the eDiary their “pain right now” scores twice daily (once immediately prior to Hysingla ER dosing and once at approximately 8 pm every evening) until visit 7, and their daily “average pain over the last 24 hours” scores (at approximately 8 pm every evening) until completion of the maintenance period or study drug discontinuation (visit 17).

Patient Disposition: Of the 1365 patients enrolled, 922 patients (mean age 51.8 years; range 19 to 86 years) entered the study and were treated with ≥ 1 dose of Hysingla ER. The highest incidences of disease conditions for patients entering study were back pain (53%), osteoarthritis (14%), arthralgia (10%), intervertebral disc degeneration (5%), and spinal osteoarthritis (5%). Of the 922 patients, 728 patients (79%) completed the dose titration period and achieved a stable dose. Of these 728 patients, 410 (56%) patients completed the 12-month maintenance period. Few patients discontinued due to lack of therapeutic effect overall (6%) and especially during the maintenance period (4%). The most frequent reason for study drug discontinuation in the safety population was AEs (21%). Discontinuations and dose adjustments tended to occur most frequently during the first 30 days, after which both were less frequent. Relative to the duration of treatment, discontinuations due to AEs occurred more frequently during dose titration (10% of 922 patients discontinued), which was a relatively short period of time (mean duration of 19.3 days) compared with the maintenance period, which had a discontinuation rate due to AEs of 15% of 728 patients spread out over a longer period of time (mean duration of 248.5 days).

Out of 922 patients, there were 732 (79%) patients with ≥ 1 month of exposure to Hysingla ER, 500 (54%) with ≥ 6 months of exposure, and 364 (39%) with ≥ 12 months of exposure. The mean (SD) cumulative number of days on study drug at any dose was 216.7 (160.73).

Efficacy Results: The treatment effects of Hysingla ER, as measured by "average pain over the last 24 hours" scores, Brief Pain Inventory, SF-36, MOS Sleep-R, were obtained early with the full extent of these effects established when a stable Hysingla ER dose was achieved. These improvements in pain relief, sleep, functional health and activities of daily living were maintained during the long-term treatment (**Table 10**).

Table 10. Summary of Efficacy Variables at Baseline and Maintenance Period

Outcome Measure	Baseline Mean (SD)	End of Titration Mean (SD)	Maintenance Mean (SD)	Mean (SD) Change from Baseline to Maintenance
Average Pain Over Last 24 hours	6.43 (1.60)	3.75 (1.86)	3.61 (1.80)	-2.79 (2.10)
MOS Sleep-R^a				
Sleep disturbance	45.33 (9.75)	50.48 (9.31)	50.29 (8.88)	4.69 (8.28)
Sleep problem index II	46.72 (9.59)	50.92 (8.91)	50.99 (8.88)	4.04 (8.53)
BPI-SF^b				
Pain Interference	5.11 (2.21)	2.64 (2.12)	2.65 (2.01)	-2.39 (2.09)
Pain Score	6.12 (1.70)	3.68 (1.85)	3.62 (1.73)	-2.44 (2.07)
SF-36^c				
Physical Component	34.67 (8.26)	39.54 (8.98)	40.38 (8.96)	5.58 (6.60)
Mental Component	53.12 (10.33)	55.27 (9.27)	55.13 (8.64)	1.89 (7.53)

^a MOS Sleep-R - a higher score indicates a better sleep pattern and a negative change from baseline indicates a worsening in sleep pattern. ^b BPI-SF - a lower score indicates lower pain; therefore, a negative change from baseline indicates a reduction in pain, and a positive change from baseline indicates an increase in pain. ^c SF-36, a higher score indicates a better perception of health; therefore, a positive change from baseline indicates a better perception of health, and a negative change from baseline indicates a worsening in perception of health.

A consistent analgesic effect with Hysingla ER over the 12-month maintenance period was demonstrated. The weekly mean standard deviation (SD) pain intensity score based on daily "average pain over the last 24 hours" scores decreased (improved) from 6.43 (1.60) at baseline to 3.75 (1.86) at the end of dose titration for patients who entered the maintenance period, and this improvement was maintained throughout the maintenance period (**Table 10**). Responder analyses ($\geq 30\%$, or $\geq 50\%$ reduction in pain from baseline) for "average pain over the last 24 hours" also showed a consistently improved response to Hysingla ER treatment. Overall average pain reduction from baseline of $\geq 30\%$ was reported for 65.8% of subjects, and of $\geq 50\%$ was reported for 39.9% of subjects in the maintenance period.

Hysingla ER dosing was generally stable throughout the maintenance period. The majority of subjects (66.1%) remained on their same stabilized starting dose, 20.4% had a increase of 1 dose level, and few patients (4.3%)

had their Hysingla ER doses increased by > 1 dose level at the end of the maintenance period compared with their starting dose. Compared to the average daily dose for all patients in the maintenance period (65.4 mg), the average daily dose for patients with at least 6 months exposure and at least 12 months exposure were similar (64.8 mg and 63.6 mg, respectively).

Analyses of “pain right now” scores compared predose pain scores, coinciding with “trough” systemic exposure to hydrocodone, with evening pain scores, roughly coinciding with “peak” systemic exposure to hydrocodone. During the maintenance period, the mean (SD) predose score was 3.6 (1.92) and mean (SD) evening score (representing various subsequent time points up to 24 hours post-dose) was 3.4 (1.93). This analysis showed that pain relief was not compromised at the end of the 24-hour Hysingla ER dosing interval, supporting the conclusion that once-daily dosing provides sustained analgesia over the dosing interval. No “end of dosing failure” was observed.

Fifty-three percent of all patients felt they were “very much improved” or “much improved” from before the study (PGIC). Patients who entered into maintenance treatment period were generally satisfied with Hysingla ER treatment; 91% to 98% were satisfied with how Hysingla ER managed their pain and found the use of Hysingla ER easy and convenient. Seventy-five percent would be willing to continue the use of Hysingla ER, and 86% would recommend Hysingla ER to others.

Safety Results: Eighty-four percent of the safety population had at least one treatment emergent adverse event (TEAE). The most common TEAEs ($\geq 5\%$) included nausea, constipation, vomiting, dizziness, somnolence, headache, fatigue, upper respiratory tract infection, diarrhea, insomnia, pruritus, sinusitis, urinary tract infection, nasopharyngitis, tinnitus, and arthralgia. The majority of the TEAEs were deemed related to the study drug and were mild or moderate in severity.

There were 5 deaths reported during this study. One of the deaths (accidental overdose, hydrocodone, citalopram, and cyclobenzaprine toxicity) was considered by the investigator to be definitely related to study drug; the other 4 were considered not related.

Abuse of study drug occurred in 2 patients. There were confirmed or suspected diversion of study drug by 24 patients (2.6%). Few patients ($\leq 1\%$) experienced AEs associated with opioid withdrawal during opioid conversion and during cessation of Hysingla ER treatment.

24-Week Open-Label Extension Results

One hundred six (106) patients (mean age 50.9 years; range 19 to 81 years) enrolled in the extension period and took ≥ 1 dose of study drug: 92 (87%) patients had ≥ 12 weeks, 90 (85%) had ≥ 16 weeks, and 81 (76%) had ≥ 20 weeks of exposure to Hysingla ER. The mean (SD) cumulative number of days on Hysingla ER at any dose was 145.4 (42.45) during the extension period, and 498.2 (56.48) days during the maintenance period and extension period combined. The mean average (SD) daily dose for all patients in the extension-period safety population during the maintenance and extension periods combined (63.15 [35.057] mg/day) was similar to that for the core-study safety population during the maintenance period (65.40 [34.258] mg/day).

Improvements in efficacy variables (pain scores, BPI-SF, MOS Sleep-R, SF-36) were maintained during the additional 24 weeks. At the end of the extension period, 76 (72%) patients in the extension-period safety population reported “very much improved” or “much improved.” At the end of extension period, 80 [76%] patients in the extension-period safety population reported “very willing to continue” or “willing to continue” use of study drug, which was lower than the proportion of patients (104 [98%] patients) who reported the same responses at the end of the maintenance period. Ninety [86%] patients in the extension period reported that they would recommend the study drug for pain management.

The most common TEAEs (by $\geq 3\%$ of patients) that occurred during the extension period included constipation, urinary tract infection, nausea, upper respiratory tract infection, dizziness, and arthralgia. A lower proportion of patients discontinued extension treatment due to AEs (7 [7%]) or patient’s choice (5 [5%]) than

those of the core-study safety population during the maintenance period (106 [15%] patients and 78 [11%] patients respectively). No patients discontinued extension treatment due to lack of therapeutic effect, lost to follow up, or confirmed or suspected diversion.

Conclusions: Hysingla ER was shown to be an effective long-term treatment. Analgesia was obtained early, with the full extent of pain control generally established when a stable Hysingla ER dose was achieved. The improvements in pain relief, sleep, functional health and activities of daily living were maintained during the long-term treatment without continued requirement for dose increase. Hysingla ER was generally well tolerated in this study. There were no new safety signals of concern detected during the study.

3.1.2. Published and Unpublished Data and Clinical Studies Supporting Off-Label Indications

None

3.1.3. Clinical Evidence Table Spreadsheets of all Published and Unpublished Studies

The following table (**Table 11**) includes the summaries of Hysingla ER safety and efficacy studies.

