

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206544Orig1s000

**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 #:	206544
Product:	Morphabond (morphine sulfate extended-release tablets)
SPONSOR:	Inspiron Delivery Technologies LLC
FROM:	Judith A. Racoosin, MD, MPH
DATE:	September 21, 2015

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, Morphabond will be joining this single shared system REMS.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUDITH A RACOOSIN
09/21/2015

**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**

FINAL RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	September 17, 2015
Reviewer(s):	Danny S. Gonzalez, Pharm. D., M.S., Risk Management Analyst Division of Risk Management (DRISK) Donella Fitzgerald, Pharm. D. Risk Management Analyst DRISK Joan Blair, R.N., M.P.H. Health Communication Analyst DRISK
Team Leader:	Kim Lehrfeld, Pharm. D., BCPS DRISK
Acting Deputy Division Director:	Reema Mehta, Pharm. D., M.P.H. DRISK
Drug Name(s):	Morphabond (morphine sulfate)
Therapeutic Class:	Opioid agonist
Dosage and Route:	15 mg, 30 mg, 60 mg, and 100 mg abuse-resistant, extended-release oral tablets
Application Type/Number:	NDA 206544
Submission Number:	ORIG-1
Applicant/sponsor:	Inspirion Delivery Technologies, LLC
OSE RCM #:	2014-2439; 2014-2440

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

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1 INTRODUCTION

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 Morphabond and evaluation of a proposed modification to the extended release and long acting (ER/LA) opioid analgesic REMS for Morphabond (morphine sulfate) extended-release tablets, NDA 206544, received from Inspirion Delivery Technologies, LLC's (Inspirion) on November 21, 2014 and amended on July 31, 2015 and September 14, 2015. Inspirion is submitting an NDA under section 505(b)(2) using Purdue Pharma LP's MS Contin (NDA 019516) as the reference listed drug (RLD).

1.1 PRODUCT BACKGROUND

Morphabond (morphine sulfate), is an abuse-resistant (AR) formulation of oral, extended-release (ER) morphine sulfate tablets (morphine ARER) 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. Morphabond's abuse-resistant properties are based on Inspirion's proprietary abuse-deterrent technology, which impact the ability to manipulate the tablets, including the ability to retain ER characteristics even if the tablet is subjected to physical manipulation and/or chemical extraction, and formation of a material that resists passage through a needle when subjected to a liquid environment. These properties challenge commonly used methods of manipulation and routes of administration for abuse.

Inspirion is seeking approval for Morphabond tablet strengths of 15 mg, 30 mg, 60 mg, and 100 mg. The Morphabond tablets are formulated to deliver the active ingredient over (b) (4) 12 hours. Inspirion is submitting an NDA under section 505(b)(2) using Purdue Pharma LP's MS Contin (NDA 019516) as the RLD. The proposed indication for Morphabond is consistent with the approved indication for MS Contin. MS Contin is approved under the single shared system (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

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.

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- Letters to Professional Organizations/Licensing Boards
 - REMS website
- Timetable for Submission of Assessments

1.2 REGULATORY HISTORY

On April 10, 2014, Inspirion met with the Agency for a Type C Pre-NDA meeting. At this meeting the Agency acknowledged Inspirion's commitment to participate in the ER/LA REMS program. The Agency confirmed that the Sponsor must submit a proposed REMS with this NDA. The Agency also confirmed that the Sponsor must obtain the most recently approved ER/LA REMS documents for the Sponsor to revise and submit with the NDA from the REMS Program Companies (RPC) .

On July 2, 2013: The Agency met with the Sponsor at a Type C Pre-NDA meeting. The Agency stated that it would not require the inclusion of safety clinical trials as long as safety data submitted included any concerns regarding possible gastrointestinal (GI) adverse effects (choking, sticking, obstruction, etc) related to product formulation of the abuse deterrent tablet.

On November 21, 2014, Inspirion submitted NDA 206544 for Morphabond ER as a 505(b)(2) application using Purdue Pharma LP's MS Contin (NDA 019516) as the RLD. This submission included a proposed REMS document, appended materials, and the REMS supporting document based their proposed label and the approved ER/LA Opioid REMS (dated August 19, 2014).

