Arymo™ ER (morphine sulfate) Extended-Release Tablets for the Treatment of Chronic Pain

August 4, 2016
Egalet Corporation
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Introduction

Robert Radie
President and Chief Executive Officer
Egalet Corporation
Morphine is the Most Commonly Prescribed ER Opioid in the U.S.

- 2015: 6.4 million ER morphine prescriptions

ER Morphine Prescriptions
January-April 2016

98.5% Non-abuse-deterrent
1.5% Abuse-deterrent

IMS (National Prescription Audit) Database
Arymo ER Provides a Broad Abuse-Deterrent Profile

Arymo ER
Designed to Deter Common Routes of Abuse

**ORAL**
(chewed / manipulated)
- Hard tablet
- Difficult to chew
- Resistant to particle size reduction and morphine extraction

**NASAL**
- Difficult to reduce to a snortable powder

**INTRAVENOUS**
- Difficult to extract for injection
- Difficult to draw into syringe
Guardian™ Technology Confers Physical and Chemical Barriers to Abuse

Formulation

- Polyethylene Oxide (PEO) + Morphine

Process

- Injection Molding

ER Profile with Physical / Chemical Abuse-deterrent Properties

- Dense, hard tablet
- Resistant to particle size reduction
- Resistant to chemical extraction
- Prevents syringeability
Clinical Data Support Approval of Arymo ER

- Arymo ER was bioequivalent to MS Contin at all intended dosage strengths
- Bioequivalence scientific bridge to safety and efficacy
- No clinically significant food effect
- No evidence of alcohol dose dumping
Comprehensive Abuse-Deterrent Development Program for Arymo ER

- **Category 1**
  *In Vitro Testing*
  - Resistance to Physical & Chemical Manipulation

- **Category 2**
  *Clinical PK Studies*
  - PK not converted to an immediate-release profile
  - $C_{\text{max}}$ $T_{\text{max}}$

- **Category 3**
  *Clinical Abuse-Deterrent Studies*
  - Drug Liking
  - Take Drug Again
  - Positive Drug Effects

- Committed to fulfilling post-approval requirements
- Category 4 study to assess real-world impact of Arymo ER on misuse and abuse
Abuse-Deterrent Formulations Are Part of the Solution

- Physician Education
- Prescription Monitoring
- Proper Prescribing
- Reduce Opioid Abuse
- Patient Education
- Abuse-Deterrent Formulations
- Safe Disposal
<table>
<thead>
<tr>
<th>Agenda</th>
<th>Richard Dart, M.D., Ph.D.</th>
</tr>
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<tbody>
<tr>
<td>Public Health Need</td>
<td>Director</td>
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<tr>
<td>Abuse-Deterrent Studies</td>
<td>Jeffrey Dayno, M.D.</td>
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<td>Chief Medical Officer</td>
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<td>Clinical Relevance</td>
<td>Nathaniel Katz, M.D., M.S.</td>
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<td>Analgesic Solutions</td>
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### Additional Experts

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<th>Category</th>
<th>Expert</th>
<th>Position</th>
<th>Affiliation</th>
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<tr>
<td>Pain Management</td>
<td>Lynn Webster, M.D.</td>
<td>Vice President, Scientific Affairs</td>
<td>PRA Health Sciences</td>
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<td>Clinical Abuse Potential Studies</td>
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<tr>
<td>Category 1 Studies</td>
<td>Edward Cone, Ph.D.</td>
<td>Principal Scientist</td>
<td>PinneyAssociates</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Mona Darwish, Ph.D.</td>
<td>President</td>
<td>Sci-Med Bridge, LLC</td>
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</table>
Public Health Need for Abuse-Deterrent ER Morphine

Richard C. Dart, M.D., Ph.D.
Executive Director, RADARS® System
Director, Rocky Mountain Poison & Drug Center
Professor of Emergency Medicine,
University of Colorado School of Medicine
Abusers Chew or Manipulate ER Opioids for a Quick and Easy “High”

- Particle size reduction (PSR)
  - Defeats ER properties
  - Releases drug faster
  - Prepares drug for alternate routes of abuse (i.e., oral [chewed/manipulated], intranasal, intravenous)

- Smaller particle sizes = faster extraction
Attractiveness for Manipulated Abuse is Based on Effort, Yield, and Liking

Category 1

Effort

↓

Yield

How difficult is the product to manipulate?

