CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207975Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

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

NDA #:	207975
Product:	Vantrela ER (hydrocodone bitartrate extended-release tablets)
SPONSOR:	Teva Branded Pharmaceutical Products R&D, Inc.
FROM:	Judith A. Racoosin, MD, MPH
DATE:	January 11, 2017

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 addiction, unintentional overdose, and death. 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 addiction, unintentional overdose, 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 addiction, unintentional overdose, and death, 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: morphine, oxycodone, hydrocodone, fentanyl, buprenorphine, methadone, hydromorphone, oxymorphone, and tapentadol; none of these active drug substances are new molecular entities.

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 on July 9, 2012. Upon approval, Vantrela ER will be joining this single shared system REMS.

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/s/

JUDITH A RACOOSIN
01/11/2017

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

FINAL RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	December 22, 2016
Reviewer/Team Leader:	Kim Lehrfeld, Pharm. D. Division of Risk Management (DRISK)
Director:	Cynthia LaCivita, Pharm. D. DRISK
Subject:	Review of proposed REMS
Drug Name(s):	Vantrela (hydrocodone bitartrate) extended-release (ER) tablets
Therapeutic Class:	Opioid agonist
Dosage and Route:	15 mg, 30 mg, 45 mg, 60 mg, and 90 mg abuse-deterrent, extended-release oral tablets
Application Type/Number:	NDA 207975
Submission Number:	ORIG-1
Applicant/sponsor:	Teva Branded Pharmaceutical Products R and D, Inc.
OSE RCM #:	2014-2070; 2014-2514

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EXECUTIVE SUMMARY

The purpose of this review is to document the Division of Risk Management's (DRISK's) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Vantrela (hydrocodone bitartrate) extended-release (ER) tablets (NDA 207975) received from Teva Branded Pharmaceutical Products R and D, Inc. (Teva) on September 30, 2014 (Sequence No. 0000) and amended on December 23, 2014 (Sequence No. 0001), July 1, 2015 (Sequence No. 0016), July 22, 2015 (Sequence No. 0021), and December 19, 2016 (Sequence No. 0042).

If approved, a REMS will be necessary to ensure the benefits outweigh Vantrela ER's risks of abuse/misuse, addiction, overdose and death.. DRISK recommends Teva be required to join the single, shared system Extended-Release/Long-Acting Opioid Analgesic REMS (ER/LA REMS) for Vantrela ER.[1] DRISK agrees with the Sponsor's proposed REMS for Vantrela ERtablets and recommends approval of the proposed REMS.

1 INTRODUCTION

The purpose of this review is to document DRISK's evaluation of the need for a REMS for Vantrela (hydrocodone bitartrate) ER tablets (NDA 207975) received from Teva on September 30, 2014 (Sequence No. 0000) and amended on December 23, 2014 (Sequence No. 0001), July 1, 2015 (Sequence No. 0016), July 22, 2015 (Sequence No. 0021), and December 19, 2016 (Sequence No. 0042). The amended NDA submission for Vantrela ER included a proposed REMS document, including appended materials, and REMS supporting document based on the Extended-Release/Long-Acting Opioid Analgesic REMS (ER/LA REMS), approved September 30, 2016.

1.1 PRODUCT BACKGROUND

Hydrocodone bitartrate is a semi-synthetic opioid that is widely used for the relief of pain. Until recently, hydrocodone was available in the United States for the treatment of pain only in immediate-release (IR) products that also included other analgesics such as acetaminophen or ibuprofen. These combination drugs can limit the use of hydrocodone to treat pain when the dosage of either acetaminophen or ibuprofen is not therapeutically appropriate or useful. A single-agent, extended-release hydrocodone product (Zohydro) was approved by the Agency on October 25, 2013 for opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate; however, Zohydro does not have abuse-deterrent (AD) properties. On November 20, 2014, Hysingla ER, the first single-agent, extended-release hydrocodone bitartrate product with abuse deterrent properties, was approved.

Vantrela ER is an opioid agonist product composed of hydrocodone bitartrate in an extended-release tablet with AD properties. The basis of the rationale for the development of Vantrela ER was to provide an AD formulation of extended-release

[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.

hydrocodone which maintains the benefits of an opioid agonist. Vantrela ER tablets are formulated to maintain extended-release properties despite consumption with alcohol, unintentional manipulation, or intentional manipulation for purpose of abuse.

Teva is seeking approval for the following dosage strengths of Vantrela ER: 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg. The Vantrela ER tablets are formulated to deliver the active ingredient over 12 hours. Vantrela ER's proposed indication is 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 proposed indication for Vantrela ER is consistent with the products in the single shared system (SSS) REMS for extended-release/long-acting (ER/LA) opioid analgesic drug products.

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.[2] 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

1.2 REGULATORY HISTORY

September 30, 2014: The Sponsor submitted NDA 207975 that included the ER/LA REMS document, REMS appended materials and the supporting document. The Sponsor revised the FDA Blueprint to include product-specific information for Vantrela ER.

November 20, 2014: The Agency approved Hysingla ER (hydrocodone bitartrate) NDA 206627, as part of the ER/LA REMS.

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[2] 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.

December 23, 2014: The Sponsor submitted an amendment to NDA 207975 that included the prescribing information, ER/LA REMS document, REMS appended materials and the supporting document. This submission included revisions to the product-specific information for Vantrela ER in the FDA Blueprint based on the November 20, 2014 version of the ER/LA REMS.

December 29, 2014: The Agency approved intermediate strengths of fentanyl transdermal systems ANDA 76258, as part of the ER/LA REMS.