On July 31, 2015, Inspirion amended the submission to include the REMS document, appended materials, and the REMS supporting document based on their proposed label and the approved ER/RLA Opioid REMS dated December 2015.

On September 11, 2015, the Agency requested that the Sponsor amend their application to include their proposal with the approved ER/LA REMS (dated June 26, 2015).

On September 14, 2015, Inspirion amended the submission to include the REMS document, appended materials, and the REMS supporting document based on their proposed label and the approved ER/RLA Opioid REMS (dated June 26, 2015). These documents are the focus of this review.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 206544 for the proposed ER/LA Opioid Analgesics REMS:

- Inspirion Delivery Technologies, LLC. Proposed REMS for Morphabond (morphine sulfate), received November 21, 2014. (ORIG-1; eCTD Sequence No. 0000)
 - Amendment to the proposed REMS for Morphabond (morphine sulfate), received July 31, 2015 (ORIG-1; eCTD Sequence No. 0007) and September 14, 2015 (ORIG-1; eCTD Sequence No. 0011)

2.2 MATERIALS INFORMING THIS REVIEW

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

- Inspirion Delivery Technologies, LLC. Draft Prescribing Information for Morphabond. Submitted July 9, 2015 (ORIG-1; eCTD Seq. No. 0006).
- Extended Release and Long Acting Opioid Analgesics REMS. Approved on June 26, 2015.
- Jiang T, Clinical Review Presentation for Morphabond Wrap-up meeting, dated July 15, 2015.
- Jiang T, Clinical Review for Morphabond, dated August 19, 2015.
- Tolliver J, Controlled Substance Staff Review for Morphabond, dated July 17, 2015.

3 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

3.1 SUMMARY OF EFFICACY

3.1.1 Efficacy of Morphabond for the management of pain

Inspirion relied upon clinical efficacy data obtained from MS Contin (NDA 019516) to support the efficacy for morphine ARER. The proposed indication for Morphabond is consistent with the approved indication for MS Contin. The dosing interval of every (b) (4) 12 hours for Morphabond is consistent with the dosing interval for MS Contin, and each is available in 15 mg, 30 mg, 60 mg and 100 mg (200 mg is also available for MS Contin tablets).

Bridging studies, M-ARER-004 and M-ARER-008, were conducted to assess bioavailability (BA) for Morphabond as compared to MS Contin. Based on the available data, the clinical reviewer² reported that Morphabond met the bioequivalent threshold for area under the curve (AUC) but not for maximum concentration (C_{max}) to MS Contin. Based on this data the clinical reviewer concluded that this discrepancy "will not affect the efficacy and safety of Morphabond."

3.1.2 Efficacy of the abuse deterrent properties of Morphabond

Inspirion used Category 1 testing and a combination Category 2 pharmacokinetic (PK) and Category 3 human abuse potential clinical study to evaluate the efficacy of the abuse deterrent properties for Morphabond.

Category 1- Laboratory Manipulation and Extraction studies

These studies consisted of a series of laboratory-based in-vitro manipulation and extraction studies using the 100 mg tablet. An accredited external laboratory was used to confirm the results of the physical manipulation, small and large volume extractability, injectability, syringeability, and smokeability. In summary, the Category 1 testing

² Jiang T, Clinical Review for Morphabond. August 19, 2015.

found that Morphabond does possess abuse-deterrent properties that would hinder individuals from physically manipulating it for abuse. These abuse-deterrent properties include:

- Morphabond cannot be easily crushed or cut with household items, except a (b) (4) (b) (4)
- In the event that Morphabond is manipulated by crushing or cutting, it forms a non-syringeable viscous material that cannot be injected with up to size (b) (4) needles
- Morphabond will not “dose dump” in solvents, even after physical manipulation, maintaining its extended-release property. (b) (4)

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The Sponsor completed study M-ARER-002, which was a combined Category 2 (PK)/Category 3 (pharmacodynamic-human abuse potential) study. This double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover, single-center study was conducted to determine the abuse potential of crushed and intact oral Morphabond relative to crushed intranasal MS Contin when administered intranasally and orally to non-dependent, recreational opiod users. The Drug Liking visual analog scale (VAS) was used as the primary endpoint. A secondary objective was to determine the relative BA of morphine from crushed intranasal and intact oral Morphabond compared to crushed intranasal MS Contin. In summary, the study demonstrated similar results of crushed intranasal Morphabond compared to oral intact Morphine ARER, which suggests that Morphabond retains extended release characteristics despite crushing and intranasal administration.

