CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 2, 2016
From	John Feeney, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	208603
Applicant	Egalet US, Inc.
Date of Submission	December 14, 2015
PDUFA Goal Date	October 14, 2016
Proprietary Name / Established (USAN) names	Arymo ER (morphine sulfate extended-release tablets)
Dosage forms / Strength	60, 30, and 15 mg strength tablets
Proposed Indication(s)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Recommended:	Approval

Material Reviewed	**Review Team**
Primary Medical Officer Review	John Hariadi, MD, FAAFP
Pharmacology Toxicology Review	Elizabeth Bolan, PhD, Dan Mellon, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD, Yun Xu, PhD
Bioavailability Study Site Inspection Summary	Xingfang Li, MD, RAC, Michael Skelly, PhD, Seongeun Cho, PhD
Chemistry Review, Drug Substance	Debasis Ghosh, PhD, Donna Christner, PhD
Chemistry Review, Drug Product	Chris Hough, PhD, Julia Pinto, PhD
Chemistry Review, Process	Haitao Li, PhD, Pei-I Chu, PhD
Product Quality Microbiology Review	Haitao Li, PhD, Pei-I Chu, PhD
Biopharmaceutics Review	An-Chi Lu, PharmD, Haritha Mandula, PhD
Blend Uniformity/Content Uniformity Evaluation	Tianhua Wang, PhD, Xiaoyu Dong, PhD, Yi Tsong, PhD
Chemistry Review, Category 1 Abuse-Deterrence Studies	Venkateswara Pavuluri, PhD, RPh, Julia Pinto, PhD
Controlled Substances Staff Review	James Tolliver, PhD, Michael Klein, PhD
Statistical Review (Abuse Potential Studies)	Wei Liu, PhD, Qianyu Dang, PhD, Yi Tsong, PhD
Proprietary Name Review	James Schlick, RPh, MBA, Vicky Borders-Hemphill, PharmD
DMEPA Label and Labeling Review	James Schlick, RPh, Vicky Borders-Hemphill, PharmD
Maternal Health Consult	Miriam Dinatale, DO, Lynne Yao, MD

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1. Introduction

Arymo (morphine sulfate) Extended-Release Tablets represent an extended-release (ER) oral formulation of morphine. The Sponsor has submitted a 505(b)(2) NDA for Arymo ER 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. Arymo ER has been formulated in the hope that the physicochemical properties of the tablet will provide abuse-deterrent (AD) properties.

Morphine is an opioid-receptor agonist that is relatively selective for the mu-opioid receptor. In the United States, it is available as oral and parenteral immediate-release (IR) and oral ER formulations. Embeda (morphine sulfate and naltrexone hydrochloride) ER capsules were approved in 2009. Embeda is an ER morphine product with AD properties conferred by the release of naltrexone, an opioid antagonist, when attempts are made to cut or crush Embeda tablets for purposes of abuse. Morphabond is another ER morphine product. Its AD properties are conferred by its physicochemical properties. It was approved in 2015. Currently, Embeda and Morphabond are the only AD ER formulation of morphine approved in the U.S.

Arymo ER tablets consist of a matrix containing the active drug substance, morphine sulfate, along with polyethylene oxide (PEO) and butylated hydroxytoluene. The tablets are produced using an injection molding technique which results in tablets with controlled-release properties as well as physical and chemical features intended to resist common and more rigorous methods of manipulation. Each strength tablet is then covered with a colored film coating, with different colors to help differentiate between strengths.

The tablets were developed with the goal of being bioequivalent (BE) to approved MS Contin (morphine sulfate extended-release tablets). MS Contin is supplied in 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg strengths. MS Contin was first approved in 1987 and was the first formulation of morphine that allowed for oral dosing every 8-12 hours.

In 2010, public discussions began about initiating a class-wide Risk Evaluation and Mitigation Strategy (REMS) for all Extended-Release/Long-Acting (ER/LA) opioids. The ER/LA REMS was implemented in 2012. Arymo ER is an ER/LA opioid and would fall under the REMS.

The Sponsor of this NDA is Egalet U.S., Inc. Throughout all the reviews, Arymo ER is sometimes referred to as Arymo or EG-001.

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2. Background

Arymo ER was developed under IND 117317, received on August 22, 2013. There were several meetings between the Sponsor and DAAAP during the development of Arymo. These are outlined in Dr. Hariadi's Clinical Review. The development program for Arymo was designated as a Fast Track development program on February 18, 2014.

The early goals of the development program for Arymo were to: 1) demonstrate BE (b) (4) , 3) perform the other necessary clinical pharmacology studies, 4) characterize the safety of the formulation, and 5) perform Category 1,2, and 3 AD studies to support labeling.

(b) (4) The BE study of the 15 mg strength only narrowly missed demonstrating BE in Study 067-EG-006 because of the observed Cmax. Therefore, the Sponsor included an arm with two 15 mg tablets in Study 067-EG-012, a BE study comparing the MS Contin 30 mg strength and the Arymo 30 mg strength. BE of two 15 mg Arymo tablets to the MS Contin/Arymo 30 mg strengths was established. All these results are discussed in Dr. Nallani's Clinical Pharmacology Review.

One concern that has arisen during the review of similar AD products is the propensity of the tablets to swell and cause obstruction of the gastrointestinal (GI) tract. This propensity is imparted by excipients added to provide AD properties. While this was not specifically studied during development of Arymo, the Sponsor was asked during the current review cycle to conduct an in vitro study to examine this phenomenon. The study was conducted and is reviewed in the Chemistry Review. Dr. Hariadi's Clinical Review did not identify any events of choking, sticking, or GI obstruction during development of the product.

The need for Arymo to be part of the ER/LA REMS was discussed with the Sponsor and the Sponsor has submitted REMS documents with their application. REMS elements include a MedGuide, prescriber training/certification, and a communication plan.

Arymo does not trigger PREA.

There were a number of information requests (IRs) from multiple disciplines to obtain clarifications and additional information during the review cycle. The Sponsor supplied the requested information in a timely manner.