April 2, 2015: The Agency approved revised prescribing information for Dolophine NDA 06134, which impacted the FDA Blueprint of the ER/LA REMS.

June 26, 2015: The Agency approved a revised version of the ER/LA REMS which included product specific information for Hysingla ER, titration information for Dolophine, and intermediate strengths of fentanyl transdermal systems.

July 1, 2015: The Sponsor submitted an amendment to NDA 207975 which included a revised FDA Blueprint based on the June 26, 2015 ER/LA REMS. The FDA Blueprint was the only ER/LA REMS material submitted and included product-specific information for Vantrela ER.

July 22, 2015: The Sponsor submitted an amendment to NDA 207975 which included the ER/LA REMS document, REMS appended materials and the REMS supporting document which based on the ER/LA REMS approved on June 26, 2015.

August 13, 2015: The Agency approved a REMS Modification for the ER/LA REMS for OxyContin (oxycodone hydrochloride) NDA 22272, which included an updated pediatric indication and titration information.[3]

October 2, 2015: The Agency approved Morphabond (morphine sulfate extended release tablet) NDA 206544, as part of the ER/LA REMS.[4]

October 23, 2015: The Agency approved Belbuca (buprenorphine buccal film) NDA 207932, as part of the ER/LA REMS.[5]

November 13, 2015: The Agency provided comments to the Sponsor on the proposed ER/LA REMS for Vantrela ER.[6]

June 7, 2016: The Anesthetic and Analgesic Drug Products Advisory Committee (AC) met to discuss the application for NDA 207975. The AC voted (14 for approval, 3 against approval) that Vantrela ER should be approved for marketing in the United States. The AC voted that the product should be labeled as an abuse-deterrent product by oral and nasal route of abuse (14 Yes, 3 No) and by the intravenous route of abuse (16 Yes, 1 No)

[3] Approval letter for OxyContin (oxycodone hydrochloride extended release tablet) NDA 22272, dated August 13, 2015.

[4] Approval letter for Morphabond (morphine sulfate extended release tablet) NDA 206544, dated October 2, 2015.

[5] Approval letter for Belbuca (buprenorphine buccal film) NDA 207932, dated October 23, 2015.

September 30, 2016: The Agency approved a class-wide ER/LA REMS modification which included changes made to the ER/LA Opioid REMS based on the relocation of the product specific information to the static link.

December 16, 2016: The Agency provided guidance to the Sponsor that they must submit the REMS approved by the Agency on September 30, 2016. In addition, they must submit a revised Vantrela ER product specific ERLA REMS Blueprint section based on the agreed upon PI. If approved, this section will be incorporated into the ERLA REMS Blueprint that is now located at a static link on the FDA website.

December 19, 2016: The Sponsor amended the submission to include a revised ER/LA REMS document, REMS appended materials, and the REMS supporting document, which was the ER/LA REMS approved on September 30, 2016. Additionally, the Sponsor submitted a document with Vantrela ERproduct specific information for the ERLA REMS Blueprint. This submission is the subject of this review.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed fro NDA 207975 for the proposed ER/LA Opioid REMS:

- Teva Branded Pharmaceutical Products R and D, Inc. New Drug Application 207975, September 30, 2014 (ORIG-1; eCTD Sequence No. 0000).
    - Amendment received December 23, 2014 (eCTD Sequence No. 0001).
    - Amendment received July 1, 2015 (eCTD Sequence No. 0016).
    - Amendment received July 22, 2015 (eCTD Sequence No. 0021).
    - Amendment received December 19, 2016 (eCTD Sequence No. 0042)

2.2 MATERIALS INFORMING OUR REVIEW

The following is a list of materials that were used to inform this review:

- FDA revised, Draft Prescribing Information for Vantrela ER.
- Extended-Release and Long-Acting Opioid Analgesics REMS. Approved on September 30, 2016.
- Levin R. Clinical Review and Evaluation for Vantrela ER, December 18, 2015.
- Bonson K. Controlled Substance Staff Review for Vantrela ER, September 28, 2015.
- Zhang T. Audiology Review for Vantrela ER, September 18, 2015.
- Walker M. Office of Prescription Drug Promotion /Patient Labeling Review Team Review for Vantrela ER, April 27, 2016.
- Gonzalez D. DRISK REMS Review for Vantrela ER, dated November 13, 2015.

3 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

3.1 SUMMARY OF EFFICACY[7]

The efficacy of Vantrela ER from 2 placebo-controlled Phase 3 clinical studies (Study C33237/3079 (3079) and and 3103) were submitted to support the Sponsor's efficacy claim. However, Study 3079 did not meet primary endpoints and was not considered supportive by the Agency.

3.1.1 Efficacy of Vantrela ER for the management of pain

There were 2 Phase 3 efficacy studies conducted to support this submission, Study 3079 and Study 3103.

Study 3079 was a double-blind, placebo-controlled study in patients with moderate to severe pain associated with osteoarthritis or low back pain who required opioid treatment for an extended period of time. The primary efficacy endpoint was the change from baseline average pain intensity (API) scores at week 12. Study 3079 failed to demonstrate a statistically significant treatment effect and will not be discussed further.

Study 3103 randomized 370 total subjects with 191 in the Vantrela ER group (doses = 30 mg, 45 mg, 60 mg, and 90 mg) and 179 in the placebo group. The primary efficacy endpoint was the change from baseline worst pain intensity (WPI) scores at week 12. The secondary endpoints included: (1) change from baseline of daily API scores at week 12; (2) time to loss of efficacy defined as discontinuation of study drug due to lack of efficacy or the start of excessive rescue medication; (3) percentage of patients with both a 30% or greater in crease in API score from baseline to week 12 and an API score of 5 or higher at the final on-treatment visit; and (4) change from baseline to the final on-treatment visit.