Table 11. Summary of Hysingla ER Efficacy and Safety Studies

Study	Design	Drug Regimens/Treatments	Sample Size (n)	Length of Study & Follow-Up	Key Inclusion Criteria	Key Exclusion Criteria	Endpoints	Results/Statistical Significance
HYD3002	<p>Multicenter, randomized, double-blind, placebo-controlled</p> <p>Pre-randomization phase = baseline period (14 days) and open-label titration (run-in) period (up to 45 days)</p> <p>Double-blind maintenance phase = 12 weeks</p> <p>Safety follow-up = 5-7 days</p>	<p>Hysingla ER 20 to 120 mg once daily</p> <p>Supplemental: IR oxycodone 5 mg (up to 10 mg daily), Run-in period; IR oxycodone 5 - 10mg every 4 - 6 hours (up to 30 mg/day), double-blind maintenance</p>	N = 588 (n = 210, Hysingla ER; n = 229, placebo)	12-week maintenance period, followed by 5-7 day safety follow-up	<ul style="list-style-type: none"> • Age ≥ 18 years • Moderate to severe, chronic low back pain for ≥ 3 months related to non-malignant, non-neuropathic conditions that was uncontrolled on stable non-opioid or opioid regimen (≤ 100 mg per day oxycodone equivalents) 	<ul style="list-style-type: none"> • Allergy to hydrocodone or other opioids • History of substance abuse or unstable psychiatric disease, surgery for low back pain within in the past 6 months 	<p><u>Efficacy:</u></p> <ul style="list-style-type: none"> • Primary: Weekly pain intensity score calculated using the daily “average pain over the last 24 hours” scores at week 12 • Secondary: responder analysis; sleep disturbances (MOS Sleep-R) at weeks 4, 8, and 12; PGIC at week 12 <p><u>Safety:</u></p> <ul style="list-style-type: none"> • AEs, opioid withdrawal, laboratory results, vital sign measurements, ECGs, audiology assessments, assessment of aberrant drug behavior 	<p><u>Patient Disposition:</u></p> <ul style="list-style-type: none"> • Mean (SD) age: 48 (13.2) years, Hysingla ER vs. 49 (13.5) years, placebo • Discontinuation: <ul style="list-style-type: none"> ○ Lack of effect (5%, Hysingla ER vs. 15%, placebo) ○ AEs (6%, Hysingla ER vs. 3%, placebo) • Mean (SD) dose: 56.9 (31.76) mg, double-blind; 43.7 (22.41) mg, safety population <p><u>Efficacy:</u></p> <ul style="list-style-type: none"> • LS Mean (SE) “Average pain over the last 24 hours” scores at Week 12: 3.70 (0.128), Hysingla ER vs. 4.23 (0.126), placebo; <i>P</i> = .0016 • Responder Analysis <ul style="list-style-type: none"> ○ ≥ 30% reduction in pain vs. baseline: 65%, Hysingla ER vs. 53%, placebo (<i>P</i> = 0.0033) ○ ≥ 50% reduction in pain vs. baseline: 48%, Hysingla ER vs. 39%, placebo (<i>P</i> = 0.0225) • MOS Sleep-R: Improvements in both treatment groups (Placebo: 44.72, baseline to 51.48, end of run-in vs Hysingla ER: 44.38, baseline to 50.33, end of run-in). No significant difference between Hysingla ER and placebo during the double-blind period. • PGIC: Significantly higher proportion of patients reporting “very much improved” or “much improved” with Hysingla ER vs. placebo (61% vs. 49%, respectively; <i>P</i> = .0036) <p><u>Safety:</u></p> <ul style="list-style-type: none"> • TEAEs <ul style="list-style-type: none"> ○ Run-in: 48% (431/905 patients); ≥ 5% = nausea, vomiting, constipation, dizziness, headache, somnolence ○ Maintenance: 46% (n = 136), Hysingla ER vs. 35% (n = 103), placebo; ≥ 5% = nausea and vomiting • Confirmed/suspected diversion: 4.3% (n = 39) • Opioid withdrawal: ≤ 1% during conversion or cessation of Hysingla ER

Study	Design	Drug Regimens/Treatments	Sample Size (n)	Length of Study & Follow-Up	Key Inclusion Criteria	Key Exclusion Criteria	Endpoints	Results/Statistical Significance
HYD3003 /3003S	Open-label, multicenter	Hysingla ER 20 to 120 mg once daily	N = 922 n = 728, completed up to 45-day dose titration phase and achieved stable dose	52-week maintenance period with optional 24-week extension	<ul style="list-style-type: none"> Age ≥ 18 years Moderate to severe, chronic non-malignant, non-neuropathic pain for ≥ 3 months Stable pain regimen (equivalent to: 0 -120 mg/day oxycodone for controlled pain or 0 - 100 mg/day oxycodone for uncontrolled pain) 	<ul style="list-style-type: none"> > 120 mg/day of oxycodone within 14 days of screening Chronic pain of neuropathic or malignant causes History of substance abuse or unstable psychiatric disease Significant or unstable cardiac, pulmonary, neurologic, hepatic, renal, or gastrointestinal conditions Hearing-related conditions that would have precluded an accurate assessment of hearing 	<p><u>Efficacy:</u></p> <ul style="list-style-type: none"> Pain: "Pain right now" and "Average pain over the last 24 hours" per 11-point NRS Sleep: MOS Sleep-R Functional health and well-being: SF-36 Ability to perform ADL, severity of pain, interference of pain: BPI-SF Patient satisfaction of with study drug and preference for study drug: Treatment Satisfaction Questionnaire (Part I and Part II) PGIC <p><u>Safety:</u> AEs, laboratory results, vital sign measurements, ECGs, etc</p>	<p>Maintenance</p> <p><u>Patient Disposition:</u></p> <ul style="list-style-type: none"> 51.8 years, mean age Discontinuation: <ul style="list-style-type: none"> Lack of effect (6%, overall; 4%, maintenance period) AEs (21% of the safety population) Completion of 12-month maintenance period: n = 410 Months of exposure to Hysingla ER: n = 732 (79%), ≥ 1 month; n = 500 (54%), ≥ 6 months, n = 364 (39%) with ≥ 12 months Mean cumulative number of days (SD) on Hysingla ER = 216.7 (160.73) Mean dose: 65.4 mg overall 12-month maintenance; at least 6 months exposure 64.8 mg; at least 12 months exposure 63.6 mg <p><u>Efficacy:</u></p> <ul style="list-style-type: none"> Mean (SD) "Average pain over the last 24 hours" scores: 6.43 (1.60), baseline vs. 3.61 (1.8), maintenance [mean change: -2.79 (2.10)] Mean (SD) "Pain right now" scores (maintenance): 3.63 (1.93), pre-dose score vs. 3.5 (1.91), evening score; pain relief was not compromised at the end of the 24-hour dosing interval <p><u>Safety:</u></p> <ul style="list-style-type: none"> 84% of safety population had ≥1 TEAE TEAEs (≥ 5%): nausea, constipation, vomiting, dizziness, somnolence, headache, fatigue, upper respiratory tract infection, diarrhea, insomnia, pruritus, sinusitis, urinary tract infection, nasopharyngitis, tinnitus, and arthralgia Majority of TEAEs were deemed mild/moderate in severity Deaths (n = 5): n = 1, considered by the investigator to be definitely related to study drug (accidental overdose: hydrocodone, citalopram, cyclobenzaprine)

Study	Design	Drug Regimens/ Treatments	Sample Size (n)	Length of Study & Follow-Up	Key Inclusion Criteria	Key Exclusion Criteria	Endpoints	Results/Statistical Significance
HYD3003 /3003S (cont'd)								<p>Extension Patient Disposition:</p> <ul style="list-style-type: none"> • n = 106 (50.9 years, mean age) • Discontinuation <ul style="list-style-type: none"> ◦ AEs (7%); patient choice (5%); lack of effect (0%) • Months of exposure to Hysingla ER: n = 92 (87%), ≥ 12 weeks; n = 90 (85%), ≥ 16 weeks, n = 81 (76%) with ≥ 20 weeks • Mean (SD) cumulative number of days on Hysingla ER = 145.4 (42.45), extension; 498.2 (56.48), extension and maintenance combined • Mean (SD) daily dose: 63.15 (35.06) mg/day, extension period safety population during maintenance and extension combined <p>Efficacy:</p> <ul style="list-style-type: none"> • Improvements in pain scores, BPI-SF, MOS Sleep-R, SF-36 maintained during extension • “Very much improved” or “much improved”: n = 76 (72%) • “Very willing to continue” or “willing to continue”: n = 80 (76%) <p>Safety:</p> <ul style="list-style-type: none"> • Most common TEAEs (≥ 3% of patients): constipation, urinary tract infection, nausea, upper respiratory tract infection, dizziness, and arthralgia

ADL = activities of daily living; BPI-SF: AEs = adverse events; Brief Pain Inventory – Short Form; ER = extended-release; IR = immediate-release; MOS Sleep-R = Medical Outcomes Study Sleep Scale – Revised; NRS = Numerical Rating Scale; PGIC = Patient’s Global Impression of Change; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; TEAEs = treatment emergent adverse events

3.1.4. Summary of Evidence from Secondary Sources

None.

4. ECONOMIC VALUE AND MODELING REPORT

Abstract

Introduction

A budget impact model was developed to estimate the impact on a managed care organization's pharmacy budget of including Hysingla™ ER as a treatment option for patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The budget impact model is based on a detailed analysis of longitudinal claims data to understand the likely economic impact of Hysingla ER based on user-selected subpopulations.

Methods

The model is based on an analysis of claims data from the Truven Health Analytics MarketScan® database (2H2011-2012). Candidates for Hysingla ER are assumed to come from patients prescribed immediate-release (IR) hydrocodone. Patients are segmented into subpopulations according to IR hydrocodone utilization levels observed in the MarketScan® database.