3. Chemistry

The Application Technical Lead for the Chemistry Review was Ciby Abraham, PhD. The review concludes, "Based on the recommendations from the following disciplines, Drug Substance, Process, Microbiology, Biopharmaceutics, Drug Product, and the Office of Compliance, CMC recommends the approval of ARYMO ER (morphine sulfate) 15 mg, 30 mg, and 60 mg tablets." The recommendation for approval is based on the following:

- Overall facility assessment acceptable
- Drug substance drug master file ((b) (4), DMF (b) (4)) reviewed and found acceptable
- Drug product specifications acceptable
- Drug product stability data support 24-month expiration dating
- Carton and container labeling were revised and found acceptable

Drug Substance/Impurities/Degradants

The Chemistry Review states, "The applicant listed (b) (4) . None of these were detected in drug product (b) (4) The drug substance impurities are controlled by impurity specification. Except (b) (4), any other individual impurity is controlled as NMT (b) (4)% which is consistent with ICHQ3A qualification thresholds. Other individual known or unknown impurities are controlled by NMT (b) (4)%. (b) (4) is (b) (4) and it is controlled in drug substance specification at NMT (b) (4)%. While (b) (4) is considered as a structural alert for genotoxic potential, the battery of genotoxic tests showed negative results. It is considered as a related substance. As noted earlier, no (b) (4) was detected in drug product (b) (4) is the only residual solvent listed in the drug substance specification."

Drug Product

The drug product is manufactured by (b) (4)
The Chemistry Review includes Dr. Li's evaluation of the drug product process. The table below provides the composition of the three different Arymo tablets.

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Table: Composition of Arymo Tablets

Component	Dosage Strengths of EG-001 Tablets			Function
	15 mg	30 mg	60 mg	
	Mg per Tablet (%)	Mg per Tablet (%)	Mg per Tablet (%)	
Morphine Sulfate	15.00 (1.98)	30.00 (3.94)	60.00 (7.83)	Drug Substance
Polyethylene Oxide 400,000 (b) (4)	(b) (4)			Release controlling; Abuse-Deterrent properties (b) (4)
Butylated Hydroxytoluene (b) (4)				
Total Weight	759.21 (100.0)	761.69 (100.00)	766.53 (100.00)	----

Source: Clinical Review, page 24.

Excipients

Polyethylene oxide (PEO) is a commonly-used release-controlling excipient in abuse-deterrent products and comprises (b) (4) % of the Arymo matrix tablet composition, (b) (4) The drug release from the Arymo tablet is controlled by erosion of the PEO tablet matrix (b) (4), thereby extending the drug release. Arymo tablets are produced using a hot-melt extrusion process resulting in a hard tablet. (b) (4)

About the excipients, the Chemistry Review states the following (pages 30-31):

(b) (4)

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(b) (4)

(b) (4)

The following table summarizes the compositions of the three coatings used by Egalet in this NDA.

Table: Coating Composition of Arymo Tablets

(b) (4)

(b) (4)

Category 1 Abuse-Deterrent Studies

Additionally, the Category 1 AD studies were evaluated as part of the Chemistry Review (pages 60-87). These included physical manipulation studies, small-volume extraction studies (with injectability and syringeability), and large-volume extraction studies comparing Arymo to MS Contin. Vaporization for smokeability was also assessed. These Category 1 results are also discussed in Dr. Tolliver's Controlled Substance Staff Review and I will defer summarizing the results to that part of my review in Section 11 below.

The Chemistry Review has recommended a number of Postmarketing Requirements (PMRs) in order to assure that marketed Arymo tablets maintain the labeled AD properties through the

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end of shelf-life and as part of life-cycle management. The recommended PMRs are listed is Section 11 below.

The propensity for the tablets to swell was also addressed in the Chemistry Review (pages 69-70). The normal tablet dimensions are 5.8 mm in width and 19.3 mm in length (page 94). Regarding swelling, the Chemistry Review states, "Swelling in vitro experiments were conducted on the 15 mg and 60 mg tablets. The tablets were submerged in 1600 mL of liquid media where they were fully submerged. When the tablets were submerged for 30 seconds, they swelled to approximately 105% of the tablets weight in the liquid media. During the first three minutes, the outer coating of the tablet started to dissolve and swelled to 114-117%. Between 3.75-4.75 hours, the range of the swelling was observed to be 249-274%." The maximum dimensions observed were about 24 mm in length, 13 mm in width, and 9 mm in height (page 70).

Environmental Assessment

The Applicant has claimed a categorical exclusion from preparing an Environmental Assessment and the chemistry reviewers have found this acceptable.

Drug Process

(b) (4) The initially-submitted (b) (4) data were reviewed in detail and found unacceptable (see also Dr. Tianhua Wang's Statistical Review of this data, dated August 15, 2016). Additional data were submitted by the Sponsor. The issue has been addressed by the Sponsor (b) (4) .

Also, the Sponsor was asked during the review how hardness of tablets was evaluated. The following IR was sent to the Sponsor on June 2, 2016:

"In the submission under module '3.2.P.2 Pharmaceutical Development' it was stated that 'tablet hardness and resistance to particle size reduction offers an impediment to abuse by multiple routes of administration'. We were unable locate the measured values for Hardness of tablets, (b) (4) . Please provide available information…"

The Sponsor responded, (b) (4) The data…demonstrate that this test did not cause EG-001 tablets to break or result in fracture when subjected to the

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maximum force of the hardness tester, 400 N (b) (4) By comparison, MS Contin (b) (4) has a tablet hardness of 63 N.

An acceptance criterion for tablet hardness has been added as recommended by the reviewers. The Chemistry Review states, " (b) (4)), the Applicant suggested the acceptance criterion of " (b) (4) This is deemed acceptable."

Microbiology

The Product Quality Microbiology Review was performed by Haitao Li, PhD with concurrence from Pei-I Chu, PhD. They conclude that "…the risk of this DP supporting microbial growth is low."

Biopharmaceutics Review

This was reviewed by An-chi Lu, PharmD with concurrence from Haritha Mandula, PhD. The Biopharmaceutics Review focused on the evaluation and acceptability of: 1) the proposed dissolution methodology and acceptance criteria, 2) the in vitro in vivo correlation (IVIVC), and 3) the in vitro alcohol dose-dumping study.

The dissolution methodology and acceptance criteria were found acceptable. Also, the results of the in vitro dose-dumping study did not show dose dumping with alcohol. However, for a number of reasons, Drs. Lu and Mandula believe the IVIVC model is inadequate. (b) (4)

The deficiencies in the IVIVC model are not considered approvability issues by Drs. Lu and Mandula, (b) (4). They believe the application is acceptable from a biopharmaceutics perspective. They have the following deficiency to be communicated to the Sponsor:

"The in vitro-in vivo correlation is inadequate due to the following reasons:

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(b) (4)

4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology Review was performed by Elizabeth Bolan, PhD with concurrence from Dan Mellon, PhD. They recommend that the NDA be approved with four postmarketing requirements (PMRs).