In Study 3103, the Sponsor's analysis of the change from baseline in the weekly average of daily WPI scores at week 12 of Vantrela ER compared to placebo-treated patients demonstrated a statistically significant lower increase from baseline (treatment difference of 0.63 [95% CI: 0.26, 1.00]; $p < 0.001$). Baseline WPI scores were similar for the Vantrela ER and placebo treatment groups (4.45 and 4.47 respectively), and mean scores at week 12 were 4.52 for the Vantrela ER group and 5.18 for the placebo group. The weekly averages of WPI scores remained relatively steady through 12 weeks of treatment for the Vantrela ER group while they increased for the placebo group. Of note, patients in the Vantrela ER group maintained pain improvement at all time points measured.

3.1.2 Efficacy of the abuse deterrent properties of Vantrela ER

Vantrela ER tablet used a (b) (4) This formulation is intended to result in abuse deterrent properties.

Teva conducted Category 1 laboratory manipulation studies, Category 2 pharmacokinetic studies, and Category 3 abuse potential studies to evaluate the efficacy of the AD properties for Vantrela ER.

[7] Levin R. Clinical Review and Evaluation Presentation for Vantrela, December 18, 2015

Dr. Katherine Bonson from the Controlled Substance Staff recommended that Vantrela ER should be allowed a label claim that it has abuse deterrence with regard to oral and intranasal abuse of manipulated tablets. In addition, Vantrela ER has physical and chemical properties that are expected to deter intravenous abuse since after extraction attemps, the mixtures are difficult to filter and pass through a needle.

3.2 SUMMARY OF SAFETY

The primary evaluation of safety in patients is based on the 2 Phase 3 studies (Study 3079 and 3103) and 2 additional open-label, long-term safety studies (3080 and 3104). The integrated safety analysis set of data consisted of all patients (n = 1176) who took at least 1 dose of Vantrela ER in Studies 3079, 3080, 3103, and 3104.

The Sponsor's analysis of the safety set revealed that of all patients enrolled in Phase 3 trials and received at least 1 dose of Vantrela ER, 73% (n = 864) of subjects reported at least 1 adverse event (AE). AEs reported by ≥ 5% of patients were constipation (276 [23%] patients), nausea (272 [23%] patients), headache (144 [12%] patients), somnolence (122 [10%] patient), vomiting (122 [10%] patients), dizziness (79 [7%] patients), pruritus (70 [6%] patients), fatigue (61 [5%] patients), and diarrhea (59 [5%] patients), which are all known class effects. For the safety set (n = 1176), 18% (n = 214) patients reported at least 1 AE causing discontinuation from the study. AEs causing discontinuation reported by more than 2% of patients were nausea (64 [5%] patients) and vomiting (32 [3%] patients). These AEs are known class effects.

Two deaths were reported in Study 3080 (Phase 3 study) in the Vantrela ER group. One cause of death was reported as unknown, however the patient was in hospice due to cancer. The second death was due to cardiac arrest secondary to hyperkalemia. Both deaths were not considered to be related to Vantrela ER by the investigator. In addition, one patient died of an unknown cause during the screening period in Study 3103.

The incidence of serious AEs was low and similar in the hydrocodone ER and placebo groups. Across the safety analysis set, 48 (4%) patients reported at least 1 serious AE. The treatment-related serious AEs were pancreatitis (2 patients), chest pain (1 patient), dyspnea (1 patient), respiratory arrest (1 patient), and accidental overdose (1 patient). A similar proportion of patients in the hydrocodone ER (6 [2%] patients) and placebo (6 [2%] patients) groups experienced serious AEs during the post-titration treatment period of the double blind studies (Studies 3079 and 3103). Pancreatitis was the only serious AE reported by more than 1 patient in the hydrocodone ER group (2 [<1%] patients); both events were considered by the investigator to be related to study drug treatment.

Of the 1176 patients who were enrolled in the Phase 3 studies and received at least 1 dose of study drug, 120 (10%) patients reported at least 1 AE that was severe. The top 10 severe AEs reported by more than 1 patient were constipation (13 [1%] patients), nausea (9 [<1%] patients), vomiting (8 [<1%] patients), back pain (6 [<1%] patients), headache(6 [<1%] patients), diarrhea (5 [<1%] patients), muscle spasms (4 [<1%] patients), osteoarthritis (3 [<1%] patients), somnolence (3 [<1%] patients), drug

withdrawal syndrome (3 [<1%] patients). These AEs are either known class effects or are related to the originally reported inclusion criteria for the study (i.e., back pain).

Effects of Vantrela ER on Hearing Loss

Hearing loss is considered an AE associated with hydrocodone and is usually observed with a hydrocodone/acetaminophen combinations. The agency ototoxicity reviewer reported that there is no clear consensus on the extent of hydrocodone's risk for ototoxic effects on hearing and vestibular function.[8] However, there were <1% (n = 3) in the Vantrela ER group and 2% (n = 5) in the placebo group reporting hearing loss during the double-blind studies. The events in the Vantrela ER group were considered treatment related by the investigators. The Sponsor concluded that no trends were observed for hearing loss in either placebo or Vantrela ER.