Utilization patterns of IR hydrocodone and extended-release (ER)/long-acting (LA) opioids and projected rates of treatment initiations, length of treatments, and doses of Hysingla ER are calculated separately for each subpopulation based upon the MarketScan® database. Drug costs of opioids in the model are based upon RED BOOK® and the list price of Hysingla ER. Other costs in the model are based on MarketScan® data. Projected market uptake of Hysingla ER is based upon user inputs.

Results

For a commercial population with 1,000,000 members the estimated budget impact is less than \$0.01 per member per month (PMPM).

Discussion

The database analysis showed that ~11.9 million commercial patients in the US were prescribed IR hydrocodone during the study baseline period (second half of 2011). For that population, the average duration of opioid therapy was approximately 2 of the 12 months in the follow-up study period. Only small subsets (ranging from 5.7% to 11.2%) of the total IR hydrocodone population (~11.9 million) are high utilizers, of which an even smaller subset (5% to 6%) initiated an ER/LA opioid during the follow-up study period. Because of the small size of the population of patients who are high utilizers and the small fraction of those who initiated an ER/LA opioid, the expected budgetary impact of Hysingla ER is nominal.

The results of the database analysis, combined with market share uptake assumptions, indicate an incremental cost PMPM of less than \$0.01 in the overall population of patients (~11.9 million) who took any IR hydrocodone in the baseline period. The model allows users to evaluate the incremental cost PMPM in various subpopulations of patients. An incremental cost PMPM of <\$0.01 is also estimated for the subpopulation of high utilizers that were prescribed IR hydrocodone for ≥60 days.

Findings of this research demonstrate that only small subsets of patients who receive IR hydrocodone are high utilizers. Those patients have high medical and pharmacy spend, with opioids representing only a fraction (approximately 3%) of their total healthcare dollars.

Introduction

A budget impact model was developed to estimate the impact on a managed care organization's budget of including Hysingla ER as a treatment option for patients with chronic pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Key uncertainties for payers include how many patients will be prescribed Hysingla ER and for how long, and what drug it will replace. The budget impact model is based on a detailed analysis of longitudinal claims data to understand the likely budgetary impact of Hysingla ER for different subpopulations. Key components of the model include an understanding of treatment patterns for patients prescribed IR hydrocodone, and, based upon those treatment patterns, a projection of the impact on pharmacy budgets. The model can be customized to payers' specific needs by allowing payers to look at specific subpopulations and to customize costs, treatment patterns, and market uptake assumptions.

The primary data source for the model was the Truven Health Analytics MarketScan database, which includes paid medical and pharmacy claims compiled from multiple payers covering a large segment of the US population (Truven Health Analytics 2011-2012). Analyses were performed on data from the second half of 2011 through 2012 (ie, a 6-month baseline period followed by a 12-month follow-up period) for all patients who received ≥ 1 prescription for IR hydrocodone in the 6-month baseline period.

Methods

Patient Population

The model population is based on an analysis of the Truven Health Analytics MarketScan database.¹ The initial model population consists of all patients who were prescribed IR hydrocodone in the second half of 2011 (the baseline period). An analysis of subsequent prescriptions for IR hydrocodone and ER/LA opioids was performed on this population for the year starting January 1, 2012.

Within this population, 2 groups are considered separately to identify candidates for Hysingla ER:

- Patients taking IR hydrocodone with a concurrent ER/LA opioid
- Patients not taking ER/LA opioids who had a large supply of IR hydrocodone (>60 pills per month or ≥ 60 days' supply prescribed)

Treatment Alternatives

The model includes both brand name and generic ER/LA opioids currently available for the treatment of pain.

Brand name ER/LA opioids included in the model are:

- Hysingla ER
- Avinza[®]
- Kadian[®]
- MS Contin[®]
- Butrans[®]
- Opana[®] ER
- Dolophine[®]
- Nucynta[®] ER
- OxyContin[®]
- Duragesic[®]
- Exalgo[®]

Generic ER/LA opioids included in the model are:

- Morphine sulfate
- Methadone hydrochloride
- Oxycodone hydrochloride
- Fentanyl transdermal
- Avinza (generic)
- Kadian (generic)

Note that Avinza and Kadian became available in generic form in 2011. The model allows the user to treat these drugs as generic or branded.

Model Perspective

The model perspective is that of a US payer (commercial, Medicare, or Medicaid). The time horizon is 1 to 3 years.

Model Structure

Subpopulations

Table 12 shows the patient characteristics that can be used to define subpopulations of high IR hydrocodone utilizers in the model. The fraction of patients in each subpopulation who convert to an ER/LA opioid during the model time horizon is determined based on longitudinal data obtained for each subpopulation.¹ In addition, any patients prescribed IR hydrocodone and ER/LA opioids during the baseline period are included in the population, regardless of the amount of IR hydrocodone or ER/LA opioids prescribed.

Table 12. Definition of Model Subpopulations

Characteristic	Possible options
Payer	Commercial, Medicare, Medicaid
Number of days' supply of IR hydrocodone*	Any, ≥ 60 , ≥ 90
Number of IR hydrocodone pills/month [†]	Any, > 60 , ≥ 90 , ≥ 120

* As indicated in the claim. Only continuous prescriptions are counted. A prescription with a gap of up to 30 days is considered continuous.

† Total number of IR hydrocodone pills prescribed in the 6-month baseline period divided by 6, even if all the prescriptions were in a single month (ie, this is an average over the entire period, regardless of the period covered by the prescriptions).

Hysingla ER Uptake

Within the selected subpopulation, ER/LA opioid market shares, including user-defined market estimates for Hysingla ER, are independently assigned to each of the following groups based on the database analysis:

1. Proportion of the market currently prescribed IR hydrocodone and a branded ER/LA opioid, who may substitute Hysingla ER for the ER/LA opioid.
2. Proportion of the market currently prescribed IR hydrocodone and a generic ER/LA opioid, who may substitute Hysingla ER for the ER/LA opioid.
3. Proportion of the market currently prescribed IR hydrocodone only, who historically have converted to a branded ER/LA opioid.
4. Proportion of the market currently prescribed IR hydrocodone only, who historically have converted to generic ER/LA opioid.
5. Proportion of the market currently prescribed IR hydrocodone who have not historically converted to an ER/LA opioid.

Projected market share values are shown in **Table 13**, and are based on an average of current market shares for Nucynta and Butrans. Within each group, Hysingla ER is assumed to take market share proportionally from each of the other ER/LA opioids (generic or branded depending on the group). The model assumes that Hysingla ER is prescribed at an equianalgesic dose of the medication it replaced, and that it is taken for an equal average duration. Duration of use is calculated from the database analysis and depends on the ER/LA opioid replaced, the patient subpopulation, and whether the patient is a new ER/LA opioid user or has switched from a different ER/LA opioid.

Table 13. Projected Hysingla ER Market Uptake in Year 1

Patient group	Percent of market taken by Hysingla ER
Patients using ER/LA opioid concurrently with IR hydrocodone*	
Concurrent branded ER/LA opioid	6%
Concurrent generic ER/LA opioid	0%
Patients in subpopulation when converting to ER/LA opioid	
Converting to branded ER/LA opioid	20%
Converting to generic ER/LA opioid	0%
Patients in subpopulation who historically remain on IR hydrocodone	
All	0%

*ER/LA=extended-release/long-acting; IR=immediate-release.

Individuals in group 5, those who historically have not converted to an ER/LA opioid but may do so in the scenario in which Hysingla ER is available, are assumed to use Hysingla ER for the same duration as they would use IR hydrocodone. This duration can be changed by the user.

Budget Impact Calculation

The budget impact is determined by calculating the incremental budget impact of Hysingla ER for each alternative in each subpopulation, and then adding all of those values together, as shown in **Figure 8**. The overall sum is then divided by the number of members, and then divided by 12 to give the PMPM budget impact.

Figure 8. Budget Impact Calculation

$$Budget\ impact = \sum_{Subpopulations} \sum_{Alternatives} (fraction * amount * incremental\ cost)$$

In the equation shown in **Figure 8**, *fraction* is the fraction of the subpopulation that converts to Hysingla ER, *amount* is the prescribed duration and dose of Hysingla ER, and *incremental cost* is the incremental cost difference between Hysingla ER and the drug that it replaced. The values *fraction* and *amount* are determined separately for each alternative in each subpopulation based on the database analysis.

Model Inputs

Population Inputs

The initial model population of all patients who were prescribed IR hydrocodone in the second half of 2011 was based on an analysis of the Truven Health Analytics MarketScan database (Truven Health Analytics 2011-2012). An analysis of subsequent prescriptions for IR hydrocodone and ER/LA opioids for this population during the year starting January 1, 2012 was performed to define the characteristics of each subpopulation shown in **Table 12**, such as the fraction of patients who initiate an ER/LA opioid, the market share of each ER/LA opioid, the dose and duration for each ER/LA opioid, non-opioid pharmaceutical costs, and non-pharmacy direct medical costs.

Cost Inputs: Drug Costs

The average daily consumption of IR hydrocodone in the model is 46.75 mg, and the unit cost is \$0.22/5 mg (Red Book 2014). Drug costs used in the model are shown in **Table 14** (branded alternatives), **Table 15** (generic alternatives), and **Table 16** (Hysingla ER).