The nonclinical development program for this 505(b)(2) NDA application relies on the Agency's previous finding of safety for MS Contin. The review states, "No new pharmacology, general toxicology, genetic toxicology, reproductive and developmental toxicology, or carcinogenicity studies were conducted or required for this application. The Applicant has submitted studies to qualify (b) (4), a drug product degradant, which exceeds the ICH Q3B(R2) threshold for qualification. Justification has also been provided for several excipients, including polyethylene oxide (b) (4) (PEO; MW: 400,000), (b) (4) when the product is consumed at the maximum theoretical daily dose of morphine."

"With the exception of the PEO, the levels of the excipients in this product are considered acceptable and do not require qualification. The levels of the PEO in this product, when used at the maximum theoretical daily dose (MTDD) of morphine, (b) (4) To support the safety of the levels of the PEO in this product, the Applicant is referencing MF (b) (4) Master File (b) (4) has been found to be inadequate because c (b) (4) These (b) (4) entities could include (b) (4) and specifications for these impurities in the excipient master file may be required. However, because of the longstanding history of use of PEO in many products which reference MF (b) (4), this deficiency will not be an approval issue for NDA 208603. The levels of PEO in Arymo ER when used at the MTDD of MS are considered acceptable from a pharmacology/toxicology perspective for this NDA. Pharmacology toxicology recommends that the Applicant conduct several studies as post-marketing requirements (PMR) to fully characterize the toxicity of the PEO."

The four PMRs recommended by Dr. Bolan are:

"PMR 1: Analyze the PEO product employed in Arymo ER for low molecular weight impurities. Identify and quantitate the impurities. Submit a toxicological risk assessment for the exposure to the impurities taking into consideration the maximum theoretical daily dose of Arymo ER.

PMR 2: Conduct an embryo-fetal development study in the rat model to assess the potential impact of PEO on development. The study must be designed to adequately qualify the safety

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of the low molecular weight PEO components (impurities/degradants) in the PEO (b) (4) when the product is consumed up to the MTDD of Arymo ER.

PMR 3: Conduct an embryo-fetal development study in the rabbit model to assess the potential impact of PEO on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO (b) (4) when the product is consumed up to the MTDD of Arymo ER.

PMR 4: Conduct a pre- and post-natal development study in the rat model to assess the potential impact of PEO on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) (b) (4) when the product is consumed up to the MTDD of Arymo ER."

5. Clinical Pharmacology

The Clinical Pharmacology Review was completed by Srikanth Nallani, PhD with concurrence from Yun Xu, PhD. They have no outstanding clinical pharmacology issues and labeling recommendations have been made.

In support of the 505(b)(2) application, the Sponsor performed a comparative bioavailability program, including Arymo 15 mg, 30 mg, 60 mg. (b) (4) tablets as well as the listed drug MS Contin. (b) (4)

The Sponsor performed single-dose PK studies of Arymo, including a food-effect study. Given the BE results with the single-dose studies, a multiple-dose PK study was not required.

The Sponsor concluded that Arymo 60 mg was bioequivalent to MS Contin 60 mg, based on both Cmax and AUC values in Study 067-EG-011. Dr. Nallani agrees. Two 15 mg Arymo tablets were BE to one 30 mg tablet of Arymo and the 30 mg Arymo tablet was BE to MS Contin 30 mg in Study 067-EG-012. In a direct comparison of the 15 mg strengths of Arymo and MS Contin in Study 067-EG-006, BE was demonstrated for AUC but was just slightly missed for Cmax. The 90% confidence interval (CI) for Cmax for the 15 mg Arymo tablet was 78.99% to 88.47%, just missing the lower bound of 80% for BE. Dr. Nallani states: "Based on team discussion, it is agreed that considering the titration to effect regimen employed for morphine extended-release formulations, this slightly lower Cmax for 15 mg is not considered clinically significant and will not prevent approval of the product."

When comparing Arymo taken in the fed versus the fasted state in Study 067-EG-011, Dr. Nallani states that the Cmax and AUC values met the BE criteria.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The primary Clinical Review was performed by John Hariadi, MD. He notes that the Sponsor is relying on previous findings of efficacy and safety for MS Contin to support the Arymo NDA. In the chronic-use setting, Arymo, dosed with the 15 mg, 30 mg, and 60 mg tablets, will provide morphine plasma levels that are BE to the levels achieved with MS Contin 15 mg, 30 mg, and 60 mg, respectively. Therefore, no formal efficacy studies were conducted with Arymo.

The indication sought by the sponsor for Arymo is 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 dosing guidelines are identical to those for MS Contin.

8. Safety

The primary review of the safety data was performed by John Hariadi, MD.

The safety database submitted in the NDA contains safety data from seven clinical pharmacology studies and two human-abuse-liability (HAL) studies. The clinical pharmacology studies were primarily conducted in normal volunteers who were naltrexone-blocked. The HAL studies were performed in healthy volunteers who were experienced opioid users but were not opioid dependent.

A total of 442 volunteers were exposed to at least one dose of Arymo across all studies. Of these, 297 received a single dose and 145 received between two and three doses. Dr. Hariadi summarizes the demographic and baseline characteristics of the enrolled subjects in Section 8.2 of his review. This safety population is not reflective of the target pain population and the duration of treatment in the nine studies is much lower than in the intended patient population. Nevertheless, Dr. Hariadi notes that, given the BE results comparing Arymo and MS Contin, we can conclude that Arymo will exhibit similar safety characteristics to MS Contin.

Serious Adverse Events

Dr. Hariadi describes one patient with a serious adverse event, a 52-year-old woman with a spontaneous abortion after exposure to Arymo 60 mg (early formulation) in Study EG-001. While the sponsor considers the event not related to study medication, attribution cannot be determined with certainty. Dr. Hariadi summarizes the report as follows:

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"The urine pregnancy test performed at screening and the serum pregnancy test performed prior to study drug administration in Period 1 were negative. However, the serum pregnancy tests performed prior to dosing in Period 2 yielded an equivocal result (Beta human chorionic gonadotropin [β-HCG] of 18.7 IU/L). A repeat serum pregnancy test was performed three days later and the result was positive (β-HCG of 29.3IU/L). The subject was withdrawn by the Medical Sub-Investigator prior to drug administration in Period 2. Approximately 6 days later the subject had an episode of spotting and was seen by a gynecologist. On the next day, her regular menses started. According to the gynecologist, the event was considered to be a spontaneous abortion after which the β-HCG result returned to negative."