Since progressive hearing loss has been associated with the abuse of hydrocodone/acetaminophen combination products, and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, the FDA requested that audiometry evaluations be performed. The Sponsor submitted the audiometry findings and individual clinically significant hearing changes for two clinical studies (3103 and 3079). The ototoxicity reviewer found that the number of patients who had clinically significant changes in hearing from baseline to final assessment in both open-label titration period and double-blind study period were comparable between the hydrocodone and placebo treatment groups. The ototoxicity reviewer found no clinically meaningful differences were seen between the hydrocodone and placebo treatment groups. The ototoxicity reviewer had the following conclusion:

> *There is no significant signal of acute decrements in hearing or vestibular function in the population studied, during the time course of the study, and under the dosage conditions studied.*[12]

Thus, the risk of otoxocity with Vantrela ER is comparable to the risk of otoxocity with placebo.

4 RATIONALE FOR A REMS FOR VANTRELA ER

DRISK agrees with the Sponsor that a REMS is needed to ensure that the benefits outweigh the risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse for Vantrela ER. While all opioid formulations have the potential for these risks, based on currently available data, the Agency believes that ER/LA opioids pose a higher risk for the aforementioned safety concerns than IR 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 IR manner, potentially resulting in overdose

[8] Zhang T. Audiology Review for Vantrela, September 18, 2015.

or death. Therefore, the ER/LA REMS was developed and approved to mitigate these risks.

Vantrela ER includes an AD formulation that may mitigate the risk of oral or intranasal abuse compared to non-AD opioid products. However, Vantrela ER contains hydrocodone in doses which could potentially result in overdose or death due to the high amounts of hydrocodone. Therefore the risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse remain despite the abuse-deterrent formulation in this opioid product.

If approved, Vantrela ER's risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse will be mitigated with labeling and a REMS. As an ER opioid, the class-wide ER/LA REMS is necessary and appropriate for this product to mitigate the risks of overdose, abuse, misuse, and addiction and to maintain a favorable risk-benefit profile for the product. Thus, it is appropriate for Vantrela ER to join the single, shared system ER/LA REMS.

5 RESULTS OF REVIEW OF THE PROPOSED REMS FOR VANTRELA

The Sponsor proposed to incorporate Vantrela ER into the approved ER/LA REMS. The only ER/LA REMS material affected by the addition of Vantrela ER is the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (FDA Blueprint).

The Office of Prescription Drug Promotion (OPDP) was consulted on July 28, 2015 to review the product-specific information for Vantrela ER in the ER/LA REMS Blueprint. OPDP received the Vantrela ER product-specific information from DRISK on December 13, 2016. Koung Lee, OPDP reviewer submitted his review to DRISK on December 13, 2016 and his review was entered into DARRTS on December 13, 2016. OPDP did not have any comments regarding proposed revisions to the Vantrela ER product-specific information in the ER/LA REMS Blueprint.

DRISK reviewed the Sponsor's proposed REMS, submitted on December 19, 2016. The following refers to the submission received on December 19, 2016.

5.1 REMS DOCUMENT

The Sponsor's proposed REMS document, received December 19, 2016 has no additional changes; therefore, DRISK finds it acceptable.

5.2 MEDICATION GUIDE

The Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) reviewed the Sponsor's proposed Vantrela ER Medication Guide under separate cover and has communicated their recommendations to the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). OPDP/PLRT has found the MG submission to be acceptable with their recommended changes.[9]

[9] Walker M, Patient Labeling Review for Vantrela ER, dated April 27, 2016.

5.3 REMS Appended Materials

The Sponsor limited their proposed changes to the product-specific information within the FDA Blueprint. No other ER/LA REMS appended materials were affected by the Sponsor's submission. DRISK agrees that the only appended material impacted by the addition of Vantrela ER to the REMS is the FDA Blueprint.

The following table includes the Sponsor's proposed product specific section of the FDA Blueprint:

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics	
Vantrela ER	Hydrocodone Bitartrate Extended-Release Tablets, 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg
Dosing Interval	Every 12 hours
Key Instructions	▪ Opioid naïve and opioid nontolerant patients: Initiate with 15 mg every 12 hours. Dose can be increased from the current dose to the next higher dose every 3 to 7 days as needed. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Mild or moderate hepatic and moderate to severe renal impairment: Initiate therapy with 1/2 of the recommended initial dose in patients with either of these impairments. If a dose less than 15 mg is needed, use alternative analgesic options.
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone exposure.
Use in Opioid-Tolerant Patients	A 90 mg tablet, a single dose greater than 60 mg, or a total daily dose greater than 120 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid.

Reviewer Comment: DRISK agrees with the Sponsor's proposed Vantrela product specific information that will be incorporated into the FDA Blueprint.

5.4 REMS Assessment Plan

The Sponsor did not propose changes to the REMS assessment plan. DRISK agrees that changes to the assessment plan are not warranted at this time.

6 DISCUSSION

The clinical reviewer recommended approval of Vantrela ER (15 mg, 30 mg, 45 mg, 60 mg, and 90 mg extended- release tablets) based on the data provided by the Sponsor.

The DAAAP clinical reviewer, Dr. Levin, summarized the Risk/Benefit of Vantrela ER as follows[10]:

> *The risk-benefit profile of Vantrela is favorable for the proposed indication and the safety data collected in the clinical studies reveal no safety concern unique to this new formulation of hydrocodone.*

Additionally, in reference to the need for a REMS, Dr.Levin stated the following[11]:

> *As a long-acting opioid, Vantrela if approved, would be required to be under the classwide risk evaluation and mitigation strategy (REMS) for extended-release/long-acting (ER/LA) opioid class of drugs to mitigate the risks of overdose, abuse, misuse, and addiction and to maintain a favorable benefit-risk profile for this product.*

DRISK agrees that Vantrela ER poses the risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse but can be managed with labeling and the ER/LA Opioid Analgesics REMS. DRISK agrees with the Sponsor's proposed addition of Vantrela ER to the approved ER/LA Opioid Analgesics REMS as appended to this review.

