CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	October 30, 2014
Reviewer(s):	Danny Gonzalez, Pharm. D., M.S., Risk Management Analyst Division of Risk Management (DRISK) Joan Blair, R.N., M.P.H. Health Communication Analyst DRISK
Team Leader:	Kim Lehrfeld, Pharm. D., BCPS DRISK
Acting Deputy Director:	Reema Mehta, Pharm. D., M.P.H. DRISK
Drug Name(s):	Hysingla ER (hydrocodone bitartrate)
Therapeutic Class:	Opioid agonist
Dosage and Route:	20mg, 30mg, 40mg, 60mg, 80mg, 100mg, and 120mg extended-release oral tablet
Application Type/Number:	NDA 206627
Submission Number:	Sequence No. 0022
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2014-873

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EXECUTIVE SUMMARY

The purpose of this review is to document Division of Risk Management's (DRISK's) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Hysingla ER (hydrocodone bitartrate) extended-release tablets (NDA 206627) and evaluation of Purdue's REMS submission, received April 28, 2014 (Sequence No. 0000) and revised and submitted as an amendment on October 30, 2014 (Sequence No. 0033).

The Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS was originally approved on July 9, 2012 to address the risks of misuse, abuse, overdose and death and REMS modifications were approved August 28, 2012, and April 15, 2013 and August 19, 2014.

As an extended-release Schedule II opioid analgesic, Hysingla ER poses a risk of abuse/misuse, tolerance, dependence and withdrawal syndrome. If approved, Hysingla ER's risks of abuse/misuse, addiction, overdose and death can be mitigated with labeling and a REMS. It is appropriate for it to join the single, shared system ER/LA REMS.

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Division of Risk Management (DRISK) review the proposed risk evaluation and mitigation strategy (REMS) for Hysingla ER (hydrocodone bitartrate), NDA 206627, submitted by Purdue, Inc. on April 28, 2014 (Sequence No. 0000) and revised and submitted as an amendment on October 30, 2014 (Sequence No. 0033). The purpose of this review is to document DRISK's evaluation of the need for a REMS for Hysingla ER and evaluation of the Sponsor's REMS submission on October 30, 2014.

1.1 PRODUCT BACKGROUND

Hysingla ER (hydrocodone bitartrate), is a 24-hour extended-release formulation of hydrocodone. If approved, Hysingla ER will be available as 20, 30, 40, 60, 80, 100, and 120 mg extended-release tablets.

The active ingredient, hydrocodone, is an opioid agonist with the proposed indication 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.

This product contains the abuse deterrent polyethylene oxide (PEO)-based formulation platform which is the (b) (4) excipient in the product that functions as release rate-control, abuse-deterrence, and resistance to alcohol-induced dose dumping. The Sponsor is using (b) (4) The finished tablet is (b) (4) The data from the Sponsor's formulation studies, as described in the Formulation and Process Development document submitted on April 28, 2014, demonstrate sustained release of hydrocodone over a 24-hour period, resistance to increasing the release rate through the physical and/or chemical manipulation of the dosage form, deterrence to intranasal and intravenous abuse, and absence of a higher drug release rate in the presence of alcohol.

While the formulation is abuse-deterrent, abuse of Hysingla ER by these routes is still possible, and therefore, this risk is not eliminated.

Thus, like other extended-release opioid products, Hysingla ER poses a risk of abuse/misuse, addiction, overdose and death. Due to the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release and long-acting (ER/LA) opioid analgesics, ER/LA opioid analgesics are approved under a single shared system (SSS) REMS program.