Discontinuations

A total of 12 volunteers withdrew from study drug treatment due to adverse events across all studies, including the SAE already described above. All were in the BE studies and none were in the abuse liability studies. With the exception of the SAE above and one case of mild headache and fever, all the AEs that led to discontinuation were consistent with the known gastrointestinal adverse event profile associated with morphine products, primarily emesis. One patient also had moderate abdominal pain that required observation in the hospital emergency unit for 16 hours; the event resolved in one day. Some patients were treated with anti-emetics, but for others, emesis improved spontaneously. All the cases of emesis were rated moderate in severity.

One 25-year-old male was noted to have a mild headache and fever (up to 38.2 C) six days after receiving MS Contin 60 mg and prior to dosing in Period 2 of Study 11. The fever resolved 13 hours later. Although the causality was unclear, the subject was discontinued from the study.

Common Adverse Events

The AEs observed are all those expected with an opioid and no significant differences are observed between Arymo and the other morphine products administered. Dr. Hariadi concludes, "…the TEAEs observed are similar to other morphine extended-release products, and thus labelling of the adverse reactions section should closely mirror that of MS Contin."

Dr. Hariadi also describes a number of laboratory abnormalities that were observed during the trials. None of these raised additional concern. Some vital sign abnormalities were observed consistent with the AE profile for opioids.

Additional Safety Considerations

As already mentioned in Section 2 of this review, one concern that has arisen during the review of similar AD products is the propensity of the tablets to swell and cause obstruction of the gastrointestinal (GI) tract. This propensity is imparted by the excipients added to provide AD properties, including PEO. During the current review, the Sponsor was asked to conduct an in vitro study to examine for tablet swelling. The study was conducted and is discussed in

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the CMC Review by Dr. Pavuluri. While the tablets do swell in liquid, maximum swelling is delayed several hours. Much less swelling is observed early and it would not be expected to interfere with swallowing. After several hours, the maximum dimensions achieved are about 24 mm for length, 13 mm for width, and 9 mm for height.

A formal study to evaluate tablet stickiness was not conducted, but the propensity for tablet stickiness exists (b) (4)
According to the Biopharmaceutics Review, "The Applicant stated that (b) (4)
USP apparatus 1 (basket) was chosen." When investigating the use of baskets for dissolution studies, "The Applicant stated that (b) (4)
. The (b) (4)
CMC reviewer, Dr. Pavuluri states, "

The meeting minutes from the End-of-Phase 2 Meeting in 2014 state, "The Sponsor stated that in their oral human abuse liability (HAL) study, both the whole product and powdered or manipulated product become sticky when placed in water…The Division asked if there is an issue with swallowing Egalet-001 when taken with water. The Sponsor responded that there were no issues swallowing Egalet-001 with the coating (b) (4) If whole tablets placed in water become sticky, the implication is that stickiness can emerge in a reasonably short period of time and present a choking risk, especially if more than a single tablet is taken.

Dr. Hariadi reviewed the safety data specifically for any AEs associated with choking, sticking, or gastrointestinal obstruction. None were found. There were six AEs classified as "oropharyngeal pain." All were described as sore throat and all were considered mild. While four were observed with Arymo, two were observed with MS Contin. Dr. Hariadi concludes that Arymo would not likely present a choking/swallowing hazard. While I agree that there was not a signal for a choking hazard in the clinical studies, these studies were conducted under a controlled environment with only one tablet administered at a time. Therefore, I believe labeling warnings about choking risk are required, given the available information.

Two other PEO-containing products, Oxycontin and Opana ER, have been associated with postmarketing cases of difficulty in swallowing tablets, including choking, gagging, regurgitation, and tablets stuck in the throat. They have also been associated with

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postmarketing cases of intestinal obstruction and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Both products carry the following warning in labeling:

> "There have been post-marketing reports of difficulty in swallowing [name] tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet [name] tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.
>
> There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen."

While no such cases were identified in Dr. Hariadi's Clinical Review, the properties of swelling and stickiness identified for Arymo warrant the same warning in labeling. Labeling should also instruct patients to to take tablets one at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Patients should also be instructed not to pre-soak, lick, or otherwise wet Arymo tablets prior to placing in the mouth. Vigilance for postmarketing reports suggestive of choking or gastrointestinal obstruction will be needed.

Discussion

Dr. Hariadi concludes, "Overall, 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." I agree with this assessment, but I also believe a warning about risk of choking and GI obstruction is warranted given the information described above.

9. Advisory Committee Meeting

A Joint Advisory Committee Meeting of the Anesthetic/Analgesic Drug Products and Drug Safety/Risk Management Advisory Committees was held on August 4, 2016. A closed session, in which the methodology for the Sponsor's Category 1 AD studies was discussed, was followed by an open session.

The committee was asked to discuss whether there are sufficient data to support a finding that Arymo has properties that can be expected to deter abuse, commenting on support for AD

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effects for oral, nasal, and intravenous abuse. The committee was asked to vote on the following questions:

1. If approved, should Arymo ER be labeled as an AD product by the oral route of abuse?
2. If approved, should Arymo ER be labeled as an AD product by the nasal route of abuse?
3. If approved, should Arymo ER be labeled as an AD product by the intravenous route of abuse?
4. Should Arymo ER be approved for the proposed indication?

As discussed further in Section 11 below, the CSS Review concluded that Study 067-EG-008 does not support an oral AD claim for Arymo. FDA materials presented to the committee suggested that the small but statistically significant reduction in Drug Liking observed for Arymo in the oral abuse liability study was of uncertain significance. The Sponsor argued that Arymo's tablet hardness would prevent abuse by chewing and that the oral abuse liability study underestimated the oral AD effect because subjects were presented with manipulated tablets (cut with a knife) and chewing was not required. Additionally, Arymo is not subject to alcohol dose-dumping, reducing the likelihood of abuse by that means.

Committee members were generally persuaded by the argument that Arymo should prevent chewing of tablets for oral abuse. Dr. Tolliver has made the argument that cutting tablets is not difficult and that any cutting (not necessarily into 32 pieces) will increase the exposed surface area and allow for faster absorption of morphine from Arymo. He also argues that chewing has not been directly assessed.

The committee voted to approve Arymo for the proposed indication (18-to-1) and to approve Arymo with AD language for the oral (16-to-3), nasal (18-to-1), and intravenous (18-to-1) routes.

10. Pediatrics

The application does not trigger the requirements of PREA.

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11. Other Relevant Regulatory Issues

Clinical Site Inspection

Both clinical abuse liability studies were performed at the same site:

Lynn Webster, MD
CRI Lifetree, Inc.
Salt Lake City, Utah

A separate inspection of that site was not performed for this NDA review because that site was recently inspected for a different NDA in July, 2015 with no significant deficiencies identified.