A REMS for Vantrela ER is necessary to ensure the benefits outweigh the risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse for Vantrela ER. DRISK agrees with the Sponsor's proposal to include Vantrela ER within the ER/LA REMS.

The Sponsor submitted a proposed ER/LA REMS for Vantrela ER on December 19, 2016. DRISK finds the proposed ER/LA REMS (attached) acceptable.

7 CONCLUSION

In conclusion, a REMS for Vantrela ER is necessary to ensure the benefits outweigh the risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse for Vantrela ER. DRISK agrees with the Sponsor's proposal to include Vantrela ER (hydrocodone bitartrate) tablets information within the ER/LA Opioid Analgesic REMS *FDA Blueprint for Prescriber Education*. The timetable for submission of assessments of the REMS and

[10] Levin R. Clinical Review and Evaluation for Vantrela ER, December 18, 2015

[11] Levin R. Clinical Review and Evaluation for Vantrela ER, December 18, 2015

the REMS assessment plan will remain the same as that approved on September 30, 2016. Therefore, the Division of Risk Management has determined that the ER/LA Opioid Analgesics REMS for Vantrela ER is acceptable as appended to this review.

8 RECOMMENDATION

DRISK recommends approval of the ER/LA REMS for Vantrela ER (hydrocodone bitartrate extended-release tablets) (NDA 207975), received December 19, 2016 and as appended to this review.

9 ATTACHMENTS

Extended-Release and Long-Acting Opioid Analgesic REMS document and appended materials.

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/s/

KIMBERLY LEHRFELD
12/22/2016

JAMIE C WILKINS PARKER on behalf of CYNTHIA L LACIVITA
12/22/2016

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:	November 11, 2015
Reviewer(s):	Danny S. 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. DRISK
Acting Deputy Director:	Reema Mehta, Pharm. D., M.P.H. DRISK
Drug Name(s):	Vantrela (hydrocodone bitartrate)
Therapeutic Class:	Opioid agonist
Dosage and Route:	15 mg, 30 mg, 45 mg, 60 mg, and 90 mg abuse-deterrent, extended-release oral tablet
Application Type/Number:	NDA 207975
Submission Number:	ORIG-1
Applicant/sponsor:	Teva Branded Pharmaceutical Products R and D, Inc.
OSE RCM #:	2014-2070; 2014-2514

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK's) evaluation of Teva Branded Pharmaceutical Products R and D, Inc. (Teva) REMS submission, received received from Teva on September 30, 2014(Sequence No. 0000) and amended on December 23, 2014 (Sequence No. 0001), July 1, 2015 (Sequence No. 0016), and July 22, 2015 (Sequence No. 0021). Teva Branded Pharmaceutical Products R and D, Inc. (Teva) is submitting NDA 207975 under section 505(b)(1). The Sponsor is currently a member in the REMS Program Companies (RPC). On July 22, 2015, Teva submitted a proposed REMS which included Vantrela in the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* of the ER/LA REMS. This submission is the focus of this review.

1.1 PRODUCT BACKGROUND

Hydrocodone bitartrate is a semi-synthetic opioid that is widely used for the relief of severe pain. Until recently, hydrocodone was available in the United States for the treatment of pain only in immediate-release products that also included other analgesics such as acetaminophen or ibuprofen. These combination drugs can limit the use of hydrocodone to treat pain when the dosage of either acetaminophen or ibuprofen is not therapeutically appropriate or useful. A single-agent, extended-release hydrocodone product (Zohydro) was approved by the Agency on October 25, 2013 for opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate; however, Zohydro does not have abuse-deterrent (AD) properties.

Vantrela is an opioid agonist product composed of hydrocodone bitartrate in an extended-release (ER) tablet with abuse-deterrent (AD) properties. The basis of the rationale for the development of Vantrela was to provide an abuse deterrent formulation of extended-release hydrocodone which maintains the benefits of an opioid agonist. Vantrela tablets are formulated to maintain extended-release properties despite consumption with alcohol, unintentional manipulation, or intentional manipulation for purpose of abuse.

Teva is seeking approval for the following dosage strengths of Vantrela: 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg. Teva is submitting Vantrela under section 505(b)(1). Vantrela's proposed indication is 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 proposed indication for Vantrela is consistent with the products in the single shared system (SSS) REMS for extended-release/long-acting (ER/LA) opioid analgesic drug products. If approved Vantrela will become a part of the SSS ER/LA opioid REMS.

On July 9, 2012, the FDA approved a SSS REMS for ER/LA opioid analgesic 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

[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.

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

1.2 REGULATORY HISTORY

October 10, 2012: The Agency agreed on study design requirements for Study 3103 at a Type A meeting. This study will provide confirmation of the efficacy of hydrocodone ER tablets for the intended indication.

September 30, 2014: The Sponsor submitted NDA 207975 (ORIG-1; eCTD Seq. No. 0000) that included the ER/LA Opioid Analgesics REMS (ER/LA REMS) document, REMS appended materials and the Supporting Document. The only revision to the ER/LA REMS approved in August 2014 was to the Blueprint which was revised to include product-specific information for Vantrela.