1.2 REGULATORY HISTORY

On July 9, 2012, the FDA approved a SSS REMS for ER/LA opioid analgesic drug products.[1] The goal of the SSS 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 ER/LA opioid analgesics SSS REMS was approved with the following elements:

- Medication Guide
- Elements to Assure Safe Use
    - Prescriber Training
        - FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (FDA Blueprint)
        - Patient Counseling Document (PCD) on Extended-Release and Long-Acting Opioid Analgesics
        - Letters to DEA-Registered Prescribers
        - Letters to Professional Organizations/Licensing Boards
        - REMS website
- Timetable for Submission of Assessments

On July 10, 2013, Purdue met with the Agency for a Pre-NDA meeting. At this meeting the proposed indication ("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 ") was presented. In addition, the Agency informed the Sponsor that Hysingla ER would be joining the class REMS for ER/LA opioids.

On April 28, 2014, Purdue submitted an NDA 206627 for Hysingla ER as a 505(b)(2) application (Sequence No. 0000) using the approved NDA product Vicoprofen (hydrocodone/ibuprofen) (NDA 020716) as the reference listed drug. The NDA submission for Hysingla ER included a REMS proposal.

[1] Details of the regulatory history, development, and rationale for the design of the REMS and REMS materials of the ER/LA Opioid Analgesic REMS are discussed in the Executive Memorandum, dated July 6, 2012.

On August 5, 2014, Purdue submitted a revised ER/LA REMS document via email based on revised labeling DAAAP provided to them on July 30, 2014.

On October 28, 2014, the Agency provided the Sponsor with an edited version of their REMS document based on the most current draft labelling.

On October 30, 2014, Purdue submitted REMS documents and materials and the REMS supporting document based on the final agreed upon label. These documents are the focus of this review.

1.3 MATERIALS REVIEWED

The following submissions, listed by date received, were reviewed from NDA 206627 for the proposed ER/LA Opioid Analgesics REMS:

- 4/28/2014 Proposed REMS (eCTD Sequence No. 0000)
    - 10/30/2014 Amendment to original NDA (eCTD Sequence No.0033)
- 8/5/2014 Revised REMS, submitted via email

1.4 OTHER MATERIALS INFORMING OUR REVIEW

- Khairuzzman A, Biopharmaceutics Filing Review, May 7, 2014
- Giusto C and Zhang T, Audiology Review, July 22, 2014
- Wei L, Dang Q, and Tsong Y, Statistical Review and Evaluation, June 20, 2014
- Zhou Y and Derr J, Statistical Review and Evaluation, July 28, 2014
- Spaulding J, Clinical Review and Evaluation, July 28, 2014
- Chung-Davies E, OPDP REMS Review, August 16, 2014

2 RESULTS OF REVIEW OF PROPOSED ER/LA OPIOID ANALGESICS RISK EVALUATION AND MITIGATION STRATEGY

2.1 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

2.1.1 Efficacy

2.1.1.1 Efficacy of Hysingla ER for the management of pain

The Sponsor demonstrated the efficacy of Hysingla ER, as required by the Agency, in a single Phase 3, multicenter, double-blind, placebo-controlled, randomized-withdrawal design study (HYD3002). This study was conducted in 588 subjects with moderate to severe chronic low back pain who received 20, 40, 60, 80, and 120mg of Hysingla once daily. Subjects who tolerated and achieved adequate analgesia with Hysingla ER by the end of the open-label run-in period were then randomized to continue on their optimal dose of Hysingla ER or to take placebo for 12 weeks. The primary efficacy endpoint was the weekly mean pain intensity (PI) score during the double-blind period. Subjects who dropped out of the study were allowed to continue submitting data for the full 12 week period of the study.

The Agency has concluded that the primary efficacy results demonstrate that the difference between placebo and Hysingla ER PI scores is statistically significant and superior to placebo. There was statistically less pain at 12 weeks in subjects with moderate to severe [chronic low back pain] treated with Hysingla ER compared to placebo. Efficacy was also supported by several secondary endpoints including: cumulative responder analysis, and subject global impression.″

2.1.1.2 Efficacy of the abuse deterrent properties of Hysingla ER

The efficacy of the abuse deterrent properties of Hysingla ER were evaluated in 2 randomized, double-blind, placebo and active-controlled clinical studies (HYD1013 and HYD1014) in non-dependent recreational opioid drug users. The abuse potential of Hysingla ER in study HYD1013 was investigated by using "Drug Liking" metrics and other visual analog scales as well as pupillometry through oral administration of Hysingla ER 60 mg, either chewed, analytically milled, or intact; and in study HYD1014, through intranasal administration of Hysingla ER 60 mg as fine (processed in an industrial mill) and coarse (processed with a razor blade) particles, for its subjective and physiologic effects compared with hydrocodone active pharmaceutical ingredient (API).