OSIS Inspections

The Office of Study Integrity and Surveillance (OSIS) conducted an on-site inspection of the site of the clinical pharmacology studies, PPD Phase I Clinic in Austin, Texas. The clinical portions of Studies 11 and 12 were audited. No objectionable conditions were identified during the audit and no Form FDA-483 was issued. The review concludes that "…results from clinical portions of studies 067-EG-011 and 067-EG-012 should be accepted for further Agency review."

OSIS did not conduct an inspection for the bioanalytical portions of BE studies conducted by (b) (4). The rationale was that OSIS had recently inspected the site with the results classified as No Action Indicated (NAI).

Abuse-Deterrence Studies/Controlled Substances Staff (CSS)

The review of the AD data submitted in the NDA was conducted as part of both the Chemistry and CSS Reviews. James Tolliver, PhD provided the CSS Review with concurrence from Michael Klein, PhD. Multiple Category 1 in vitro studies were performed to investigate the physical-chemical properties of Arymo. Dr. Tolliver summarized these Category 1 results in his review. Dr. Venkateswwara Pavuluri reviewed the in vitro AD studies from a chemistry perspective. The supporting statistical review of Studies 067-EG-008, a category 2/3 oral human abuse liability (HAL) study, and 067-EG-009, a category 2/3 nasal HAL study, was performed by Wei Liu, PhD with concurrence from Qianyu Dang, PhD and Yi Tsong, PhD.

The CSS and chemistry reviewers concluded that the data provided do support placement of abuse-deterrent language in the label.

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In Vitro Studies

The Chemistry Review states, "ARYMO ER was designed using Egalet's Guardian™ Technology, which utilizes a polymer matrix tablet technology involving an injection molding process. The tablets possess controlled- release properties as well as physical and chemical features that may resist some common methods of manipulation. Guardian™ Technology is designed to make the tablets harder than typical tablets (>400 N) which in theory would make it more resistant to particle size reduction and therefore more challenging to extract morphine sulfate. In addition, the technology results in a viscous hydrogel on contact with aqueous media, making syringeability more challenging. The majority of the physical manipulation attempts on ARYMO ER tablets resulted in particle sizes > 500 microns. Among the manually operated tools, the knife appears to be the most efficient tool in terms of producing particles less than 1,000 μm, which was not possible with the spoon, mortar and pestle, pill crusher, and hammer. Household electrical tools such as spice grinder and coffee grinder appear to be moderately effective for particle size reduction, when operated intermittently to prevent overheating and damage of the equipment components. The gelling nature of the formulation in aqueous media appears to restrict morphine extraction even when significant effort was expended for particle size reduction."

The in vitro studies were performed to investigate various methods of defeating the controlled-release properties of Arymo with the intent to abuse the product by various methods of administration, including intravenous, oral, nasal, and smoking. The active control in these studies was MS Contin. Both Dr. Tolliver's review and Dr. Pavuluri's CMC Review provide a comprehensive description of these studies and results.

Arymo resisted reduction to small particle sizes by the methods tested, except for the spice grinder, coffee grinder, and knife. With the spice grinder, a method was developed that could produce about 20% of particles < 1000 microns. Overall, Arymo was more resistant to crushing and particle size reduction compared to MS Contin.

The release of morphine into a dissolution medium consisting of 0.1 N HCl increased as a function of the number of pieces into which the tablets were cut, with more than half the morphine released within an hour when cut into 32 pieces. Dr. Tolliver states, "As EG-001 tablets are cut into increasing numbers of pieces, there is a concomitant increase in surface area associated with an increase in rate of release of morphine."

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Large volume extraction was reasonably good from cut Arymo tablets as shown in the following table.

Table: Percent Morphine Extracted from Arymo 60 mg (Cut into 32 Pieces) in Various Solvents

Solvent	Solvent Temperature	Average % Recovery Of Morphine from One 60 mg EG-001 Tablet Cut Into 32 Pieces As A Function of Extraction Time (N = 3)						
		0.083 hrs	0.25 hrs	0.5 hr	1 hr	2 hrs	4 hrs	8 hrs
Tap Water	RT	5.47	12.21	23.04	43,64	65.02	71.53	70.89
	90C	15.24	44.31	61.01	64.76	49.41	35.35	22.40
Saline	RT	7.03	15.08	26.37	48.82	70.06	77.72	80.84
	90C	19.35	53.06	75.47	86.22	83.11	82.78	77.87
Vinegar	RT	9.21	16.66	27.22	47.40	71.26	75.46	73.79
	90C	21.4	55.86	72.42	77.84	76.00	73.07	65.50
0.1M HCl	RT	8.17	16.53	27.47	47.41	71.45	78.48	78.34
	90C	19.68	57.75	79.10	84.48	81.20	81.36	75.81
pH2 Buffer	RT	7.18	14.70	25.03	42.16	65.09	63.30	71.60
	90C	17.19	45.30	64.84	68.33	69.15	63.97	43.68
pH 4 Buffer	RT	6.84	14.20	23.92	46.95	64.00	67.08	65.82
	90C	13.87	40.75	64.96	70.44	70.05	71.34	72.28
pH 6 Buffer	RT	7.16	14.35	25.04	43.22	67.40	70.84	71.17
	90C	14.74	43.82	63.72	73.32	71.28	73.52	73.65
pH 8 Buffer	RT	4.86	12.58	22.96	46.34	57.30	71.98	76.27
	90C	11.19	34.38	54.34	70.53	73.04	66.82	67.57
pH 10 Buffer	RT	3.09	8.75	20.21	41.76	59.13	68.67	71.84
	90C	6.13	23.06	50.51	69.40	67.22	63.34	50.13
20% Ethanol	RT	3.31	8.29	14.48	26.62	47.87	68.03	72.06
	60C	9.77	26.54	48.40	66.57	71.31	71.64	68.09
50% Ethanol	RT	2.87	6.32	11.47	22.64	41.98	67.68	79.64
	60C	8.87	25.45	52.80	77.57	83.80	78.14	78.87
95% Ethanol	RT	0.00	2.10	2.86	4.55	6.67	10.61	16.02
Methanol	RT	3.96	6.11	8.16	12.07	17.52	24.52	34.33
Isopropanol	RT	0.00	0.00	0.00	0.00	2.68	4.26	7.08
Acetone	RT	0.00	0.00	0.00	3.54	5.73	8.69	12.48
Methylene Chloride	RT	5.22	23.81	43.49	66.35	57.93	61.81	65.19
Ethyl Acetate	RT	0.00	0.00	0.00	0.00	2.96	5.04	8.04
Hexane	RT	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Source: CSS Review, Table 2, page 12.

