**Abuse-Deterrent Opioids – Evidence Evaluation & Labeling**

Medication: \_\_\_\_\_\_\_\_\_\_\_\_\_Arymo ER®\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Evaluation Date: \_\_05/18/17\_\_\_\_\_\_\_ Evaluation History: [x]  Initial Version 1.0, or [ ]  Version \_\_\_\_\_\_\_\_\_

Current Product Labeling established: [ ]  Prior to or [x]  After publication of FDA Guidance to Industry Document (4/2015)

This is a: (Check all that apply)

[x]  New product

[ ]  Existing product, new formulation

[ ]  Existing product with new/updated labeling

[ ]  Other: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Product Abuse Deterrent Property Classification:** – Check all that apply

[x]  Physical / Chemical barrier

[ ]  Agonist / Antagonist combination

[ ]  Aversion

[ ]  Delivery System

[ ]  New Molecular entity or Prodrug

[ ]  Combination (check combined items)

[ ]  Novel Approach

**Product Labeling:**

Does the product have FDA abuse deterrent labeling? [x]  Yes or [ ]  No Year obtained: \_\_2017\_\_\_\_\_\_

**Abuse Deterrent Evidence provided.** Summary of in-depth literature review and product evaluation based on FDA Guidance to Industry Document

[x]  Laboratory-based in vitro manipulation and extraction studies (Category 1)

 Description of Research: *In vitro* manipulation and extraction data indicates tablets resist manipulation using most household tools, particle size reduction is difficult, a viscous gel is formed when subjected to liquid, the gel that is formed generally resists passage through a needle, extraction in large volumes of liquid takes extended periods of time, free-base morphine cannot readily be extracted and smoking is not a viable method of abuse.\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

[x]  Pharmacokinetic Studies (Category 2)

 Description of Research: Pharmacokinetic studies reveal that manipulation of Arymo ER® results in a shorter time to peak concentration (Tmax) by a mean of approximately 1.1 hours, the mean exposure (AUC) to morphine is slightly lower with manipulated compared to intact tablets, and the peak plasma concentration (Cmax) is slightly increased with manipulated tablets compared to intact (19.0 [9.6] ng/mL versus 17.2 [4.3] ng/mL, respectively). \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

[x]  Clinical Abuse potential studies (Category 3)

 Description of Research: Oral clinical abuse potential study assessed peak effect for drug liking on VAS of manipulated Arymo ER® compared to morphine ER tablet (generic MS Contin®) as the primary endpoint. Peak drug liking was significantly lower for manipulated Arymo ER® compared to manipulated morphine ER (P=0.007).\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

[x]  Clinical Abuse potential studies (Category 3)

 Description of Research: Intranasal clinical abuse potential study assessed peak effect for drug liking on VAS of manipulated high volume and low volume Arymo ER® intranasally and intact Arymo ER® orally compared to morphine ER tablet (generic MS Contin®) intranasally. Peak drug liking for manipulated high and low volume Arymo ER® intranasally and intact Arymo ER® was significantly lower compared to manipulated morphine ER intranasally (P<0.0001 for all comparisons). \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

[ ]  Additional Studies / Post Market data which assessed the impact of abuse-deterrent formulation (Category 4)

[ ]  Post market

[ ]  Formal studies included recommended study design features (see page 19 FDA Guidance

document)

Description of Research: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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[ ]  Determination if use of product results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death

Description of Research: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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[x]  Outcome Measures and Data Interpretation in Abuse Potential Studies

* + Standardized Instruments

[x]  Visual Analogue Scales (VAS)

Description of Research: Drug liking, take drug again, Drug Effects Questionnaire, ease of snorting\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

[ ]  Profile of Mood States

Description of Research: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

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* + Data Interpretation

[x]  Primary Analysis

Description of Research: Comparison of median peak drug liking VAS scores (both studies)

[x]  Statistical Analysis

Description of Research: Provided descriptive statistics (both studies); both studies followed FDA guidance to industry on statistical analysis for abuse-deterrence studies based upon comparison of median drug liking VAS (acceptable per FDA when nonparametric method necessary); analyzed using a linear mixed-effects model with fixed effects for sequence, period, and treatment, and random effect for participant nested in sequence (both studies)\_\_\_\_\_\_\_\_\_

[x]  Data and dropout for non-completers

Description of Research: Data regarding dropout and non-completers accounted for (both studies)\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

[ ]  None of the above

**Strength of Evidence of Abuse Deterrent Properties:**

[ ]  Evidence is based on physical/chemical property, theoretical assumptions or manufacturer’s claims and is not yet supported by scientifically sound outcome data which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available (Category III)

[x]  Evidence is based on physical/chemical property, clinical abuse potential studies or laboratory manipulation studies and is not yet supported by scientifically sound outcome data which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without-abuse-deterrent properties were available (Category II)

[ ]  There is evidence, supported by scientifically sound outcome data, which demonstrates a reduction in the abuse of the product in the community setting compared to levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available (Category I)