In study HYD1013, the oral abuse potential of chewed Hysingla ER 60 mg tablet and milled Hysingla ER (processed in an industrial mill) 60 mg tablet were compared to intact Hysingla ER 60 mg tablet, hydrocodone API 60 mg solution, and placebo. HYD1013 was a single-center, randomized, double-blind, 5-way crossover study conducted in male and female nondependent recreational drug users with moderate opioid experience, aged 18 to 55 years, to evaluate the oral abuse potential, pharmacodynamics, pharmacokinetic, and safety of Hysingla ER in various dosage forms. This study enrolled 37 healthy subjects total. Mean maximum pharmacodynamics (PD) effect (E_{max}) values for positive PD measures were greatest for the hydrocodone API solution, followed in descending order by milled Hysingla ER, chewed Hysingla ER, intact Hysingla ER, and placebo. Although statistically significant decreases were observed for the two primary endpoints at level of 0.05 for all three Hysingla ER treatments, the milled Hysingla ER treatment was similar to hydrocodone 60 mg solution in some properties of important secondary PD endpoints. Relatively large reductions in abuse potential were observed with intact and chewed Hysingla ER while the differences in abuse potential were less with the milled Hysingla ER treatment. Overall, the results of this study suggest that when Hysingla ER is administered by the oral route as intact or chewed, it has lower oral abuse potential than hydrocodone 60 mg solution.

In study HYD1014, the intranasal abuse potential of fine and coarse particle size Hysingla ER 60 mg (produced using an industrial mill and razor blade, respectively) were compared to hydrocodone API powder (60 mg) and placebo. Study HYD1014 was a single-center, randomized, double-blind, placebo-controlled, 4-way crossover study conducted in male and female non-dependent recreational opioid users with moderate opioid experience and a history of intranasal abuse, aged 18 to 55 years, to evaluate the intranasal abuse potential, PD, pharmacokinetic (PK), and safety profile of intranasally administered Hysingla ER (fine and coarse particle size) compared with hydrocodone

API powder and placebo. This study enrolled 28 subjects total. Mean E_{max} values for positive PD measures were greatest for 60 mg hydrocodone powder, followed by the fine and coarse particle size of Hysingla ER 60 mg treatments and placebo. The results of the study suggest that Hysingla ER has lower intranasal abuse potential than non-abuse-deterrent hydrocodone 60 mg.

The limitations of these two studies include dropouts and the lack of statistically significant differences for some secondary endpoints. The missing rates of subjects from the two studies are high, 13% for Study HYD1013 and 22% for Study HYD1014. The effects of this missing data was not considered in the statistical analyses, which could change the conclusion under worst scenario in the abuse-deterrence effect of Hysingla ER.

The Agency's statistics reviewers, Wei Liu, Ph.D., Dang Qianyu, Ph.D., and Tsong Yi, Ph.D., concluded for HYD1013 that Hysingla ER demonstrated significantly lower subjective effects compared to hydrocodone API solution, when administered by the oral route as intact or chewed. The reviewer noted that Hysingla ER 60mg milled and hydrocodone 60mg solution had similar drug abuse potential due to findings from secondary endpoints. The conclusion by the Agency for HYD1014 was that the Hysingla ER formulation demonstrated significantly lower subjective and physiologic effects and greater intranasal irritation when compared to hydrocodone API powder administered intranasally. Thus, Hysingla ER has a lower overall abuse potential compared to the test group in both studies. The clinical reviewer, Jaqueline Spaulding, M.D., agreed with this conclusion. She stated that the "preliminary findings of CSS demonstrate that Hysingla ER has abuse-deterrent features that may mitigate abuse by the intravenous and nasal routes."