All drug costs are based on RED BOOK, with the exception of Hysingla ER, which was based on list price (Red Book 2014). For branded drugs, costs are determined by pill strength. Patients who use Hysingla ER in place of branded products are assumed to do so at an equianalgesic daily dose. It is assumed that patients are prescribed the pills according to the prescribing information[†] in terms of frequency (ie, daily consumption) and then a distribution of pill strengths was used that resulted in total daily doses that matched those observed for each branded product in the database analyses. For generic products, the lowest per milligram price from RED BOOK was used, regardless of pill strength, and that price was multiplied by the average daily dose to calculate a daily cost for each generic opioid.

Table 14. Costs of Branded ER/LA Opioid Alternatives

Alternative	Average daily consumption (unit)	WAC unit cost	WAC monthly cost	AWP unit cost	AWP monthly cost
Avinza[®]					
30 mg	1.00	\$5.31	\$161.54	\$6.37	\$193.85
45 mg	1.00	\$7.87	\$239.53	\$9.44	\$287.43
60 mg	1.00	\$10.30	\$313.70	\$12.36	\$376.44
75 mg	1.00	\$13.11	\$399.21	\$15.73	\$479.05
90 mg	1.00	\$15.49	\$471.67	\$18.59	\$566.00
120 mg	1.00	\$18.28	\$556.52	\$21.93	\$667.83
Kadian[®]					
10 mg	1.00	\$5.84	\$177.83	\$7.01	\$213.39

[†]Avinza FPI 2014; Butrans FPI 2014; Dolophine FPI 2014; Duragesic FPI 2014; Exalgo FPI 2014; Fentanyl Transdermal FPI 2014; Kadian FPI 2014; Methadone FPI 2013; Morphine Sulfate ER FPI 2014; MS Contin FPI 2014; OxyContin FPI 2014; Nucynta ER FPI 2014; Opana ER FPI 2014; Oxymorphone HCl ER FPI 2011.

Alternative	Average daily consumption (unit)	WAC unit cost	WAC monthly cost	AWP unit cost	AWP monthly cost
20 mg	1.00	\$6.45	\$196.40	\$7.74	\$235.68
30 mg	1.00	\$7.02	\$213.76	\$8.42	\$256.51
40 mg	1.00	\$9.36	\$285.01	\$11.23	\$342.01
50 mg	1.00	\$11.73	\$357.18	\$14.08	\$428.61
60 mg	1.00	\$14.04	\$427.52	\$16.85	\$513.02
70 mg	1.00	\$19.88	\$605.35	\$23.86	\$726.42
80 mg	1.00	\$18.70	\$569.42	\$22.44	\$683.30
100 mg	1.00	\$23.07	\$702.48	\$27.68	\$842.98
130 mg	1.00	\$30.09	\$916.24	\$36.11	\$1,099.49
150 mg	1.00	\$34.80	\$1,059.66	\$41.76	\$1,271.59
200 mg	1.00	\$47.40	\$1,433.33	\$56.88	\$1,732.00
MS Contin®					
15 mg	2.00	\$2.23	\$136.04	\$2.68	\$163.25
30 mg	2.00	\$4.24	\$258.50	\$5.09	\$310.19
60 mg	2.00	\$8.28	\$504.42	\$9.94	\$605.30
100 mg	2.00	\$12.26	\$746.82	\$14.72	\$896.19
200 mg	2.00	\$22.46	\$1,367.70	\$26.95	\$1,641.24
Butrans®					
5 mcg/hr	0.14	\$40.22	\$174.96	\$48.27	\$209.95
10 mcg/hr	0.14	\$60.33	\$262.42	\$72.39	\$314.91
15 mcg/hr	0.14	\$87.03	\$378.56	\$104.43	\$454.27
20 mcg/hr	0.14	\$106.80	\$464.59	\$128.16	\$557.51
Opana® ER					
5 mg	2.00	\$1.89	\$114.99	\$2.27	\$137.98
10 mg	2.00	\$3.63	\$220.81	\$4.35	\$264.96
20 mg	2.00	\$6.43	\$391.62	\$7.72	\$469.94
30 mg	2.00	\$9.26	\$563.67	\$11.11	\$676.40
40 mg	2.00	\$12.08	\$735.73	\$14.50	\$882.88
Dolophine®					
5 mg	2.00	\$0.10	\$6.33	\$0.13	\$7.91
10 mg	2.00	\$0.17	\$10.28	\$0.21	\$12.85
Nucynta® ER					
50 mg	2.00	\$2.84	\$172.95	\$3.41	\$207.54

Alternative	Average daily consumption (unit)	WAC unit cost	WAC monthly cost	AWP unit cost	AWP monthly cost
75 mg	2.00	\$4.26	\$259.42	\$5.11	\$311.31
100 mg	2.00	\$5.25	\$319.56	\$6.30	\$383.48
OxyContin®					
10 mg	2.00	\$2.28	\$138.92	\$2.74	\$166.70
15 mg	2.00	\$3.42	\$208.05	\$4.10	\$249.65
20 mg	2.00	\$4.37	\$265.83	\$5.24	\$319.00
30 mg	2.00	\$6.18	\$376.26	\$7.41	\$451.51
40 mg	2.00	\$7.75	\$471.68	\$9.29	\$566.02
60 mg	2.00	\$11.27	\$686.38	\$13.52	\$823.65
80 mg	2.00	\$14.56	\$887.00	\$17.48	\$1,064.40
Duragesic®					
12 mcg/hr	0.33	\$24.96	\$253.30	\$29.95	\$303.97
25 mcg/hr	0.33	\$30.13	\$305.84	\$36.16	\$367.00
50 mcg/hr	0.33	\$55.69	\$565.27	\$66.11	\$671.02
75 mcg/hr	0.33	\$84.03	\$852.92	\$100.84	\$1,023.51
100 mcg/hr	0.33	\$111.53	\$1,132.01	\$133.83	\$1,358.42
Exalgo®					
8 mg	1.00	\$12.68	\$386.04	\$15.21	\$463.24
12 mg	1.00	\$19.02	\$579.06	\$22.82	\$694.87
16 mg	1.00	\$25.36	\$772.07	\$30.43	\$926.49
32 mg	1.00	\$50.71	\$1,544.14	\$60.85	\$1,852.97

AWP=average wholesale price; ER/LA=extended-release/long-acting; WAC=wholesale acquisition cost.

Table 15. Costs of Generic ER/LA Opioid Alternatives (Red Book 2014)

Alternative	Monthly cost
Morphine sulfate	\$56.10
Methadone hydrochloride	\$5.86
Oxymorphone hydrochloride	\$108.46
Fentanyl transdermal	\$72.37
Avinza (generic)	\$56.10
Kadian (generic)	\$56.10

ER/LA=extended-release/long-acting.

Table 16. Costs of Hysingla ER

Hysingla ER Dose	Average daily consumption (unit)	WAC unit cost	WAC monthly cost
20 mg	1.00	\$6.57	\$200.06
30 mg	1.00	\$9.59	\$292.02
40 mg	1.00	\$12.92	\$393.41
60 mg	1.00	\$17.89	\$544.75
80 mg	1.00	\$24.12	\$734.45
100 mg	1.00	\$30.69	\$934.51
120 mg	1.00	\$134.01	\$1,035.60

ER/LA=extended-release/long-acting; WAC=wholesale acquisition cost.

WAC monthly cost is annualized to reflect a 365 day year.

Market Share

Market shares are calculated separately for each subpopulation based on the database analysis. In addition, the market share gained by Hysingla ER is estimated separately for patients in each of the 5 groups described in the [Hysingla ER Uptake Section](#) (ie, currently taking an ER/LA opioid versus initiating an ER/LA opioid, patients prescribed a branded drug versus a generic drug, and patients who historically would not convert to an ER/LA opioid but may with the availability of Hysingla ER). Baseline year 1 values for each group are shown in [Table 13](#).

Dose Calculations

Dosing of ER/LA opioids and the equivalent dosage of Hysingla ER were based on the prescribing information for each drug (Avinza FPI 2014; Butrans FPI 2014; Dolophine FPI 2014; Duragesic FPI 2014; Exalgo FPI 2014; Fentanyl Transdermal FPI 2014; Kadian FPI 2014; Methadone FPI 2013; Morphine Sulfate ER FPI 2014; MS Contin FPI 2014; OxyContin FPI 2014; Nucynta ER FPI 2014; Opana ER FPI 2014; Oxymorphone HCl ER FPI 2011).

Model Assumptions

Important assumptions made in the model are:

- Medical resource use is assumed not to change as a result of switching to a different opioid.
- For the proportion of patients who convert to an ER/LA opioid, Hysingla ER is assumed to take market share proportionally from all alternative ER/LA opioids.
- Patients who convert to Hysingla ER in place of another ER/LA opioid are assumed to replace the alternative opioid as precisely as possible. They receive an equivalent analgesic dose (rounded to the nearest planned Hysingla ER dose) for the same duration of treatment, and continue with the same amount of IR hydrocodone use.
- Of the proportion of patients who do not convert to an ER/LA opioid in the database analyses, some fraction are assumed to convert to Hysingla ER. These patients are assumed to receive Hysingla ER equal to their IR hydrocodone dose (rounded to the nearest planned Hysingla ER dose), and to receive additional IR hydrocodone equal to the average of those patients who convert to other ER/LA opioids.

Model Outputs

The primary output of the model is the estimated incremental cost PMPM to the managed care organization when Hysingla ER is made available to the organization’s patient population.

Results

Base Case Analysis

For a commercial population with 1,000,000 members, based on an eligible subpopulation of members who were prescribed any amount of IR hydrocodone in the baseline period, the estimated budget impact of Hysingla ER in the following year was less than \$0.01. For the subpopulation of high utilizers who were prescribed IR hydrocodone for ≥ 60 days in the baseline period, the estimated incremental cost PMPM in the following year was also < \$0.01.