Arymo 60 mg tablets were also compared to MS Contin 60 mg tablets for producing small volume solutions suitable for intravenous injections. While MS Contin could be readily used to produce a suitable intravenous solution, the recovery of morphine from ground Arymo in small volumes was limited producing low-concentration solutions with total extraction less than 5.6 mg. According to the Chemistry Review, "The gelling nature of the formulation in aqueous media appears to restrict morphine extraction in aqueous media even when significant effort was expended for particle size reduction."

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Smokeability studies were performed and showed that under the simulated conditions Arymo tablets could not be abused by smoking. However, in the absence of a positive control of MS Contin no AD claims can be supported.

Nasal Abuse Potential Study, Study 067-EG-009

The Sponsor conducted a category 2/3 nasal HAL study in non-dependent recreational opioid users to investigate the AD properties of Arymo following nasal administration. The primary objective of the study was to determine the abuse potential of crushed Arymo 60 mg administered intranasally and intact Arymo 60 mg administered orally, both relative to crushed intranasal MS Contin 60 mg. A total of 83 subjects were screened with 80 entering the qualification phase. After a Naloxone Challenge Test and a Drug Discrimination Test, there were 50 subjects that were randomized in the Treatment Phase of the study, with 46 completing. There were 46 subjects included in the pharmacodynamics assessment and 46 included in the PK assessment. The study was a 5-way crossover study with the following treatment groups, administered in a double-dummy fashion:

- Treatment A: crushed IN Arymo (all particle sizes) and intact PO placebo
- Treatment B: crushed IN Arymo (< 1000 microns) and intact PO placebo
- Treatment C: crushed IN MS Contin and intact PO placebo
- Treatment D: crushed IN placebo and intact PO Arymo
- Treatment E: crushed IN placebo and intact PO placebo

Arymo and MS Contin tablets were 60 mg. The volume of powder provided for IN administration for Treatments C, D, and E was matched to the volume of powder achieved for Treatment B after sieving out particle sizes > 1000 microns. The Arymo IN Treatment A was referred to as "high volume," while the Arymo IN Treatment B was referred to as "low volume." The IN Treatments C, D, and E were therefore considered "low volume." All subjects received the high volume Arymo treatment first to minimize a sequence effect; subjects received the remaining treatments in random order.

The preparation of Arymo tablets and MS Contin tablets differed and was optimized based on Category 1 testing to produce the smallest particle sizes. Arymo tablets were cut and then ground using a spice grinder, while MS Contin was ground using a mortar and pestle.

PK parameters were determined and the following measures of drug-liking were obtained: Bipolar Drug Liking on a 0-100 point VAS, Unipolar High on a 0-100 point VAS, Bipolar Take Drug Again on a 0-100 point VAS, and Overall Drug Liking VAS. Primary parameters for Drug Liking were: maximum drug effect (E_{max}) and time to reach maximum drug effect (TE_{max}). Ease of Snorting was also assessed.

The primary treatment comparisons were Treatment C versus Treatment A (high volume Arymo) and Treatment C versus Treatment B (low volume Arymo) for Bipolar Drug Liking. The comparison of Treatment C versus Treatment A (high volume Arymo) for Bipolar Drug

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Liking represents a more challenging test because a greater amount of morphine was available from Treatment A than from Treatment B.

Results

Pharmacodynamic

Summary statistics for the pharmacodynamics measures are shown in the table below.

Table: Descriptive Statistics for Pharmacodynamic Measures

Measures	Statistics	Treatments – Maximum Effect (Emax)				
		Intranasal EG001 60 mg High Volume (n=46)	Intranasal EG001 60 mg Low Volume (n=46)	Oral EG001 60 mg Intact (n=46)	Intranasal MS Contin 60 mg (n=46)	Placebo (n=46)
Bipolar Drug Liking VAS	Mean (SD)	65.5 (14.3)	59.6 (12.5)	68.5 (13.6)	77.7 (11.7)	54.7 (10.6)
	Median	62.0	52.5	68.0	77.5	51.0
	Q1,Q2	52, 76	51, 65	59, 77	70, 85	50, 58
Unipolar High VAS	Mean (SD)	27.7 (28.2)	16.0 (23.2)	36.7 (28.1)	61.2 (23.6)	10.7 (20.2)
	Median	20	5	34	65.5	0
	Q1, Q2	2, 50	0, 20	11, 52	42,79	0, 9
Bipolar Take Drug Again VAS	Mean (SD)	43.1 (29.6)	52.6 (17.2)	58.9 (24.9)	69.9 (27.4)	52.5 (12.7)
	Median	50.0	50.0	56.0	73.0	50.0
	Q1, Q2	19, 66	50, 58	45.75	57, 90	50, 51
Bipolar Overall Drug Liking VAS	Mean (SD)	53.9 (21.7)	54.4 (13.6)	59.4 (24.2)	72.7 (18.1)	52.1 (11.2)
	Median	51.0	50.5	59.0	71.0	50.0
	Q1, Q2	50, 67	50, 55	50, 77	61, 87	50, 51

Source: Clinical Review, page 45.

The primary analysis was a comparison of Drug Liking Emax between IN crushed Arymo and IN crushed MS Contin. The result for that comparison, whether relying on the high volume or the low volume Arymo treatments, was statistically significant as were the comparisons for Take Drug Again. Note that, while Ease of Snorting was rated as "difficult" for the high volume Arymo group (the other IN treatments were all rated as "easy"), the greater amount of morphine delivered with the high volume suggests that the high volume Arymo versus MS Contin may be the most informative comparison.

The results support an AD effect of Arymo to intranasal abuse compared to MS Contin. Also, all of the PD measures are the same or lower with IN Arymo compared to oral Arymo. While Drug Liking and High are higher with IN Arymo compared to IN placebo, Take Drug Again is lower with IN Arymo compared to IN placebo.

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Pharmacokinetic

The pharmacokinetic results are consistent with the observed pharmacodynamic results. The PK results were supportive of the Drug Liking results, with substantially higher peak plasma concentrations (Cmax) for IN crushed MS Contin relative to IN crushed Arymo. The Cmax of morphine after IN crushed Arymo was similar to that seen after PO intact Arymo, but the Tmax was shorter.