2.1.2 Safety Concerns

The data presented by the Sponsor consisted of several clinical trials assessing abuse deterrence (Studies HYD1013 and HYD1014), one Phase 3 efficacy trial (HYD3002), and one Phase 3 long-term safety study (HYD3003). The safety profile of Hysingla ER was assessed in 1,827 healthy subjects and /or patients with chronic pain of nonmalignant and/or non-neuropathic origin enrolled in HYD3002 and HYD 3003. In addition, the potential risk of ototoxicity was examined in a pooled audiology safety population using data from HYD3002 and HYD3003. The results are summarized in this section.

2.1.2.1 Overall Safety

There were a total of seven deaths observed in HYD3002 and HYD3003, six of which occurred in Hysingla-treated patients in the clinical development program. The death of one Hysingla-treated subject was possibly related to hydrocodone use (acute hydrocodone, cyclobenzaprine and citalopram toxicity). The clinical reviewer also concluded that Hysingla ER use may have contributed to a second case of death due to hypoxia.

The overall incidence of nonfatal serious adverse events (SAEs) was low for both the Hysingla ER and placebo groups (1% for each group) in study HYD3002. No

unexpected, nonfatal SAEs were noted by the Agency clinical reviewer. One case of gastroparesis and one case of proximal esophageal obstruction were reported and may be possibly related to Hysingla ER use. In addition, the overall incidence of discontinuation of Hysingla ER was 17%. The clinical reviewer noted 7 cases of mild, non-fatal QT-prolongation with the 120 mg Hysingla ER in the pooled chronic pain studies. A recommendation for language describing these findings in the label has been made by the clinical reviewer.

The clinical reviewer also assessed the most common adverse events (AEs) in HYD3002. Overall, Hysingla ER-treated subjects experienced more treatment emergent AEs (TEAEs) than placebo subjects. The most commonly reported AEs in HYD3002 for Hysingla ER-treated subjects during the double-blind period were: nausea (8%), vomiting (6%), constipation (3%), dizziness (3%), insomnia (3%), upper respiratory infection (2%) and influenza (2%). The Agency clinical reviewer concluded that the common adverse events identified were usual for the opioid drug class. In addition, the incidence of subjects with shifts in lab values was considered small and not clinically meaningful.

2.1.2.2 Auditory Safety

The review of ototoxicity was initiated by reports in the literature of hearing loss associated with the use of hydrocodone usually with a hydrocodone/acetaminophen formulation. Reviewers note that there is currently no consensus on the extent of hydrocodone's risk for ototoxic effects on hearing and vestibular function. Dr. Cherish Giusto of DAAAP recommended that the Sponsor conduct an audiology assessment at the Pre-NDA meeting on July 10, 2013. The audiology review consisted of audiology data and hearing impairment and vestibular disorder AE data from the HYD3002 and HYD3003 which were pooled. A total of 1,827 subjects were examined in this analysis.

The Agency clinical evaluator concluded that "the audiology data provides a reasonable assurance that there is not a significantly increased risk for hearing impairment or vestibular disorders with the use of Hysingla ER in the doses and time periods investigated during these Phase 3 trials from a clinical audiology perspective." In addition, the clinical reviewer recommended inclusion of the audiology findings in the label.

2.2 DRISK RATIONALE FOR A REMS FOR HYSINGLA ER

All opioid formulations have the potential for misuse, abuse, overdose and death. The Agency believes that ER/LA opioids pose a higher risk for the aforementioned safety concerns than immediate-release opioid formulations because they contain more opioid per tablet, capsule or patch and either stay in the body longer or are released into the body over longer periods of time. Additionally, when the extended-release features of some of these formulations are manipulated, either deliberately or inadvertently, these products deliver high doses of opioid in an immediate-release manner, potentially resulting in overdose or death. Therefore, the ER/LA Opioid Analgesic REMS was developed and approved to mitigate these risks.