How many small particles are produced?

How much drug is in abusable form?

Category 2/3

Liking

How much do abusers like the result?

Attractiveness for Manipulated Abuse

Can the product be expected to lead to a reduction in abuse?
Two Primary Approaches to Abuse Deterrence

- Physical / chemical barriers (e.g., OxyContin)
  - Physical barriers against PSR
  - Chemical barriers against extraction
- Agonist / antagonist (e.g., Embeda)
  - More easily manipulated
  - Manipulation (e.g., chewing) releases antagonist (e.g., naltrexone)
ADFs May Intervene at Several Points in Progression of Substance Abuse
## Abuse-Deterrent ER Oxycodone Has Been Effective in Deterring Abuse

<table>
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<tr>
<th>Outcome</th>
<th>Source</th>
<th>% Change [95% CI] Pre vs. Post Reformulation</th>
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<tbody>
<tr>
<td>Misuse</td>
<td>RADARS (Poison Centers)</td>
<td><img src="image1" alt="Graph" /></td>
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<td>Abuse</td>
<td>RADARS (Poison Centers)</td>
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<td>NPDS (Poison Centers)</td>
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<td>NAVIPPRO (Treatment Centers)</td>
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<td>RADARS SKIP (Treatment Centers)</td>
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<td>RADARS OTP (Treatment Centers)</td>
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<td>Opioid Use Disorder</td>
<td>Marketscan - Opioid Users</td>
<td><img src="image7" alt="Graph" /></td>
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<tr>
<td>Overdose</td>
<td>Marketscan - Opioid Users</td>
<td><img src="image8" alt="Graph" /></td>
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<td>Diversion</td>
<td>RADARS (Drug Diversion)</td>
<td><img src="image9" alt="Graph" /></td>
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<tr>
<td>Doctor Shopping</td>
<td>IMS Prescription Data</td>
<td><img src="image10" alt="Graph" /></td>
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</tbody>
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Data adjusted for prescription volume

Abuse-Deterrent ER Oxycodone Reduces IV Abuse in Australia

ER Opioid Prescriptions Have Been Decreasing Over Last 5 Years

Dispensed ER Prescriptions (in millions)

<table>
<thead>
<tr>
<th>Year</th>
<th>Dispensed ER Prescriptions</th>
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<tbody>
<tr>
<td>2011</td>
<td>22.3</td>
</tr>
<tr>
<td>2012</td>
<td>21.8</td>
</tr>
<tr>
<td>2013</td>
<td>21.4</td>
</tr>
<tr>
<td>2014</td>
<td>21.3</td>
</tr>
<tr>
<td>2015</td>
<td>20.7</td>
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IMS National Prescription Audit (2011-2015)
Morphine Most Commonly Prescribed ER Opioid in the U.S.

IMS National Prescription Audit (2011-2015)
ER Morphine is Abused by Oral, Nasal, and IV Routes

RADARS® System
Poison Center Program

% of Abusers of Morphine Products

All Oral: 72%
IV Injection: 24%
Snorting: 4%

NAVIPPRO™ ASI-MV®
Substance Abuse Treatment
(past 30-day abuse)

IV Injection: 57%
Oral Intact: 40%
Snort: 25%
Chew: 11%
Dissolve: 5%
Drink: 1%

Public Health Need: ER Morphine Products with Physical / Chemical Barriers to Abuse

- ADFs with physical / chemical barriers should prevent chewing, hinder particle size reduction (PSR) and resist being turned into IR
- ADFs associated with significant reductions in misuse, abuse, and diversion
- ADFs have not led to more prescribing
- ER morphine is most commonly prescribed opioid and is abused through chewing, manipulated oral, snorting, and IV injection
Abuse-Deterrent Studies