November 20, 2014: The Agency approved Hysingla ER(hydrocodone bitartrate) NDA 206627, as part of the ER/LA REMS.

December 23, 2014: The Sponsor submitted an amendment to NDA 207975 (ORIG-1; eCTD Seq. No. 0001) that included the ER/LA REMS document, REMS appended materials and the Supporting Document. The proposed the addition of product-specific information to to the ER/LA Blueprint.

December 29, 2014:. The Agency approved intermediate strengths of fentanyl transdermal systems ANDA 76258, as part of the ER/LA REMS.

June 26, 2015: The Agency approved a revised version of the ER/LA Opioid REMS which included Hysingla ER, titration information for Dolophine, and intermediate strengths of fentanyl transdermal systems.

July 1, 2015: The Sponsor submitted an amendment to NDA 207975 (ORIG-1; eCTD Seq. No. 0016) which included a revised Blueprint based on the June 26, 2015 ER/LA Opioid REMS. The Blueprint was the only ER/LA REMS material submittedand included product-specific information for Vantrela.

July 22, 2015: The Sponsor submitted an amendment to NDA 207975 (ORIG-1; eCTD Seq. No. 0021) which included the ER/LA REMS document, REMS appended materials

and the REMS Supporting Document which based on the ER/LA Opioid REMS approved on June 26, 2015.

August 13, 2015: The Agency approved a REMS Modification for the ER/LA Opioid Analgesics REMS for OxyContin (oxycodone hydrochloride) NDA 22272, as part of the ER/LA REMS, which included an updated pediatric indication and titration information.

October 2, 2015: The Agency approved Morphabond (morphine sulfate extended release tablet) NDA 206544, as part of the ER/LA REMS.[2]

October 23, 2015: The Agency approved Belbuca (buprenorphine buccal film) NDA 207932, as part of the ER/LA REMS.[3]

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 207975 for the proposed ER/LA Opioid Analgesics REMS:

- Teva Branded Pharmaceutical Products R and D, Inc. New Drug Application 207975, September 30, 2014 (ORIG-1; eCTD Seq. No. 0000).
    - Amendment received December 23, 2014 (ORIG-1; eCTD Seq. No. 0001).
    - Amendment received July 1, 2015 (ORIG-1; eCTD Seq. No. 0016).
    - Amendment received July 22, 2015 (ORIG-1; eCTD Seq. No. 0021).

2.2 MATERIALS INFORMING OUR REVIEW

- Teva Branded Pharmaceutical Products R and D, Inc. Draft Prescribing Information for Vantrela. Submitted September 28, 2015 (ORIG-1; eCTD Seq. No. 0030)
    - Amendment received October 1, 2015 (ORIG-1; eCTD Seq. No. 0031)
    - FDA revised, Draft Prescribing Information for Vantrela, which was last reviewed by the Agency on October 20, 2015.
- Extended Release and Long Acting Opioid Analgesics REMS. Approved on October 23, 2015.
- Levin R. Clinical Review and Evaluation Presentation for Vantrela, May 29, 2015.
- Bonson K. Controlled Substance Staff Review for Vantrela, September 28, 2015.
- Zhang T. Audiology Review for Vantrela, September 18, 2015.

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[2] Approval letter for Morphabond (morphine sulfate extended release tablet) NDA 206544, dated October 2, 2015.

[3] Approval letter for Belbuca (buprenorphine buccal film) NDA 207932, dated October 23, 2015.

- Walker M. OPDP/Patient Labeling Review Team Review for Vantrela, September 30, 2015.
- Liberatore M. Approval Letter for OxyContin (NDA 22272) including the ER/LA REMS and appended materials, dated June 26, 2015.
- Hilfiger C. Approval Letter for Morphabond (NDA 206544) including the ER/LA REMS and appended materials, dated October 2, 2015.
- Nicols S. Approval Letter for Belbuca (NDA 207932) including the ER/LA REMS and appended materials, dated October 23, 2015.

3 DRISKS'S EVALUATION OF THE PROPOSED REMS

On August 13, 2015 changes to the indication and titration for OxyContin were approved with a revised ER/LA REMS. In addition, on October 2 and October 23, 2015, new ER/LA products, Morphabond extended-release tablets and Belbuca buccal film, were approved with a revised ER/LA REMS. These revisions will also need to be incorporated into the Sponsor's next submission and are included in the redlined, attached materials and described below.

3.1 MEDICATION GUIDE

The Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) has reviewed the Sponsor's proposed Vantrela Medication Guide (MG) under separate cover and has communicated their recommendations to DAAAP. OPDP/PLRT has found the MG submission to be acceptable.[4]

3.2 REMS DOCUMENT

The Sponsor's proposed REMS document, originally received September 30, 2014 (ORIG-1; eCTD Seq. No. 0000) and last amended on July 22, 2015 (ORIG-1; eCTD Seq. No. 0021) has no additional changes; therefore, DRISK finds them acceptable.

3.3 APPENDED MATERIALS

3.3.1 Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics

The Sponsor's proposal, originally received September 30, 2014 (ORIG-1; eCTD Seq. No. 0000) and last amended on July 22, 2015 (ORIG-1; eCTD Seq. No. 0021) has no additional changes.

DRISK Comment: The recent actions for OxyContin, as described below, will also need to be incorporated into the Sponsor's next submission and are included in the redlined, attached materials. Details are described in the image below.

- *A child has taken this medicine by accident*

[4] Walker M. OPDP/Patient Labeling Review Team Review for Vantrela. September 30, 2015.