Hysingla includes an abuse-deterrent formulation that may mitigate the risk of intravenous or intranasal abuse; in addition, intact and chewed tablets had some abuse

deterrent effect. However, Hysingla ER contains hydrocodone in doses which, when further manipulated (i.e. milled) and taken orally, could potentially result in overdose or death. Therefore the risks of abuse, misuse, addiction, unintentional overdose, and death remain despite the abuse-deterrent formulation in this opioid product. If approved Hysingla ER's risks of abuse, misuse, overdose and death can be mitigated with labeling and a REMS. It is appropriate for it to join the single, shared system ER/LA REMS.

2.3 REVIEW OF PROPOSED REMS FOR HYSINGLA ER

2.3.1 FDA Blueprint

The focus of the review of the proposed REMS for Hysingla ER was to incorporate Hysingla ER into the approved ER/LA REMS. The version below incorporates the Office of Prescription and Drug Promotion's (OPDP) recommendations which DRISK accepted. Any OPDP comments which were not accepted are noted below in section 2.3.2.

Hysingla ER	Hydrocodone bitartrate Extended-release tablets, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg
Dosing Interval	Every 24 hours (once-daily)
Key Instructions	▪ Opioid-naïve patients: initiate treatment with 20 mg orally once daily. During titration, adjust the dose in increments of 10 mg to 20 mg every 3 to 5 days until adequate analgesia is achieved. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Consider use of an alternative analgesic in patients who have difficulty swallowing or have underlying gastrointestinal disorders that may predispose them to obstruction. ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Use 1/2 of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation, when administering Hysingla ER to patients with severe hepatic impairment or patients with moderate to severe renal impairment.
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone exposure ▪ Concomitant use of Hysingla ER with strong laxatives (e.g., Lactulose) that rapidly increase GI motility may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. ▪ The use of MAO inhibitors or tricyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER.
Use in Opioid-Tolerant Patients	▪ A single dose of Hysingla ER greater than or equal to 80 mg is only for use in opioid tolerant patients.

Product-Specific Safety Concerns	▪ Use with caution in patients with difficulty swallowing the tablet or underlying gastrointestinal disorders that may predispose patients to obstruction. ▪ Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER. ▪ In nursing mothers, discontinue nursing or discontinue drug. ▪ QTc prolongation has been observed with Hysingla ER following doses of 160 mg. Avoid use in patients with congenital long QT syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong QTc interval. In patients who develop QTc prolongation, consider reducing the dose.
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid

Reviewer Comment: The Sponsor's proposed revisions to align the Hysingla ER product specific information in the ER/LA REMS Blueprint with the final Hysingla ER label were submitted to the Agency on October 30, 2014. All revisions above are acceptable.

2.3.2 OPDP Comments

DRISK did not accept the following OPDP comments. The reason is noted after each comment.

- Prescriber Letters #1 and #2, Professional Organization/Licensing Board Letters #1 and 2

  We note that these letters state (emphasis added), "Extended-release and long-acting (ER/LA) opioid analgesics are approved for the **management of chronic moderate-to-severe pain** in the U.S...." We recommend revising to language that is consistent with the currently approved ER/LA products. For example, we would not object to revising in a manner consistent with Prescriber letter #3 (i.e., "ER/LA opioid analgesics are used 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...")

- Prescriber Letter #1 and Professional Organization/Licensing Board Letter #1

  Please consider adding "hydrocodone" to the following, if appropriate:,

  "The branded and generic drug products subject to this REMS include *all*:
  - extended-release, oral-dosage forms containing
    - hydromorphone,
    - morphine,
    - oxycodone,
    - oxymorphone, or

- tapentadol; …"

Reviewer Comment: DRISK did not accept changes to the letters noted above as they are no longer being distributed. Only Prescriber Letter #3 has been revised in previous REMS modifications as it the only one being distributed.