Pharmacodynamic findings focused on the Drug Liking VAS as the primary abuse potential assessment. The maximum effect (E_{max}) and area under the effect curves (AUC) were examined using critical intervals for abuse potential for AUC of 0 to 0.5 hr, 0 to 1 hr and 0 to 2 hrs. The mean percentage reduction in E_{max} with crushed intranasal Morphabond compared to crushed intranasal MS Contin was 39.7%. Additionally, the least square (LS) mean for Drug Liking VAS E_{max} was 13.65mm lower for the crushed intranasal Morphabond than the crushed intranasal MS Contin, which was statistically significant ($p \leq 0.0001$). All the supporting AUC findings demonstrated statistically significantly less "drug liking" for the crushed intranasal Morphabond than the crushed intranasal MS Contin.

The clinical reviewer concluded that the overall findings of the in vitro studies and the intranasal human abuse potential study suggest a possible intranasal abuse deterrent effect of Morphabond tablets relative to MS Contin. These findings were supported by the Controlled Substance reviewer's original review³. The studies demonstrate that

Morphabond tablets retain the ER properties upon crushing and extraction. In addition, Morphabond tablets, compared to MS Contin resist manipulation for purposes of intravenous abuse and smoking of Morphabond. The Controlled Substance Staff reviewer also found that M-ARER-002 provided evidence that the insufflation of crushed Morphabond 60 mg compared to crushed MS Contin 60 mg is associated with less subjective effects of Drug Liking and High compared to MS Contin.³

3.2 SUMMARY OF SAFETY

Inspirion relied upon clinical safety data obtained from MS Contin (NDA 019516) to support the safety for morphine ARER and BA and PK studies, including M-ARER-004 and M-ARER-008. Safety data was also collected during five other BA and PK studies (M-ARER-002, M-ARER-005, M-ARER-006, M-ARER-007 and M-ARER-0012) on the efficacy of the abuse deterrent properties of morphine sulfate ARER. All volunteers, with the exception of those in study M-ARER-002 were classified as young and healthy. The participants from M-ARER-002 were classified as experienced, non-therapeutic, recreational opioid users.

Treatment emergent adverse events were reported in 74 out of 241 (30.7%) subjects for Morphabond and 66 out of 220 (30.0%) subjects for MS Contin. Twenty subjects (7 subjects for Morphabond and 13 subjects for MS Contin) had an adverse event that led to withdrawal from the study, with one serious adverse event in a subject receiving Morphabond. The symptoms reported among the 20 subjects that withdrew included acute onset abdominal pain, associated with nausea, vomiting and diarrhea.

No cases of death were reported in the above trials. Only one serious adverse event was reported in the multi-dose studies (M-ARER-007) regarding a patient treated in an emergency room for gastrointestinal symptoms such as abdominal cramp, nausea, vomiting, and diarrhea; however, the clinical reviewer³ concluded that the outcome of the case did not suggest GI obstruction.

Throughout the clinical trials the most common adverse events leading to discontinuation in multiple dose studies included nausea and vomiting, which are known class effects of opioids. The clinical trial data supports the similarity of adverse events occurring in the Morphabond treated subjects when compared to the MS Contin group. The safety signals observed for Morphabond in the pooled data correspond to expected adverse events in for the active ingredient, morphine sulfate.

Gastrointestinal Obstruction

It has been suggested that previously approved oral ER tablet formulations may have been associated with GI obstruction due to esophageal mucosa tablet sticking. Because of this risk, ER medications are often contraindicated in patients with gastric disorders. To examine safety issues specifically related to tablet formulation, the Agency requested Inspirion provide safety data regarding gastrointestinal adverse events, such as choking, sticking or obstruction (Type C meeting, July 2, 2013). In the pooled data for all doses, there were a total of 39 (16.2%) GI events reported for Morphabond and 30 events (15.5%) for MS Contin, with nausea being the highest reported at 34 (14.1%) and 20

³ Tolliver J, Controlled Substance Staff Review for Morphabond, dated July 17, 2015

(10.4%) respectively. Other commonly reported side effects for both drugs included vomiting, constipation and dyspepsia, which are characteristic of the opioid class. Overall, as there were similar adverse effects reported for both Morphabond and MS Contin, it appears that the abuse deterrent tablet formulation does not pose an elevated safety risk of GI obstructions.