3.3.2 FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

The Sponsor's proposal, originally received September 30, 2014 (eCTD Seq. No. 0000) and last amended on July 22, 2015 (eCTD Seq. No. 0021) incorporates the Vantrela product-specific information throughout the *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*.

DRISK Comments: DRISK and DAAAP have reviewed the Sponsor's submission, from July 22, 2015, and recommend the changes summarized below. The Agency's agreed upon document is appended to this review. Overall, the Agency's proposed changes to the Sponsor's submission align the document with the ER/LA REMS goals as well as the Vantrela Prescribing Information.

Agency Comments for *Drug Information Common to the Class of ER/LA Opioid Analgesics* (Section VI):

Use in Opioid-Tolerant Patients	▪ Patients considered opioid tolerant are those receiving, for one week or longer: ▪ at least 60 mg oral morphine/day ▪ 25 mcg transdermal fentanyl/hour ▪ 30 mg oral oxycodone/day ▪ 8 mg oral hydromorphone/day ▪ 25 mg oral oxymorphone/day ▪ 60 mg oral hydrocodone/day ▪ See individual product information for which products: - Have strengths or total daily doses only for use in opioid-tolerant

DRISK Comment: DRISK and DAAAP have reviewed the Sponsor's submission. The proposed changes to the Sponsor's submission align with the document Vantrela Prescribing Information.

Agency Proposal for Vantrela product-specific section (Section VI):

Vantrela ER	Hydrocodone Bitartrate Extended-Release Tablets, 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg
Dosing Interval	Every 12 hours
Key Instructions	▪ (b) (4) Opioid naive and opioid non-tolerant patients: Initiate with 15 mg every 12 hours ▪ Dose can be increased from the current dose to the next higher dose every 3 to 7 days as needed ▪ Swallow tablets whole (do not chew, crush, or dissolve) ▪ Hepatic and Moderate or Severe Renal Impairment: Initiate therapy with 1/2 of the initial dose in patients with either of these impairments. If a dose less than 15 mg is needed use alternate analgesic options
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone exposure. ~~CYP3A4 inducers may decrease hydrocodone exposure.~~
Use in Opioid-Tolerant Patients	A 90 mg tablet, a single dose greater than 60 mg or total daily dose greater than 120 mg are for use in opioid-tolerant patients only. (b) (4)
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid.

DRISK Comments: DRISK and DAAAP have reviewed the Sponsor's submission and recommend the changes summarized above for Vantrela's product-specific entry in the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (Section VI). The proposed changes to the Sponsor's submission align the Vantrela product-specific information with the ER/LA REMS goals as well as the Vantrela Prescribing Information.

In addition, the recent actions for OxyContin, Morphabond, and Belbuca, as described above in Section 1.2, will also need to be incorporated into the Sponsor's next submission and are included in the redlined materials appended ot this review.

3.3.3 Prescriber Letters

The Sponsor's proposal, originally received September 30, 2014 (ORIG-1; eCTD Seq. No. 0000) and last amended on July 22, 2015 (ORIG-1; eCTD Seq. No. 0021) included a correction to grammer in the Prescriber letter #3 (see below).

Prescriber Letter #3

FDA-Required REMS Program for Serious Drug Risks

Subject:	Risk Evaluation and Mitigation Strategy (REMS) for all extended-release/long-acting opioid analgesic drug products due to their risks of misuse, abuse, addiction, and overdose

Dear DEA-Registered Prescriber:

You are receiving this letter because you recently registered with DEA to prescribe Schedule II or III drugs. The purpose of this letter is to inform you about a Risk Evaluation and Mitigation Strategy (REMS) that has been required by the U.S. Food and Drug Administration (FDA) for all extended-release and long-acting (ER/LA) opioid analgesic drug products.

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. 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 ER/LA opioid analgesics 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 (b) (4) inadequate to provide sufficient management of pain.

DRISK Comments: DRISK has reviewed the Sponsor's submission and find this change acceptable. In addition, the addition of Belbuca, see section 1.2, to the ER/LA REMS required the following revision to these letters.

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral dosage forms containing
  - hydrocodone,
  - hydromorphone,
  - morphine,
  - oxycodone,
  - oxymorphone, or
  - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- (b) (4)
- methadone tablets and solutions as well as buprenorphine-containing buccal films that are indicated for use as analgesics.

3.3.4 Professional Organization/Licensing Board Letters

The Sponsor's proposal, originally received September 30, 2014 (ORIG-1; eCTD Seq. No. 0000) and last amended on July 22, 2015 (ORIG-1; eCTD Seq. No. 0021) has no additional changes; therefore, DRISK finds them acceptable.

3.3.5 ER/LA Opioid Analgesic REMS website

The Sponsor's proposal, originally received September 30, 2014 (ORIG-1; eCTD Seq. No. 0000) and last amended on July 22, 2015 (ORIG-1; eCTD Seq. No. 0021) has no additional changes;.

DRISK Comment: The approval of OxyContin pediatric indication and the addition of Belbuca, see section 1.2, to the ER/LA REMS required revisions to the Important Safety Information on the ER/LA REMS website. See the attached, redlined ER/LA REMS website

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral dosage forms containing
  - hydrocodone,
  - hydromorphone,
  - morphine,
  - oxycodone,
  - oxymorphone, or
  - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- buprenorphine-containing buccal films; *and*
- methadone tablets and solutions as well as buprenorphine-containing buccal films that are indicated for use as analgesics.

ER/LA opioid analgesics containing buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol 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. Extended-release oxycodone (OxyContin) is also indicated in pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent. ER/LA opioid analgesics are not indicated for acute pain.