Table: Plasma Pharmacokinetics of Morphine following Treatments

Plasma PK Parameter for Morphine	Statistic	Intranasal MS Contin 60 mg (n = 37)	Intranasal EG001 60 mg High Volume (n = 45)	Intranasal EG001 60 mg Low Volume (n = 46)	Intact Oral EG001 60 mg (n = 39)
Cmax (ng/mL)	Mean (SD)	36.33 (12.90)	19.02 (9.56)	4.47 (2.25)	17.20 (4.26)
	Median	34.60	19.80	4.08	18.10
	Range	6.5 – 62.3	4.2 – 40.1	1.0 – 11.3	9.3 – 24.8
Tmax (h)	Median	1.13	2.17	2.66	3.65
	Range	0.42 – 2.67	1.13 – 6.13	0.85 – 6.10	1.13 – 6.17

Source: Clinical Review, page 44.

Oral Abuse Potential Study, Study 067-EG-008

The Sponsor conducted a category 2/3 oral HAL study in non-dependent recreational opioid users to investigate the AD properties of Arymo following oral administration. The primary objective of the study was to determine the abuse potential of manipulated Arymo 60 mg administered orally and intact Arymo 60 mg administered orally, both relative to manipulated oral MS Contin 60 mg. A total of 78 subjects were screened with 78 entering the qualification phase. After a Naloxone Challenge Test and a Drug Discrimination Test, there were 39 subjects that were randomized in the Treatment Phase of the study, with 38 completing. There were 38 subjects included in the pharmacodynamics assessment and 39 included in the PK assessment. The study was a 4-way crossover study with the following treatment groups, administered in a triple-dummy fashion:

- Treatment A: Intact Arymo tablet, 32-pieces placebo, crushed placebo
- Treatment B: Intact placebo tablet, 32-pieces Arymo, crushed placebo
- Treatment C: Intact placebo tablet, 32-pieces placebo, crushed MS Contin
- Treatment D: Intact placebo tablet, 32-pieces placebo, crushed placebo

The preparation of Arymo tablets and MS Contin tablets differed and was optimized based on Category 1 testing. Arymo tablets were cut into 32 pieces, while MS Contin was ground using a mortar and pestle. The treatments were dispensed onto the tongue and followed by several rinses with liquid not to exceed 240 mL.

Reference ID: 3993553

PK parameters were determined and the following measures of drug-liking were obtained: Bipolar Drug Liking on a 0-100 point VAS, Unipolar High on a 0-100 point VAS, Bipolar Take Drug Again on a 0-100 point VAS, and Overall Drug Liking VAS. Primary parameters for Drug Liking were: maximum drug effect (E_{max}) and time to reach maximum drug effect (TE_{max}).

The primary treatment comparison was Treatment B versus Treatment C for Bipolar Drug Liking.

Results

Pharmacodynamic

Summary statistics for the pharmacodynamics measures are shown in the table below.

Table: Descriptive Statistics for Pharmacodynamic Measures

Measure	Statistics	Maximum Effect (Emax)			
		EG001 60 mg		Manipulated MS Contin 60 mg (n=38)	Placebo (n=38)
		Manipulated (n=38)	Intact (n=38)		
Bipolar Drug Liking VAS	Mean (SE)	68.3 (2.0)	63.2 (1.64)	73.3 (1.59)	53.3 (1.27)
	Median	67.0	62.0	74.0	50.0
	Q1,Q2	61, 75	56, 68	68, 79	50, 52
Unipolar High VAS	Mean (SE)	38.8 (4.15)	26.8 (3.97)	51.9 (3.83)	5.3 (1.87)
	Median	38.0	18.5	49.0	0
	Q1, Q2	18, 58	7, 47	34, 72	0, 1
Bipolar Take Drug Again VAS	Mean (SE)	62.9 (3.18)	54.8 (3.37)	70.1 (2.84)	51.0 (1.65)
	Median	61.5	56.0	68.0	50.0
	Q1, Q2	51, 71	50, 65	56, 80	50, 50
Bipolar Overall Drug Liking VAS	Mean (SE)	65.1 (3.02)	55.7 (3.21)	69.8 (2.50)	52.2 (1.31)
	Median	63.5	57.0	67.5	50.0
	Q1, Q2	51, 75	50, 66	57, 81	50, 50

Source: Clinical Review, page 40.

The primary analysis was a comparison of Drug Liking Emax between manipulated Arymo and manipulated MS Contin. The result for that comparison was statistically significant, but the between-group difference was very small, 5 points on the VAS scale. Dr. Tolliver questions the clinical significance of this difference in his review. His concerns are supported by the observation that the comparison of Take Drug Again between manipulated Arymo and manipulated MS Contin was not statistically significant. Other outcome measures provided inconsistent results in support of an oral AD claim.

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During the Advisory Committee Meeting (discussed in Section 9 above), the point was made that subjects in Study 067-EG-008 were presented with pre-manipulated Arymo and MS Contin and therefore the study did not capture the added difficulty that abusers would encounter in preparing suitable manipulated drug product. The tablet hardness of Arymo versus MS Contin was discussed and committee members were generally persuaded by the argument that Arymo should prevent chewing of tablets for oral abuse. Dr. Tolliver has made the argument that cutting tablets is not difficult and that any cutting (not necessarily into 32 pieces) will increase the exposed surface area and allow for faster absorption of morphine from Arymo. He also argues that chewing has not been directly assessed.

The CSS Review concludes that the results of Study 067-EG-008 do not support an AD effect of Arymo to oral abuse compared to MS Contin.

Pharmacokinetic

Treatment with manipulated Arymo 60 mg produced a lower Cmax (28.74 ng/mL) compared to treatment with manipulated MS Contin 60mg (42.34 ng/mL), but a higher plasma level than intact Arymo 60 mg (17.81ng/mL). Values for Tmax were 0.88, 2.12, and 4.12 hours for manipulated MS Contin, manipulated Arymo, and intact Arymo, respectively.

Table: Plasma Pharmacokinetics of Morphine following Treatments

Morphine Plasma Pharmacokinetic Parameter	Statistic	Manipulated MS Contin 60mg (N=39)	Manipulated EG-001 60 mg (N=38)	Intact EG-001 60 mg (N=38)
Cmax (ng/mL	Mean (SD)	42.34 (14.31)	28.74 (9.09)	17.81 (6.60)
	Median	42.20	29.20	16.70
	Range	14.2, 79.0	12.5, 47.8	8.5, 32.3
	% CV	33.8	31.6	37.0
Tmax (hours)	Median	0.880	2.120	4.120
	Range	0.63, 4.13	0.88, 4.15	1.63, 6.13

Source: Clinical Review, page 40.