- ER/LA Opioid Analgesic REMS SSS website (www.ER-LA-opioidREMS.com)

  We note the presence of a yellow button with the text "Looking for Accredited REMS CME/CE? Click Here" (we note that this link currently exists on the active shared REMS website). This button links to a list of available REMS CME/CE programs. As previously discussed on May 7, 2014, we are concerned that it may appear that the Agency is endorsing these sites. Therefore, please ensure that the linked content is appropriate and that the FDA is comfortable with the content of each CE program listed on the CME/CE site. Please also check with the Office of Communications to see if they have any policies on linking to external sites.

  Reviewer Comment: DRISK did not accept this recommendation as this has been discussed internally in recent months, including input from Office of Center Director (OCD). The CME/CE programs are part of the elements to assure safe use (ETASU) associated with this REMS, so sharing information about these programs is appropriate. The FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics provides clear guidance and content for the CME/CE programs to ensure accuracy and completeness of information shared in each CME/CE program.

3 DISCUSSION

DAAAP recommended approval of Hysingla ER (20, 30, 40, 60, 80, 100 mg and 120 mg) based on demonstrated efficacy and a safety profile which is consistent with other ER opioid analgesics.

The DAAAP clinical reviewer summarized the Risk/Benefit of Hysingla ER as follows:

> "As an extended-release Schedule II opioid, the risks (including overdose, misuse and abuse) and adverse events associated with the use of Hysingla ER appear to be manageable with labeling and the REMS and should not preclude approval. It appears from preliminary findings that Hysingla ER may have potential benefit in the reduction of abuse related via the intranasal and/or intravenous/injection routes."

DRISK agrees that Hysingla ER poses a risk of abuse, misuse, tolerance, dependence and withdrawal syndrome despite the abuse-deterrent formulation. If this product is approved, Hysingla ER's risks can be mitigated with labeling and a REMS.

DRISK recommends the addition of Hysingla ER to the approved ER/LA Opioid Analgesics REMS.

4 CONCLUSION

In conclusion, the amended ER/LA Opioid Analgesic REMS to incorporate the approval for Hysingla ER (hydrocodone bitartrate), received April 28, 2014, and amended on October 30, 2014, contains the appropriate and agreed upon revisions on the REMS components as stipulated by the Agency. The REMS Supporting Document outlines the information and content that the applicant will use to assess the effectiveness of the ER/LA Opioid Analgesics REMS in achieving the goals. The timetable for submission of assessments of the REMS and the REMS assessment plan will remain the same as that approved on July 9, 2012.

Therefore, the modified ER/LA Opioid Analgesics REMS is acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management.

5 RECOMMENDATIONS

The OSE, DRISK recommends approval of the modified ER/LA Opioid Analgesics REMS submitted October 30, 2014 and appended to this review.

The Approval Letter should reference the REMS assessment plan included with the July 9, 2012 REMS approval.

A REMS Modification Notification Letter should be sent to the Sponsors covered under the ER/LA Opioid Analgesics REMS to include the revised information.

ATTACHMENTS

Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS

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/s/

DANNY S GONZALEZ
11/04/2014

REEMA J MEHTA
11/06/2014

Risk Evaluation and Mitigation Strategy (REMS) Memorandum - Correction

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Anesthesia, Analgesia, and Rheumatology Products

NDA/BLA #s:	206627
Products:	Hysingla ER (hydrocodone bitartrate extended-release oral tablets)
SPONSOR:	Purdue Pharma
FROM:	Judith A. Racoosin, MD, MPH
DATE:	July 28, 2014