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 ER/LA opioid analgesics reserved for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise be inadequate to provide sufficient management of pain. (b) (4)

For some of the ER/LA opioid analgesics, certain (b) (4)-strength (b) (4), certain daily doses, and in specific indicated patient populations (e.g., pediatric patients) are for use in opioid-tolerant patients only. Consult the individual Full Prescribing Information for the definition of opioid tolerance and dosing instructions for patients (b) (4) (b) (4) ER/LA opioid analgesics are not intended for acute pain, pain that is mild or not expected to persist for an extended period of time, or for use on an as-needed basis.

(b) (4)

ER/LA opioid analgesics are contraindicated in patients with a known hypersensitivity to any of the components of ER/LA opioid analgesics, including the respective active ingredients, or in any situation where opioids are contraindicated; in patients who have significant respiratory depression; in patients who have acute or severe bronchial asthma; or in patients who have or are suspected of having paralytic ileus. (b) (4) (b) (4) **These contraindications are not all-inclusive of those for each individual ER/LA opioid analgesic;** therefore, the Full Prescribing Information for the individual ER/LA opioid analgesics must be consulted.

The Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids is a tool unique to this REMS designed to facilitate important discussions with your patients and their caregivers for whom you select an ER/LA opioid analgesic. The PCD should be provided to the patient and/or their caregiver at the time of prescribing. It contains important safety information about the drug products subject to this REMS and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely.

Patients and their caregivers should be counseled on: the importance of taking these medicines exactly as you prescribe them, the need to store ER/LA opioid analgesics safely and securely—out of the reach of children, pets, and household acquaintances to avoid risks from unintended exposure, the importance of not sharing these medications, even if someone has the same symptoms as the patient, and the proper methods of disposal of unneeded ER/LA opioid analgesics.

It is important that you encourage your patients and their caregivers to read the relevant Medication Guide when they pick up their prescription from the pharmacy. The Medication Guide provides important information on the safe and effective use of the specific ER/LA opioid analgesic prescribed.

3.4 REMS SUPPORTING DOCUMENT

The Sponsor's proposal, originally received September 30, 2014 (ORIG-1; eCTD Seq. No. 0000) and last amended on July 22, 2015 (ORIG-1; eCTD Seq. No. 0021) does not include the most recently approved supporting document; therefore DRISK does not find this acceptable.

DRISK Comment: The recent actions for OxyContin and Belbuca, which both impacted the REMS Supporting Document, will also need to be incorporated into the Sponsor's next submission.

4 CONCLUSION AND RECOMMENDATION

DRISK recommends that Vantrela (hydrocodone bitartrate) product-specific information should be included within the ER/LA Opioid Analgesic REMS Blueprint as appended to this review. The product specific information for OxyContin (approved August 13, 2015), Morphabond (approved October 2, 2015), and Belbuca (approved October 23, 2015) must also be incorporated in thte ER/LA REMS materials (Blueprint, Prescriber Letters, and Website) as appended to this review. The timetable for submission of assessments of the REMS and the REMS assessment plan will remain the same as that approved on June 26, 2015.

5 RECOMMENDATIONS FOR THE REVIEW DIVISION

DRISK recommends that the redlined ER/LA Opioid Analgesic REMS for Vantrela (hydrocodone bitartrate) (NDA 207975) appended to this review be shared with the Sponsor along with the following comments (Section *6: Comments for the Applicant)*. DRISK requests that the Sponsor respond to these comments within 5 days of receiving these comments to facilitate further review for this submission.

6 COMMENTS FOR THE APPLICANT

The Office of Surveillance and Epidemiology (OSE), DRISK has completed the review of ER/LA Opioid Analgesic REMS document, appended materials originally received September 30, 2014 (ORIG-1; eCTD Seq. No. 0000) and last amended on July 22, 2015 (ORIG-1; eCTD Seq. No. 0021). DRISK has the following comments, below, in response to the Sponsor's proposal, including redlined/highlighted changes to the ER/LA Opioid Analgesic REMS document and appended materials.

1. Please note the additional track changes and comments in the attached *FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics.*
2. NOTE: New ER/LA products/indications were approved on August 13, 2015 (OxyContin pediatric indication), October 2, 2015 (Morphabond), and on October 23, 2015 (Belbuca) with a revised ER/LA REMS. The attached ER/LA REMS includeds OxyContin®, Morphabond® and Belbuca's ® product specific information in the Blueprint, Prescriber Letters, and Website where noted. If approved, Vantrela must include the above product specific information. This document must be aligned with any changes, if any, made to the Vantrela's Prescribing Information.
3. The "Most Recent Modification" date on the REMS document must be changed to "XX/XXXX" as indicated in the redlined, attached REMS document when resubmitted to the Agency. If this product is approved, this date will be updated by the Agency to reflect the approval date.
4. Resubmission/Format Requirements and Instructions:
    a. Submit the following as an amendment to your NDA:
        i. The attached, revised, redlined proposed ER/LA Opioid Analgesic REMS for Vantrela with appended materials.
        ii. The attached, revised, clean proposed ER/LA Opioid Analgesic REMS for Vantrela with appended materials.
        iii. The ER/LA REMS Supporting Document which was approved by the Agency on October 23, 2015 when Belbuca was approved. The ER/LA REMS Product Companies must provide a copy of this document.

APPENDIX

Extended-Release and Long-Acting Opioid Anagesic REMS document and appended materials

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/s/

DANNY S GONZALEZ
11/12/2015

KIMBERLY LEHRFELD
11/13/2015