Recommendations from the CSS Review

The CSS Review includes Dr. Tolliver's detailed conclusions after review of the Category 1-3 data. Based on those conclusions, he has the following four recommendations:

"1. Consideration should be given to allowing abuse deterrent claims for EG-001 Tablets with respect to abuse by intravenous injection. The Category 1 injectability/syringeability studies demonstrated that it was difficult to produce suitable intravenous solutions using EG-001 tablets. At the same time, these studies demonstrated that the positive control, MS Contin, could be readily used to produce intravenous solutions.

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2. Consideration should be given to allowing abuse deterrent claims for EG-001 Tablets with respect to abuse by snorting (insufflation). Category 1 physical manipulation studies demonstrated that with use of available household tools it was difficult to crush/ground EG-001 tablets, whereas MS Contin tablets could be easily ground into a fine powder. Category 3 intranasal HAP study 067-EG-009 demonstrated that the insufflation of ground EG-001 was associated with statistically significant, lower maximum scores for Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS compared to that produced by the insufflation of the positive control, ground MS Contin.

3. Consideration should be given to not allowing abuse deterrent claims for EG-001 Tablets with respect to oral abuse. In oral HAP study 067-EG-008, although the Emax of Drug Liking is statistically significantly lower following oral manipulated 60 mg EG-001 compared to following oral manipulated 60 mg MS Contin (positive control), this difference is small and of questionable clinical relevance. Subjects expressed a similar willingness to take again, if given the opportunity either oral manipulated 60 mg EG-001 or oral manipulated 60 mg MS Contin as revealed by Take Drug Again VAS. With use of the Overall Drug Liking VAS, subjects displayed a similar drug liking experience when given either of the oral manipulated treatments. (b) (4)

4. Consideration should be given to not granting a deterrent claim to EG-001 Tablets with respect to smoking. Although the in vitro data suggests that EG-001 tablets may not likely be smoked, Sponsor did not conduct similar simulated smoking studies on the positive control, MS Contin, to determine the likelihood it might be abused by smoking. (b) (4)

Recommendations from the Chemistry Review

CMC has recommended a number of PMRs in order to assure that marketed Arymo tablets maintain the labeled AD properties through the end of shelf-life and as part of life-cycle management. The recommended PMRs are:

(b) (4)

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Schedule

Arymo tablets will be in Schedule II of the Controlled Substances Act.

Financial Disclosures

According to Dr. Hariadi's Clinical Review, the Sponsor has not identified any financial arrangements that would affect the approvability of this application. The Clinical Review states, "The Applicant's submission included the completed FDA form 3454: Certification of Financial Interests and Arrangements of Clinical Investigators, in compliance with 21CFR part 54. This certified that the Applicant has not entered into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study…" Additionally, no clinical investigator had interests to disclose and no investigator received significant payments of other sorts.

REMS

Arymo ER will be part of the ER/LA REMS.

Maternal Health Consult

The Division of Pediatric and Maternal Health (DPMH) was consulted to assist in the review of labeling consistent with the new Pregnancy and Lactation Labeling Rule (PLLR) format. Dr. Miriam Dinatale provided the review with concurrence from Dr. Lynne Yao. DPMH provided labeling recommendations for Arymo labeling to comply with the PLLR.

12. Labeling

Proprietary Name

The proposed proprietary name, Arymo, was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found acceptable from both a promotional and a safety perspective (reviews dated November 6, 2014 and February 29, 2016). The Sponsor was notified that the name was acceptable in a letter dated November 6, 2014. In that letter, the Sponsor was encouraged to adopt a modifier for the proposed proprietary name in order to reduce the potential for confusion with immediate-release products. The proposed name with the NDA submission is Arymo ER.

Carton and Container Labeling

The DMEPA reviewer for Arymo was James Schlick, RPh, MBA with concurrence from Vicky Borders-Hemphill, PharmD. The review dated March 11, 2016 evaluated the carton and container labels for Arymo to assess risk for medication errors. The review identified several items to improve readability and increase prominence of important information. These issues were shared with the sponsor and revised carton and container labels were submitted on March 22, 2016. The DMEPA review team found the new changes acceptable and has no further recommendations.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend an Approval action for the Arymo ER application. The data submitted support AD labeling for the intravenous and intranasal routes of administration.

Risk Benefit Assessment

Arymo has physicochemical properties that are expected to reduce, but not totally prevent, abuse of the drug. In particular, the properties of Arymo are expected to reduce the risks of intranasal and intravenous abuse. The development of opioids with AD properties is a valuable component of the broader approach to reducing abuse and misuse, while still making appropriate treatments available for patients. Currently, Embeda (morphine sulfate and naltrexone hydrochloride) ER capsules and Morphabond (morphine sulfate extended-release) represent the only two AD ER formulations of morphine approved in the U.S. Embeda was approved in 2009 and Morphabond was approved in 2015.

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The Arymo application relies on the previous findings of efficacy and safety for MS Contin. The Sponsor has demonstrated BE between the 60 mg, 30 mg, and 15 mg strength tablets of Arymo and MS Contin in single-dose studies. While BE between the 15 mg strength tablets of Arymo and MS Contin was narrowly missed in one study, two 15 mg tablets of Arymo were BE to MS Contin 30 mg in another study. Dosing recommendations will be identical to MS Contin. The data across the Category 1, 2, and 3 AD studies support AD labeling for the product.

In vitro data demonstrate that Arymo tablets have a propensity to swell and become sticky. Therefore, labeling should include a warning about difficulty in swallowing and risk for GI obstruction in patients at risk for a small gastrointestinal lumen. Labeling should instruct patients to take tablets one at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Vigilance for postmarketing reports suggestive of choking or gastrointestinal obstruction will be needed.

Recommendation for Postmarketing Risk Management Activity

Arymo ER will be part of the ER/LA REMS.

Recommendation for Postmarketing Study Requirements

CMC has recommended a number of PMRs in order to ensure that marketed Arymo tablets maintain the labeled AD properties through the end of shelf-life and as part of life-cycle management. The recommended PMRs are described in Section 11 above.

The Pharmacology/Toxicology Review has recommended the four PMRs described in Section 4 above.

Postmarketing studies of Arymo will be needed to assess the effects of the AD features on the risk for abuse of Arymo and the consequences of that abuse in the community.

In addition, Arymo is part of the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS), which requires companies to make available to health care professionals educational programs on how to safely prescribe ER/LA opioid analgesics and to provide Medication Guides and patient counseling documents containing information on the safe use, storage, and disposal of ER/LA opioids. The postmarketing study requirements under the ER/LA REMS will apply for Arymo ER.

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/s/

JOHN J FEENEY
10/02/2016