Sensitivity Analysis

A sensitivity analysis was performed to examine the impact of the selected subpopulation (1,000,000 commercial lives) and of assumptions made regarding the market uptake of Hysingla ER. Results are shown in **Table 17**.

Table 17. Sensitivity Analysis Results

Parameter	Base Case Value	Alternate Value	Cost PMPM
Base case	-	-	< \$0.01
Selected subpopulation	≥ 60 days’ supply IR hydrocodone (in the baseline period)	Any IR hydrocodone	< \$0.01
		≥ 90 days’ supply IR hydrocodone	< \$0.01
		> 60 pills/month IR hydrocodone	< \$0.01
		≥ 90 pills/months IR hydrocodone	< \$0.01
		≥ 120 pills/month IR hydrocodone	< \$0.01
Hysingla ER uptake	6% of concurrent branded ER/LA opioid users 0% of concurrent generic ER/LA opioid users 20% of conversions to branded ER/LA opioid 0% of conversions to generic ER/LA opioid 0% additional conversion to ER/LA opioid	6% of concurrent branded ER/LA opioid users 0% of concurrent generic ER/LA opioid users 20% of conversions to branded ER/LA opioid 0% of conversions to generic ER/LA opioid 1% additional conversion to ER/LA opioid	\$0.02
		6% of concurrent branded ER/LA opioid users 6% of concurrent generic ER/LA opioid users 20% of conversions to branded ER/LA opioid 20% of conversions to generic ER/LA opioid 1% additional conversion to ER/LA opioid	\$0.04
		6% of concurrent branded ER/LA opioid users 0% of concurrent generic ER/LA opioid users 20% of conversions to branded ER/LA opioid 0% of conversions to generic ER/LA opioid 3% additional conversion to ER/LA opioid	\$0.04

Prevalence and Costs of Opioid Abuse

Separately from the budget impact model, additional database analysis was performed to estimate the prevalence of and costs associated with opioid abuse. Patients diagnosed with opioid abuse or misuse represent a major driver of cost in the IR hydrocodone using population, particularly among those with longer durations or larger amounts of prescribed IR hydrocodone.

The analysis considered patients “diagnosed abusers” if they were prescribed IR hydrocodone and had ≥1 medical claim with an ICD-9-CM diagnosis code related to opioid abuse, dependency, or overdose.

Estimating the excess costs of diagnosed abusers based on differences in direct medical costs between patients diagnosed with opioid abuse and a propensity-matched set of patients without diagnosed abuse yields an average excess annual cost of \$14,720. The prevalence of diagnosed abuse varies strongly with the amount of prescribed opioids ranging from 0.63% among those with < 60 days’ supply prescribed to 3.47% for those with ≥ 60 days’ supply or 3.68% for those with > 60 pills/month **Table 18**. Given these increases in rates of diagnosed abuse, the excess costs of diagnosed abusers on a per patient per month (PPPM) basis varies from \$7.73/month for those patients with < 60 days’ supply to \$42.57/month for those with ≥ 60 days’ supply or \$45.14/month for those with > 60 pills/month.

Table 18. Subpopulation Rates and Costs of Diagnosed Opioid Abuse

Subpopulation	Rate of diagnosed abuse	Excess cost, PPPM
Any amount of IR hydrocodone	0.91%	\$11.16
< 60 days’ supply IR hydrocodone	0.63%	\$7.73
≥ 60 days’ supply IR hydrocodone	3.47%	\$42.57
≥ 90 days’ supply IR hydrocodone	3.62%	\$44.41
> 60 pills/month IR hydrocodone	3.68%	\$45.14
≥ 90 pills/months IR hydrocodone	3.90%	\$47.84
≥ 120 pills/month IR hydrocodone	4.29%	\$52.62

PPPM=per patient per month.

Limitations

Limitations of the model are:

- Claims data may not reflect the full patient population.
- Claims data do not account for services that patients pay for out-of-pocket.
- Historical claims data from 2011 to 2012 may not reflect current prescribing practices and may not account for changes in the population since 2012.
- Changes in IR hydrocodone use after converting to Hysingla ER may alter the budget impact.
- There may be value associated with continuing with a previously prescribed opioid. This value is not represented in the model.
- Patients may use Hysingla ER differently than alternative ER/LA opioids.
- The model does not project the impact of Hysingla ER on the cost of opioid abuse or resource utilization other than for ER/LA opioids.

Discussion

The database analysis showed that ~11.9 million commercial patients in the US were prescribed IR hydrocodone during the study baseline period (2H2011). For that population, the average duration of opioid therapy was approximately 2 of the 12 months in the follow-up study period. Only small subsets (ranging from

5.7% to 11.2%) of the total IR hydrocodone population (~11.9 million) are high utilizers, of which an even smaller subset (5% to 6%) initiated an ER/LA opioid during the follow-up study period. Because of the small size of the population of patients who are high-utilizers and the small fraction of those who initiated an ER/LA opioid, the expected budgetary impact of Hysingla ER is nominal.

The results of the database analysis, combined with market share uptake assumptions, indicate an incremental cost PMPM of less than \$0.01 in the overall population of patients (~11.9 million) who took any amount of IR hydrocodone in the baseline period. The model allows users to evaluate the incremental cost PMPM in various subpopulations of patients. An incremental cost PMPM of < \$0.01 is also estimated for the subpopulation of high utilizers that were prescribed IR hydrocodone for ≥ 60 days. A range of subpopulation definitions and market share uptake assumptions were tested; the cost PMPM was \$0.05 or below in each case tested.

Findings of this research demonstrate that only small subsets of patients who receive IR hydrocodone are high utilizers. Those patients have high medical and pharmacy spend, with opioids representing only a fraction (approximately 3%) of their total healthcare dollars.

5. OTHER SUPPORTING EVIDENCE

5.1. Summarizing Other Relevant Evidence

5.1.1. Published and Unpublished Studies Supporting Labeled and Off-Label Indications

Hysingla ER Abuse-Deterrence Studies

Hysingla ER is formulated with RESISTEC™ technology. RESISTEC is Purdue Pharma's proprietary extended-release solid oral dosage formulation platform. RESISTEC uses a unique combination of polymer and processing that confers tablet hardness and imparts viscosity when dissolved in aqueous solutions [Data on file, NDA - Quality Overall Summary].

Abuse-deterrent Technology

The physicochemical attributes of Hysingla ER are intended to make the tablets more difficult to manipulate for the purpose of misuse and abuse by various routes of administration and to reduce the likelihood of certain inadvertent medication errors. Hysingla ER has physicochemical properties that confer resistance to crushing, dissolving and breaking – manipulations often required or preferred for abuse through intravenous and intranasal routes, and it maintains some extended-release characteristics even if the tablet is physically compromised.

This technology is not expected to have a direct impact on nonmedical use by swallowing a single or multiple intact tablets. It should be noted that not all opioid formulations that incorporate abuse-deterrent technologies possess equivalent degrees of abuse deterrence; a comprehensive *in vitro* and *in vivo* research program is required to determine whether a given product meets FDA standards for abuse-deterrent properties.

As a Schedule II controlled substance, Hysingla ER has a high potential for abuse. Use, misuse, or abuse of the drug may lead to physical dependence, addiction, or both. The Hysingla ER Full Prescribing Information and its boxed warning contain warnings about the potential for addiction, abuse, misuse, diversion, and overdose, including the risk of fatal overdose from consuming tablets that have been altered or as the result of accidental ingestion, such as in children.

Abuse Deterrence Studies

Purdue conducted laboratory manipulation and extraction studies, and clinical abuse potential studies with Hysingla ER, in accordance with the FDA's 2013 Draft Guidance on Abuse-Deterrent Opioids: Evaluation and Labeling [FDA Draft Guidance, 2013]. Based on their review of the results of these studies, FDA has concluded that Hysingla ER has abuse-deterrent properties that are expected to deter misuse and abuse via chewing, snorting and injection, resulting in Tier 1 and Tier 3 abuse-deterrence labeling claims. Tier 1 labeling indicates that the product is formulated with physicochemical barriers to abuse and Tier 3 labeling indicates the product is expected to result in a meaningful reduction in abuse. However, abuse of Hysingla ER by the intravenous, intranasal, and oral routes is still possible. The methodology and results of these studies are summarized in section 9.2 of the Hysingla ER Full Prescribing Information. Additional data, including epidemiological data, when available, may provide further information regarding the real-world abuse liability and other real-world characteristics of Hysingla ER. Accordingly, section 9.2 may be updated in the future, as appropriate.

To evaluate the ability of Hysingla ER's physicochemical properties to reduce the potential for abuse of Hysingla ER, a series of *in vitro* laboratory studies and human clinical abuse potential studies was conducted.

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the resistance of Hysingla ER to different extraction methods intended to defeat the extended-release formulation. Results demonstrate that Hysingla ER tablets resist crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation. Attempts to dissolve Hysingla

ER in small volumes of aqueous solutions result in formation of a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

Clinical Abuse Potential Studies

Two randomized, double-blind, placebo- and positive-controlled studies in non-dependent opioid abusers were conducted to characterize the abuse potential of Hysingla ER following physical manipulation and administration via the intranasal ([HYD1014](#)) and oral ([HYD1013](#)) routes. For both studies, drug liking was measured on a bipolar drug liking scale of 0 to 100 where 0 represents maximum disliking, 50 represents a neutral response of neither liking nor disliking, and 100 represents maximum liking. Response to whether the subject would take each study drug treatment 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”).

