CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208603Orig1s000

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 #:	208603
Product:	Arymo ER (morphine sulfate) extended-release tablets
SPONSOR:	Egalet US, Inc.
FROM:	Judith A. Racoosin, MD, MPH
DATE:	See electronic signature

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, or 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, Arymo ER will be joining this single shared system REMS.

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/s/

JUDITH A RACOOSIN
01/06/2017

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:	October 13, 2016
Reviewer(s):	Danny S. Gonzalez, Pharm. D., M.S., Risk Management Analyst Division of Risk Management (DRISK) Sangeeta Tandon, Pharm.D., M.P.H. Risk Management Analyst DRISK
Team Leader:	Kim Lehrfeld, Pharm. D. DRISK
Director:	Cynthia LaCivita, Pharm.D. DRISK
Drug Name(s):	Arymo (morphine sulfate)
Therapeutic Class:	Opioid agonist
Dosage and Route:	15 mg, 30 mg, 60 mg extended-release oral tablets
Application Type/Number:	NDA 208603
Submission Number:	ORIG-1
Applicant/sponsor:	Egalet Corporation
OSE RCM #:	2015-2713, 2015-2714

CONTENTS

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 Arymo ER (morphine sulfate) and evaluation of a proposed REMS submission for Arymo ER (morphine sulfate) extended- release tablets, NDA 208603, received from Egalet Corporation's (Egalet) on December 14, 2015 and resubmitted on October 5, 2016. Egalet 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

Arymo ER (morphine sulfate) is an oral, extended- release (ER) morphine sulfate tablets 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 rationale for the development of Arymo ER is to provide a morphine sulfate formulation with abuse deterrent properties. Arymo ER's abuse-resistant properties are based on Egalet's proprietary abuse-deterrent technology, which utilizes (b) (4) polyethylene oxide and results in tablets that are extremely hard, resistant to particle size reduction, and that inhibit/block attempts at chemical extraction of the morphine sulfate. In addition, the polymer results in a viscous hydrogel when mixed with liquid, which makes syringeability and injections difficult.

Egalet is seeking approval for Arymo ER tablet strengths of 15 mg, 30 mg, and 60 mg. The Arymo ER tablets are formulated to deliver the active ingredient over 8 to 12 hours. Egalet 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 Arymo ER 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
        - Letters to DEA Registered Prescribers

[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.

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

1.2 REGULATORY HISTORY

December 14, 2015: Egalet submitted a draft REMS for Arymo ER (NDA 208603). This submission included a REMS document, appended materials and supporting document based on the ER/LA REMS approved on October 23, 2015.

August 4, 2016: The Agency's Advisory Committee (AC) met with the Sponsor to discuss the application for NDA 208603, which is now the policy for any extended-release/long-acting opioid analgesic seeking FDA approval. The AC voted 18-1 for approval that Arymo ER should be approved for marketing in the United States.

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.

October 3, 2016: The Agency requested, via email, that the Sponsor amend their submission to include the ER/LA Opioid REMS that was approved on September 30, 2016 and a separate document which includes Arymo's product specific information to be included in the FDA Blueprint.

October 5, 2016: The sponsor amended their submission to include ER/LA Opioid REMS that was approved on September 30, 2016 and a separate document which includes Arymo's product specific information to be included in the FDA Blueprint as requested by the Agency. This submission is the subject of this review.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 208603 for the proposed ER/LA Opioid Analgesics REMS:

- Egalet Corporation. Proposed REMS for Arymo ER (morphine sulfate), received December 14, 2015. (ORIG-1; eCTD Sequence No. 0001)
    - Amendment to the proposed REMS for Arymo ER (morphine sulfate), received October 5, 2016 (ORIG-1; eCTD Sequence No. 0028).

2.2 MATERIALS INFORMING THIS REVIEW

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

- Extended-Release and Long-Acting Opioid Analgesics REMS. Approved on September 30, 2016.
- Hariadi J, Clinical Review for Arymo ER, dated September 24, 2016.
- Tolliver J, Controlled Substance Staff Review for Arymo ER, dated August 15, 2016.
- Lee, Koung Office of Promotion of Drug Products (OPDP) review of ER/LA REMS, dated September 30, 2016.

3 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

3.1 SUMMARY OF EFFICACY

3.1.1 Efficacy of Arymo ER for the management of pain

Egalet relied upon clinical efficacy data obtained from MS Contin (NDA 019516) to support the efficacy for morphine sulfate for the management of pain. The proposed indication for Arymo ER is consistent with the approved indication for MS Contin. The dosing interval of every eight to 12 hours for Arymo ER is consistent with the dosing interval for MS Contin, and each is available in 15 mg, 30 mg, and 60 mg (100 mg and 200 mg is also available for MS Contin tablets).

The Applicant has not conducted any clinical studies evaluating or comparing the analgesic effectiveness of Arymo ER in the target pain population. They are relying on FDA's previous finding of safety and efficacy for MS Contin (NDA 019516) under the provision of section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The clinical program for Arymo ER consisted of five Phase 1 comparative bioavailability studies and two Phase 3 human abuse liability studies. The clinical reviewer reported that Phase 1 studies showed bioequivalence of Arymo ER to MS Contin in the proposed dosage strengths of 15 mg, 30 mg and 60 mg. In addition, the reviewer stated- Phase 3 studies indicate that Arymo ER has properties that are expected to reduce misuse or abuse via intravenous injection and nasal insufflation, although misuse or abuse by these routes may still be possible.