4 RATIONALE FOR A REMS FOR MORPHABOND

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 Morphabond. 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 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 ER 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.

Morphabond includes an abuse-deterrent formulation that may mitigate the risk of intravenous or intranasal abuse; in addition, tablets retained the extended release properties upon crushing and extraction. Also, Morphabond tablets, compared to MS Contin, resisted manipulation for purposes of smoking.

However, Morphabond contains morphine sulfate in doses which could potentially result in overdose or death due to the high amounts of morphine sulfate. 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, Morphabond's risks of serious adverse outcomes (e.g., addiction, unintentional overdose, and death) resulting from inappropriate prescribing, misuse, and abuse can be mitigated with labeling and a REMS. It is appropriate for it to join the single, shared system ER/LA REMS.

5 RESULTS OF REVIEW OF THE PROPOSED REMS FOR MORPHABOND

The Sponsor proposed to incorporate Morphabond into the approved ER/LA REMS. The only ER/LA REMS material affected by the addition of Morphabond is the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (FDA Blueprint). DRISK reviewed Inspirion's proposed REMS, initially submitted on November 21, 2014 and last amended on September 14, 2015. The following refers to the submission received on September 14, 2015.

5.1 REMS DOCUMENT

The Sponsor did not propose changes to the ER/LA REMS Document. DRISK agrees that changes to the REMS Document are not warranted at this time.

5.2 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 Morphabond to the REMS is the FDA Blueprint.

The following table includes the Sponsor's proposed changes to the FDA Blueprint:

Morphabond	Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	<ul style="list-style-type: none">▪ (b) (4)▪ Swallow (b) (4) whole (do not chew, crush, or dissolve). (b) (4)
Specific Drug Interactions	P-gp inhibitors (e.g. quinidine) may increase the (b) (4) exposure (4) morphine (b) (4) by about two-fold.
Use in Opioid-Tolerant Patients	(b) (4)
Product-Specific Safety Concerns	None

Reviewer Comment: DRISK agrees with the Sponsor's proposed changes to the FDA Blueprint.

5.3 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 approval³ of Morphabond (15, 30, 60, and 100 mg tablets) based on the data provided by the Sponsor.

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

From the perspective of risk, the safety data submitted (albeit not in target pain population), were, overall, consistent with those of the opioid class of drugs. There were no deaths or non-fatal SAE reported in the clinical studies, and no unexpected or unusual adverse events of special interest were identified.

All opioids pose the risk of abuse and misuse. The development of abuse-deterrent formulations of opioid analgesics is an important approach to reducing abuse of prescription opioids.

These risks (including overdose, misuse and abuse), however, appear to be manageable with the labeling with a REMS...

DRISK agrees that Morphabond 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 Morphabond to the approved ER/LA Opioid Analgesics REMS as appended to this review.

7 CONCLUSION

In conclusion, a REMS for Morphabond 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 Morphabond. DRISK agrees with the Sponsor's proposal to include Morphabond (morphine sulfate) ER tablets information within the ER/LA Opioid Analgesic REMS Blueprint. 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.

Therefore, the ER/LA Opioid Analgesics REMS for Morphabond is acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management as appended to this review.

8 RECOMMENDATIONS

DRISK recommends approval of the ER/LA Opioid REMS for Morphabond (morphine sulfate) ER tablets (NDA 206544) received September 14, 2015 and as appended to this review.

A REMS Modification Notification Letter should be sent to the other members of the ER/LA Opioid REMS to request the inclusion of these changes in their respective REMS.

9 ATTACHMENTS

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

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/s/

DANNY S GONZALEZ
09/17/2015

REEMA J MEHTA
09/17/2015
I concur.