In both studies, primary pharmacodynamic (PD) and pharmacokinetic (PK) measurements were conducted up to 36 hours postdose. Primary PD measures included Visual analog scales (VAS) for ‘At the Moment Drug Liking’ and ‘High’. Secondary measures included VAS for ‘Overall Drug Liking’ and ‘Take Drug Again’, as well as assessments of Subjective Drug Value, intranasal irritation, and pupillometry (an objective measure of opioid effects).

Intranasal Abuse Potential Study (HYD1014; Harris et al, APS 2014 [#441])

This was a single-center, double-blind, randomized, placebo-controlled and positive-controlled, 4-period crossover study in non-dependent opioid abusers with a history of intranasal opioid abuse.

The objectives of the study were to evaluate intranasal abuse potential and pharmacodynamic (PD) effects of intranasally administered fine particle size and coarse particle size manipulated Hysingla ER 60 mg tablets (produced using an industrial mill and razor blade, respectively) compared to hydrocodone 60 mg powder and placebo; evaluate the safety and tolerability of intranasally administered Hysingla ER (fine and coarse particle size); and to determine the pharmacokinetics (PK) profile of intranasally administered Hysingla ER (fine and coarse particle size) compared to hydrocodone powder. The fine-particle size manipulated Hysingla ER treatment was included to be consistent with FDA’s draft guidance on evaluation of abuse-deterrent opioids which specifies that the abuse-deterrent formulation should be manipulated to cause the highest release of the opioid and the highest plasma opioid concentrations. Reproducible production of fine particles from Hysingla ER tablets required the use of an industrial mill and consequently is not representative of a practical, real-world manipulation. The coarse-particle size Hysingla ER treatment included in the study represents a method of manipulation that is more likely to be representative of real-world manipulations of Hysingla ER.

Eligibility criteria for study enrollment included healthy male and female adults (aged 18 to 55 years) recreational opioid users who did not meet criteria for addiction as determined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria and who were non-physically-dependent on opioids, as confirmed by naloxone challenge. Subjects had a history of non-therapeutic use (ie, for psychoactive effects) of opioids, including reported intranasal use on at least 3 occasions within the 12 months prior to screening, and reported taking an opioid dose equivalent to 40 mg hydrocodone (by any route of administration) or higher on at least 1 occasion within the past year.

Following completion of an initial separate dose selection phase, the primary study consisted of 4 phases: screening, qualification, treatment, and follow-up. The screening phase included 2 visits: a screening visit (visit 1) and a naloxone challenge visit (visit 2). All subjects completed the naloxone challenge test at least 12 hours prior to drug administration in the dose selection or qualification phases, to confirm that subjects were not opioid dependent.

Thirty-one subjects were dosed and 25 subjects completed all treatment periods. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 82% (n = 23) of subjects receiving tampered Hysingla ER (n = 28) compared to no subjects with powdered hydrocodone or placebo.

The intranasal administration of manipulated Hysingla ER was associated with statistically significantly lower mean and median scores for drug liking and take drug again ($P < .001$ for both), compared with powdered hydrocodone as summarized in **Table 19**.

Table 19. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again Following Intranasal Administration of Hysingla ER and Hydrocodone Powder in Non-dependent Opioid Abusers

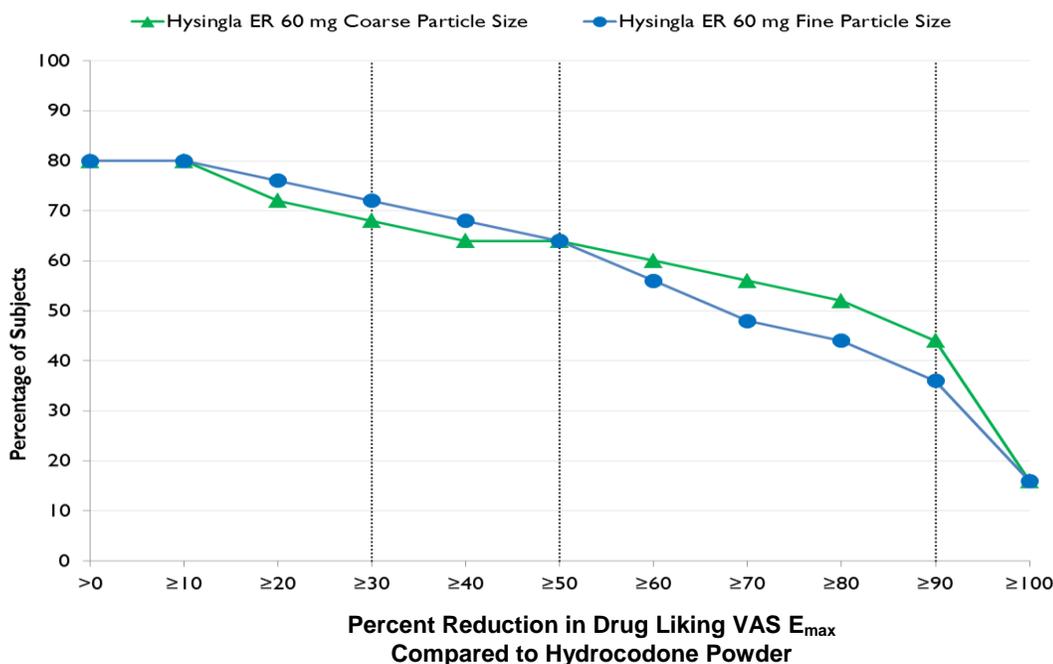
VAS Scale (n=25)	Hydrocodone Powder 60 mg	Hysingla ER Coarse 60 mg	Hysingla ER Fine 60 mg	P-value
Drug Liking*				
Mean (SE)	90.4 (2.6)	65.4 (3.7)	66.8 (3.7)	$P < .001$
Median (Range)	100 (51 - 100)	56 (50 - 100)	61 (50 - 100)	
Take Drug Again**				
Mean (SE)	85.2 (5.0)	36.4 (8.2)	40.7 (7.7)	$P < .001$
Median (Range)	100 (1 - 100)	14 (0 - 100)	50 (0 - 100)	

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

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

An analysis of percent reduction in peak drug liking scores for coarse particle size Hysingla ER compared to powdered hydrocodone found that among subjects (n = 25) who insufflated both treatments showed that 80% (n = 20) had some reduction in drug liking, 20% (n = 5) had no reduction in liking, 68% (n = 17) had a reduction of at least 30%, 64% (n = 16) had a reduction of at least 50%, and 44% (n = 11) had a reduction of at least 90%. Drug liking for fine particle size Hysingla ER compared to powdered hydrocodone showed that 80% (n = 20) had some reduction, 20% (n = 5) had no reduction, 72% (n = 18) had at least 30% reduction, 64% (n = 16) had at least 50% reduction, and 36% (n = 9) had at least 90% reduction (**Figure 9**).

Figure 9. Percent Reduction Profiles for E_{max} of Drug Liking VAS for Manipulated Hysingla ER vs. Hydrocodone Powder Following Intranasal Administration, N = 25



Mean C_{max} values of hydrocodone were considerably lower following Hysingla ER fine (36.5 ng/mL) and coarse (27.5 ng/mL) than following hydrocodone powder (106 ng/mL), which may be related to the lower percentage of the dose observed to have been inhaled for Hysingla ER fine and coarse than for hydrocodone powder. Additionally, median T_{max} was also observed later following Hysingla ER fine (3.1 hours) and coarse (4.1 hours) than following hydrocodone powder (1.6 hours). The mean AUC_t values following Hysingla ER fine and coarse were considerably lower than the AUC_t value for hydrocodone powder (902 h*ng/mL). The results were similar for AUC_{inf} .

Overall, the highest incidence of treatment-emergent adverse events (TEAEs) was observed after administration of hydrocodone powder (96.3%), followed by Hysingla ER fine (78.6%) and coarse (64.3%). The incidence of TEAEs was lowest following administration of placebo (7.4%). The most common types of TEAEs ($\geq 5\%$ of subjects) were those classified as psychiatric disorders; skin and subcutaneous tissue disorders; nervous system disorders; respiratory, thoracic, and mediastinal disorders; gastrointestinal disorders; and general disorders and administration site conditions. There were no deaths in this study.

Oral Abuse Potential Study (HYD1013; Harris et al, APS 2014 [#440])

This was a single-center, double-blind/quadruple-dummy, randomized, placebo-controlled and positive-controlled, 5-period crossover study in nondependent opioids abusers.

The objectives of the study were to evaluate oral abuse potential and pharmacodynamic (PD) effects of Hysingla ER 60 mg tablets intact, milled (produced using an industrial mill), and chewed, compared to hydrocodone 60 mg oral solution and placebo; to evaluate the safety and tolerability of orally administered intact, milled, and chewed Hysingla ER; to determine the PK profile of orally administered intact, milled, and chewed Hysingla ER compared to hydrocodone in oral solution. The milled manipulated Hysingla ER treatment was included to be consistent with FDA's draft guidance on evaluation of abuse-deterrent opioids which specifies that the abuse deterrent formulation should be manipulated to cause the highest release of the opioid and the highest plasma opioid concentrations. Reproducible production of milled Hysingla ER tablets required the use of an industrial mill and consequently is not representative of a practical, real-world manipulation. The chewed Hysingla ER treatment included in the study represents a method of manipulation that is likely to be commonly attempted as a method of manipulation for oral abuse of Hysingla ER.