3.1.2 Efficacy of the abuse deterrent properties of Arymo ER

The Sponsor used Category 1 laboratory manipulation and extraction studies as well as Category 2/3 pharmacokinetic and clinical abuse potential studies to evaluate the efficacy of the abuse deterrent properties for Arymo ER.

Arymo is formulated with physical and chemical features that have been shown to resist common manipulation and extraction, while maintaining some of its extended-release properties when manipulated. Results of syringeability/injectibility studies, indicate a potential deterrent effect for intravenous abuse. Category 1 physical manipulation studies provide additional support that the tablets have an insufflation abuse deterrent effect. Based on results of Category 3 oral study, Arymo ER does not appear to have a deterrent effect to oral abuse.

3.2 SUMMARY OF SAFETY

There were no clinical studies evaluating or comparing the safety of Arymo in the target pain population. The applicant conducted seven bioavailability and pharmacokinetic studies that compared the use of Arymo to MS Contin in healthy volunteers between the ages of 18 and 55 years. The applicant also conducted two clinical abuse potential studies in which the pharmacodynamic parameter of drug liking and pharmacokinetics following intranasal and oral administration were determined. The participants were healthy volunteers between ages 18 and 55 who were experienced opioid users that were not dependent upon the drug. A total of 442 healthy adult subjects from nine studies were exposed to Arymo: 297 subjects received one single-dose and 145 subjects received between two and three doses. Overall, 400 subjects were exposed to the to-be-marketed formulation. This database is adequate to assess any formulation-related safety concerns, as agreed upon between the applicant and review division during the pre-NDA meeting. During the pre-NDA meeting, there was an agreement that the safety profile needed to have a minimum of 100 subjects exposed to the to-be-marketed formulation. Per the clinical reviewer's analysis of the Sponsor submission, there were no deaths, and one reported serious adverse event in the entire clinical development program. That subject experienced a spontaneous abortion approximately 16 days following administration of a preliminary formulation of Arymo during one of the pilot clinical trials (067-EG-001). The common AEs were nausea, vomiting, somnolence, and headache.

Based on the available data and safety findings, the clinical reviewer agreed that the adverse events seen in the safety population, albeit not in target pain population, are generally consistent with the known safety profile of extended-release morphine sulfate.

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4 RATIONALE FOR A REMS FOR ARYMO 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 Arymo ER. Arymo ER will be subject to the already established single, shared system REMS (ER/LA Opioid Analgesic REMS). While all opioid formulations have the potential for these risks, based on currently available data, the 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.

Arymo ER has abuse-deterrent properties that may mitigate the risk of intravenous or intranasal abuse. However, Arymo ER 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, Arymo ER'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 ARYMO ER

The Sponsor proposed to incorporate Arymo ER into the approved ER/LA REMS. The only ER/LA REMS material affected by the addition of Arymo 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 August 15, 2016 to review the product-specific information for Arymo ER in the ER/LA REMS Blueprint. OPDP received the Arymo product-specific information from DRISK on September 29, 2016. Koung Lee, OPDP reviewer submitted his review to DRISK on September 30, 2016 and his review was entered into DARRTS on September 30, 2016. OPDP did not have any comments regarding proposed revisions to the Arymo ER product-specific information in the ER/LA REMS Blueprint.

DRISK reviewed the Sponsor's proposed REMS, initially submitted on December 14, 2015 and resubmitted on October 5, 2016. The following refers to the submission received on October 5, 2016.

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 Arymo 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 (ER/LA opioid analgesics)	
Arymo ER	Morphine Sulfate extended-release tablets, 15 mg, 30 mg, 60 mg
Dosing Interval	Every 8 or 12 hours

Key Instructions	▪ Initial dose in opioid-naïve and opioid non-tolerant patients is 15 mg every 8 or 12 hours ▪ Dosage adjustment may be done every 1 to 2 days. ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
Specific Drug Interactions	P-gp inhibitors (e.g. quinidine) can increase the exposure of morphine by about two-fold and increase risk of respiratory depression
Use in Opioid-Tolerant Patients	A single dose of ARYMO ER greater than 60 mg, or total daily dose greater than 120 mg, is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	▪ Do not attempt to chew, crush, or dissolve. Swallow whole. ▪ Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen.

Reviewer Comment: DRISK agrees with the Sponsor's proposed Arymo product specific information that will be incorporated into 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 approval of Arymo ER (15, 30, and 60 mg extended- release tablets) based on the data provided by the Sponsor.

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

> *I agree with the Applicant's review of the safety findings that the AEs seen in the safety population, albeit not in target pain population, are generally consistent with those of the known safety profile of extended-release morphine sulfate.*

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

7 CONCLUSION

In conclusion, a REMS for Arymo 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 Arymo ER. DRISK agrees with the Sponsor's proposal to include Arymo ER (morphine sulfate) 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 Division of Risk Management has determined that the ER/LA Opioid Analgesics REMS for Arymo ER is acceptable as appended to this review.

8 RECOMMENDATIONS

DRISK recommends approval of the ER/LA Opioid REMS for Arymo ER (morphine sulfate) ER tablets (NDA 208603) received October 5, 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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