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

The use of prescription opioid drug products has nearly doubled in the past decade, and with that increase in use, there has been a concordant rise in the abuse and misuse of prescription opioid drug products, resulting in increased reports of serious adverse outcomes such as death, overdose and addiction. The spectrum of behaviors contributing to these problems include inappropriate prescribing such as improper dosing, patient selection, and patient counseling, as well as inappropriate patient behaviors such as improper use, storage, and disposal of prescription opioid products. Extended-release and long-acting (ER/LA) opioid analgesic formulations pose unique risks to patients due to their pharmacokinetic properties, duration of use, and the amount of active ingredient contained in the drug product in comparison to their immediate-release opioid counterparts. The amount of opioid contained in an extended-release tablet can be much more than the amount of opioid contained in an immediate-release tablet because extended-release tablets are designed to release the opioid over a longer period of time. Long-acting opioids can take many hours to be cleared out of the body. Improper use of any opioid can result in serious side effects including overdose and death, and this risk is magnified with ER/LA opioid analgesics. Because it is important that these products are prescribed and used safely among the intended population, FDA has determined that a

REMS is necessary to address the issues of unintentional overdose, addiction, and death resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics.

After consultations with the Office of New Drugs, the Office of Surveillance and Epidemiology, and members of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management committees in July 2010, we have determined that a class-wide REMS is necessary to ensure that the benefits of ER/LA opioid analgesics outweigh their risks. In reaching this determination, we considered the following:

A. Approximately 24-33% of Americans suffer from chronic, non-cancer pain such as arthritis, lower back pain, and fibromyalgia. In year 2009, an estimated 3.8 million unique patients received a dispensed prescription for an ER/LA opioid analgesic product from outpatient retail pharmacies.

B. ER/LA opioid analgesic products are 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. The majority of use for ER/LA opioid analgesic products is associated with "diseases of the musculoskeletal system and connective tissue" (ICD-9 codes 710-739) which include chronic pain conditions such as arthritis and back pain.

C. ER/LA opioid analgesic products are an important part of the armamentarium of drugs used to treat chronic pain. Some advantages of these types of formulations over the short-acting opioids are: 1) less frequent dosing; 2) better control of pain achieved through more stable drug levels; 3) improved patient compliance; and 4) fewer opioid side-effects. It is important to note that patients respond differently to different opioid drug substances and some patients develop tolerance to an opioid after chronic exposure. Physicians use a technique known as "opioid rotation" whereby they switch patients from one opioid to another if patients develop tolerance and cannot get adequate pain relief from any given opioid. Therefore, having different opioid analgesics available as modified-release formulations provides important pain relief options for these patients.

D. The expected duration of treatment with ER/LA opioid analgesics will be from weeks to months or longer. Data from outpatient prescription claims databases suggest that ER/LA opioid analgesics are typically prescribed for approximately 30-days at a time, whereas immediate-release opioid products are prescribed for 13-21 days at a time.

E. ER/LA opioid analgesic products have distinguished themselves among the class of opioid pain medications with their disproportionately high rate of serious adverse outcomes including deaths, unintentional overdose, and addiction, in comparison to immediate-release opioid analgesic products. The goal of the REMS would be to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to these medications. Serious adverse outcomes of concern including addiction, unintentional overdose, and death have been reported for each of the ER/LA opioid analgesics.

F. ER/LA opioid analgesic products contain one of the following active drug substances such as oxycodone, morphine, fentanyl, buprenorphine, methadone, and hydromorphone; none of these active drug substances are new molecular entities. Hydrocodone, the extended release opioid in Hysingla ER, is also not a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that ER/LA opioid analgesic products pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of ER/LA opioid analgesic products. FDA has determined that ER/LA opioid analgesics are products that have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, ER/LA opioid analgesic products for which patient labeling could help prevent serious adverse events related to the use of these products.

The elements of the REMS will be a Medication Guide, Elements to Assure Safe Use, and a timetable for submission of assessments of the REMS.

The ER/LA opioid analgesic single shared system REMS was approved July 9, 2012. Upon approval, Hysingla ER will be joining this single shared system REMS.

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/s/

JUDITH A RACOOSIN
07/30/2014