Eligibility criteria for study enrollment was similar to that of the intranasal abuse potential study and included subjects with a history of non-therapeutic use of opioids including at least 3 occasions of chewing an opioid medication within the 12 months prior to screening and reported taking an opioid dose equivalent to 60 mg hydrocodone (by any route of administration) or higher on at least 1 occasion in their lifetime.

Forty subjects were dosed and 35 subjects completed the study. 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 ($P < .001$), compared to hydrocodone solution as summarized in **Table 20**.

Table 20. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again Following Oral Administration of Hysingla ER and Hydrocodone Solution in Non-dependent Opioid Abusers

VAS Scale (n=35)	Hydrocodone Solution 60 mg	Hysingla ER Intact 60 mg	Hysingla ER Chewed 60 mg	Hysingla ER Milled 60 mg
Drug Liking*				
Mean (SE)	94.0 (1.7)	63.3 (2.7) [†]	69.0 (3.0) [†]	89.2 (2.4) [‡]
Median (Range)	100 (51 - 100)	58 (50 - 100)	66 (50-100)	93 (50 - 100)
Take Drug Again**				
Mean (SE)	89.7 (3.6)	34.3 (6.1) [†]	44.3 (6.9) [†]	84.1 (4.7)
Median (Range)	100 (1 - 100)	24 (0 - 100)	55 (0-100)	100 (0 - 100)

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

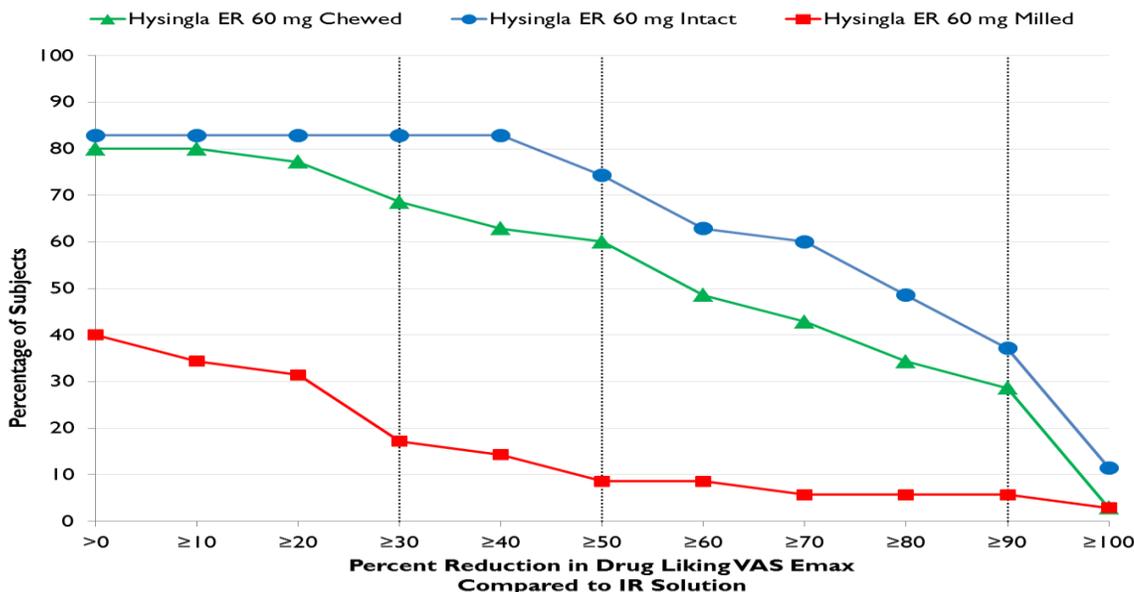
** Unipolar scale (0=maximum negative response, 100=maximum positive response)

[†]P < .001

[‡]P = .015

Plots of percent reduction in peak drug liking scores included chewed, intact, and milled Hysingla ER compared with hydrocodone solution in subjects (n = 35) who received both treatments orally, and are shown in **Figure 10**. Drug liking for chewed Hysingla ER showed that 80% (n = 28) had some reduction in drug liking, 20% (n = 7) had no reduction in liking, 69% (n = 24) had a reduction of at least 30%, 60% (n = 21) had a reduction of at least 50%, and 29% (n = 10) had a reduction of at least 90%. Drug liking results 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. Approximately 17% (n = 6) had no reduction in drug liking, 83% (n = 29) of subjects had a reduction of at least 30%, approximately 74% (n = 26) of subjects had a reduction of at least 50%, and 37% had a reduction of at least 90% in peak drug liking scores with intact Hysingla ER compared with hydrocodone solution. Drug liking for milled Hysingla ER showed 40% (n = 14) had some reduction in drug liking, 60% (n = 21) had no reduction, approximately 17% (n = 6) of subjects had a reduction of at least 30%, 9% (n = 3) had a reduction of at least 50%, and approximately 6% (n = 2) had a reduction of at least 90% in drug liking compared to hydrocodone solution (**Figure 10**).

Figure 10. Percent Reduction Profiles for E_{max} of Drug Liking VAS for Chewed, Intact, and Milled Hysingla ER vs. Hydrocodone Solution Following Oral Administration, N=35



Mean C_{max} of hydrocodone was highest following the hydrocodone solution (127 ng/mL). C_{max} values were lower following Hysingla ER milled (81.0 ng/mL) and chewed (67.3 ng/mL) and lowest following intact Hysingla ER (48.4 ng/mL). Median T_{max} of hydrocodone was 1.1 hours following the hydrocodone solution, was observed later following Hysingla ER milled (1.6 hours) and chewed (8.0 hours) and latest following intact Hysingla ER (15.1 hours). Mean AUC_t values of hydrocodone were similar following Hysingla ER intact (886 h*ng/mL), chewed (913 h*ng/mL), and the hydrocodone solution (951 h*ng/mL). Mean AUC_t values were lower following milled Hysingla ER (648 h*ng/mL). The results were similar for AUC_{inf} .

Overall, the highest incidence of treatment-emergent adverse events (TEAEs) was observed after administration of hydrocodone solution (97.4%), followed by Hysingla ER milled (94.6%), Hysingla ER chewed (75.0%), and Hysingla ER intact (69.4%). The most common types of TEAEs were those classified as psychiatric disorders, skin and subcutaneous tissue disorders, nervous system disorders, gastrointestinal disorders, and general disorders and administration site conditions. Most TEAEs were mild in severity, with the exception of 3 TEAEs of moderate severity (1 episode each of presyncope, sinus bradycardia, and headache in 3 different subjects). There were no deaths in this study.

Non-interventional Tamper Survey (HYD1015)

A non-interventional, interview-based study was performed to assess the attractiveness of Hysingla ER for abuse and tampering compared to other opioid formulations. No drugs were administered in this study.

Thirty subjects with current recreational opioid use, who had experience tampering with and administering prescription formulations by alternative routes of administration (28 to 65 years of age) were included in the study. All subjects completed the interview and were included in the analyses. Subjects were categorized into 1 of 3 groups based on their stated tampering preference (minimum of 6 subjects per group): (1) oral administration (eg, crushing, wrapping, and ingesting [“parachuting”]; dissolving/crushing into oral solution; chewing); (2) intravenous administration, and (3) intranasal administration.

Subjects were first asked to respond to questions about their opioid use and tampering history and preferences. Subjects were presented with opioid formulations including Hysingla ER, original OxyContin[®], Hycodan[®], Vicodin[®], and hypothetical hydrocodone transdermal patch, in a randomized manner using standardized information cards (including photographs, brand names, street names [if any], active ingredient[s], doses, solubility, potency, physical and pharmacologic properties, and release characteristics). For all products, subjects were asked to respond to open-ended questions about the products and their abuse, misuse, and tampering potential. Ranking procedures were performed (overall desirability and estimation of street value) after all the other presentations and assessments had been completed.

Hysingla ER was found to be the least attractive of the opioid products by recreational opioid abusers/users with tampering experience. Although potential tampering methods were suggested by the study population, the overall conclusion of this study is that the Hysingla ER technology and characteristics of the formulation will constitute significant deterrents against abuse and tampering.

Summary of In Vitro and In Vivo Data

Hysingla ER has approved labeling describing the product’s abuse-deterrent properties consistent with the FDA’s 2013 draft guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. This labeling includes those findings from both the *in vitro* and the *in vivo* Hysingla ER abuse deterrence studies that are considered relevant to health care providers when making prescribing decisions.

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.

5.1.2. Evidence Table Spreadsheets of all Published and Unpublished Studies

Table 21. Summary of Hysingla ER Abuse-Deterrence Studies

Study	Study Design	Sample Size	Treatments	Eligibility	Measurements	Results
HYD1013 – Oral Abuse Potential Study	Single-center, double-blind/quadruple-dummy, randomized, placebo-controlled and active controlled, crossover	N=40 n=35, completed	<ul style="list-style-type: none"> • Hysingla ER 60 mg tablets intact • Hysingla ER 60 mg tablets chewed • Hydrocodone API 60 mg oral solution • Placebo 	<ul style="list-style-type: none"> • Adults (ages, 18-55 years) • Recreational opioid user with reported chewing on opioid on ≥3 occasions within 12 months prior to screening and taking an opioid dose equivalent to ≥ 60 mg hydrocodone (any route) at least once in lifetime • Did not meet criteria for addiction • Non-dependent on opioids 	<p><u>Pharmacodynamic:</u> Primary:</p> <ul style="list-style-type: none"> • ‘At the Moment Drug Liking’ (VAS, Bipolar scale) <p>Secondary:</p> <ul style="list-style-type: none"> • ‘Take Drug Again’ (VAS, Unipolar scale) <p><u>Pharmacokinetic:</u></p> <ul style="list-style-type: none"> • Profile compared to hydrocodone oral solution <p><u>Safety:</u></p> <ul style="list-style-type: none"> • TEAs 	<p><u>Pharmacodynamics</u></p> <ul style="list-style-type: none"> • Drug Liking: <ul style="list-style-type: none"> ○ Mean [SE] scores were significantly lower with oral administration of intact, chewed, and milled Hysingla ER vs.oral hydrocodone solution (63.3 [2.7], intact Hysingla ER; 69.0 [3.0] chewed Hysingla ER; 89.2 [2.4], milled Hysingla ER; 94.0 [1.7], hydrocodone solution, respectively; $P<.015$) ○ Median [Range] scores were significantly lower with oral administration of intact, chewed, and milled Hysingla ER vs.oral hydrocodone solution (58 [50-100], intact Hysingla ER; 93 [50-100], milled Hysingla ER; 66 [50-100], chewed Hysingla ER; 100 [51-100], hydrocodone solution, respectively; $P<.001$) ○ Percent Reduction in Peak Drug Liking Scores (Chewed Hysingla ER vs hydrocodone solution): 20% (n=7), no reduction; 80% (n=28), some reduction; 69% (n=24), ≥30% reduction; 60% (n=21), ≥50% reduction ○ Percent Reduction in Peak Drug Liking Scores (Intact Hysingla ER vs hydrocodone solution): ~17% (n=6), no reduction; ~83% (n=29), some reduction; ~83% (n=29), ≥30% reduction; ~74% (n=26), ≥50% reduction ○ Percent Reduction in Peak Drug Liking Scores (Milled Hysingla ER vs hydrocodone solution): 60% (n = 21), no reduction; 40% (n = 14),some reduction; ~ 17% (n = 6), ≥30% reduction; 9% (n = 3), ≥50% reduction • Take Drug Again: <ul style="list-style-type: none"> ○ Mean [SE] scores were significantly lower with oral administration of intact and chewed Hysingla ER vs.oral hydrocodone solution (34.3 [6.1], intact Hysingla ER; 44.3 [6.9] chewed Hysingla ER; 89.7 [3.6], hydrocodone solution, respectively; $P<.001$) ○ Median [Range] scores were significantly lower with oral administration of intact and chewed Hysingla ER vs.oral hydrocodone solution (24 [0-100], intact Hysingla ER; 55 [0-100] chewed Hysingla ER; 100 [1-100], hydrocodone solution, respectively; $P<.001$)

Study	Study Design	Sample Size	Treatments	Eligibility	Measurements	Results
HYD1013 – Oral Abuse Potential Study (cont'd)						<p><u>Pharmacokinetics</u></p> <ul style="list-style-type: none"> • Mean Cmax: 48.4 ng/mL, intact Hysingla ER; 67.3 ng/ml, chewed Hysingla ER; 81 ng/mL, milled Hysingla ER; 127 ng/mL, hydrocodone solution • Median Tmax: 15.1 hours, intact Hysingla ER; 8.0 hours, chewed Hysingla ER; 1.6 hours, milled Hysingla ER; 1.1 hours, hydrocodone solution Mean AUCt were similar following administration of intact Hysingla ER (886 h*ng/ml), chewed Hysingla ER (913 h*ng/ml), and hydrocodone solution (951 h*ng/ml). Mean AUCt values were lower following milled Hysingla ER (648 h*ng/mL). <p><u>Safety</u></p> <ul style="list-style-type: none"> • Incidence of TEAEs: 69.4%, intact Hysingla ER; 75.0%, chewed Hysingla ER; 94.6%, milled Hysingla ER; 97.4%, hydrocodone solution Most common types of TEAEs (≥5% of subjects: psychiatric disorders; skin and subcutaneous tissue disorders; nervous system disorders; gastrointestinal disorders; general disorders and administration site conditions • Most TEAEs were mild, with the exception of 3 TEAEs of moderate severity (1 episode each of presyncope, sinus bradycardia, and headache in 3 different subjects)

Study	Study Design	Sample Size	Treatments	Eligibility	Measurements	Results
HYD1014 – Intranasal Abuse Potential Study	<p>Single-center, double-blind, randomized, placebo-controlled, active-controlled, 4-period crossover</p> <p>5 phases: screening (screening visit and naloxone challenge), dose selection, qualification, treatment, and follow-up</p>	<p>N=31</p> <p>n=25, completed the study</p>	<ul style="list-style-type: none"> Hysingla ER 60mg tablets Hydrocodone API 60 mg powder Placebo 	<ul style="list-style-type: none"> Adults (ages, 18-55 years) Recreational opioid user with reported IN use ≥ 3 occasions within 12 months prior to screening and taking an opioid dose equivalent to ≥ 40 mg hydrocodone (any route) at least once in the past year Did not meet criteria for addiction Non-dependent on opioids 	<p><u>Pharmacodynamic:</u></p> <p>Primary:</p> <ul style="list-style-type: none"> 'At the Moment Drug Liking' (VAS, Bipolar scale) <p>Secondary:</p> <ul style="list-style-type: none"> 'Take Drug Again' (VAS, Unipolar scale) <p><u>Pharmacokinetic:</u></p> <ul style="list-style-type: none"> Profile compared to hydrocodone API powder <p><u>Safety:</u></p> <ul style="list-style-type: none"> TEAEs 	<ul style="list-style-type: none"> 82% (n=23) of subjects receiving Hysingla ER (n = 28) had incomplete dosing due to granules falling from subjects' nostril compared to no subjects with powdered hydrocodone or placebo <p><u>Pharmacodynamics</u></p> <ul style="list-style-type: none"> Drug Liking (Hysingla ER vs. powdered hydrocodone): <ul style="list-style-type: none"> Mean [SE] scores were significantly lower with IN administration of Hysingla ER coarse and fine vs. powdered hydrocodone (65.4 [3.7], coarse; (66.8 [3.7], fine vs. 90.4 [2.6], respectively; $P < .001$) Median [Range] scores were significantly lower with IN administration of Hysingla ER coarse and fine vs. powdered hydrocodone (56 [50-100], coarse; (61 [50-100], fine vs. 100 [51-100], respectively; $P < .001$) Percent Reduction in Peak Drug Liking Scores (Coarse Hysingla ER vs hydrocodone powder): 20% (n=5), no reduction; 80% (n=20), some reduction; 68% (n=17), $\geq 30\%$ reduction; 64% (n=16), $\geq 50\%$ reduction Percent Reduction in Peak Drug Liking Scores (Fine Hysingla ER vs hydrocodone powder): 20% (n=5), no reduction; 80% (n=20), some reduction; 72% (n=18), $\geq 30\%$ reduction; 64% (n=16), $\geq 50\%$ reduction Take Drug Again (Hysingla ER vs. powdered hydrocodone): <ul style="list-style-type: none"> Mean [SE] scores were significantly lower with IN administration of Hysingla ER coarse and fine vs. powdered hydrocodone (36.4 [8.2], coarse; (40.4 [7.7], fine vs. 85.2 [5.0], respectively; $P < .001$) Median [Range] scores were significantly lower with IN administration of Hysingla ER coarse and fine vs. powdered hydrocodone (14 [0-100], coarse; 50 [0-100], fine vs. 100 [1-100], respectively; $P < .001$) <p><u>Pharmacokinetics</u></p> <ul style="list-style-type: none"> Mean Cmax: 36.5 ng/mL, fine Hysingla ER; 27.5 ng/mL, coarse Hysingla ER vs. 106 ng/mL, hydrocodone powder Median Tmax: 3.1 hour, fine Hysingla ER; 4.1 hours, coarse Hysingla ER vs. 1.6 hours, hydrocodone powder Mean AUC_t and AUC_{inf} were considerably lower with Hysingla ER compared to hydrocodone powder

Study	Study Design	Sample Size	Treatments	Eligibility	Measurements	Results
HYD1014 – Intranasal Abuse Potential Study (cont'd)						<u>Safety</u> <ul style="list-style-type: none"> • Incidence of TEAEs: 78.6%, fine Hysingla ER; 64.3%, coarse Hysingla ER vs. 96.3%, hydrocodone powder vs. 7.4%, placebo • Most common types of TEAEs (≥5% of subjects): psychiatric disorders; skin and subcutaneous tissue disorders; nervous system disorders; respiratory, thoracic, and mediastinal disorders; gastrointestinal disorders; general disorders and administration site conditions
HYD1015 – Survey for Attractiveness for Abuse and Tampering	Non-interventional, interview-based study	N=30	<p>No treatment were administered</p> <p>Subjects were categorized based on tampering preference:</p> <ul style="list-style-type: none"> • Oral administration (crushing, wrapping, ingestion; dissolving/ crushing into oral solution; chewing) • Intravenous administration • Intranasal administration 	<ul style="list-style-type: none"> • Adults (ages, 28-65 years) • Recreational opioid users with experience tampering with and administering prescription formulations by alternative routes of administration 	<ul style="list-style-type: none"> • Series of questions to assess attractiveness of Hysingla ER for abuse and tampering compared to other opioid formulations 	<ul style="list-style-type: none"> • Hysingla ER was deemed the least attractive opioid product • Study population provided suggested methods of potential tampering of Hysingla ER, but concluded that abuse-deterrent characteristics of the formulation will constitute significant deterrents against abuse and tampering

API = Active pharmaceutical ingredient; ER = extended-release; IN = intranasal; TEAEs = treatment-emergent adverse events

6. SUPPORTING INFORMATION

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