Jeffrey M. Dayno, M.D.
Chief Medical Officer
Egalet Corporation
Development Program for Arymo ER Followed FDA Guidance

Routes of Abuse
- Oral
- Intranasal
- Intravenous

Two Clinical Trials
EG-008 – Oral PK and HAP Study
EG-009 – Intranasal PK and HAP Study

Category 1
*In Vitro Testing*
Resistance to Physical & Chemical Manipulation

Category 2
*Clinical PK Studies*
PK not converted to an immediate-release profile
$C_{\text{max}}$ $T_{\text{max}}$

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*Clinical Abuse-Deterrent Studies*
Drug Liking
Take Drug Again
Positive Drug Effects
## Category 1 Assessments to Evaluate Common Routes of Abuse

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PSR = particle size reduction
Arymo ER More Resistant to Particle Size Reduction than MS Contin

% Particles <500 Microns

<table>
<thead>
<tr>
<th>Tool</th>
<th>Arymo ER (100 mg)</th>
<th>MS Contin (100 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>B</td>
<td>57%</td>
<td>56%</td>
</tr>
<tr>
<td>C</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>D</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>E</td>
<td>1%</td>
<td>50%</td>
</tr>
<tr>
<td>F</td>
<td>1%</td>
<td>47%</td>
</tr>
<tr>
<td>G</td>
<td>71%</td>
<td>62%</td>
</tr>
<tr>
<td>H</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>I</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>J</td>
<td>40%</td>
<td>4%</td>
</tr>
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</table>

Category 1
ALERRRT™ Instrument

- Developed to measure “work” involved in physical manipulation of a formulation
- Assesses combination of time, effort, and resources
- Scores measured on VAS
  - 0 = “very easy” (uncoated aspirin)
  - 100 = “extremely difficult” (metal nut)
Methods for ALERRT™ Study

- Evaluated tools representative of instruments for cutting, crushing, grating, and grinding
- 4 trained laboratory technicians independently conducted physical manipulation on:
  - Arymo ER
  - MS Contin
  - IR morphine sulfate
ALERRRT™: Arymo ER More Difficult to Manipulate than MS Contin and IR Morphine

![Graph showing Work VAS Score (SD) for Arymo ER, MS Contin, and IR Morphine Sulfate for tools B, D, G, and J. The x-axis represents the tools, and the y-axis represents the Work VAS Score. The chart indicates that Arymo ER is perceived as the most difficult to manipulate, followed by MS Contin and IR Morphine Sulfate. The bars for each tool show the mean with error bars for the standard deviation.]

Category 1
Many Tools Broke During Attempts to Manipulate Arymo ER
No Significant Increase in Particle Size Reduction with Multi-Tool Procedures

- Tool F → Tool B
  - No additional PSR achieved
- Tool F → Tool J
  - Minimal additional PSR achieved
- Tool F → Tool J → Tool B
  - No additional PSR achieved
Optimal Particle Size Reduction Methods

- Optimal PSR methods for Arymo ER
  - Single-tool: Tool F
  - Multi-tool: Tool F → Tool J
- Optimal PSR method for MS Contin
  - Single-tool: Tool B
Distribution of Particle Sizes Using Optimized PSR Methods

## Category 1 Assessments to Evaluate Common Routes of Abuse

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**PSR = particle size reduction**
Pre-Treatment Was Not Effective in Enhancing Particle Size Reduction of Arymo ER

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<thead>
<tr>
<th>Pre-Treatment</th>
<th>% Particles &lt;500 Microns</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>73%</td>
</tr>
<tr>
<td>None</td>
<td>2%</td>
</tr>
<tr>
<td>A</td>
<td>3%</td>
</tr>
<tr>
<td>B</td>
<td>3%</td>
</tr>
<tr>
<td>C</td>
<td>5%</td>
</tr>
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Mean % Particles <500 Microns [SD]

Category 1
# Category 1 Assessments to Evaluate Common Routes of Abuse

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**PSR = particle size reduction**
Hardness Testing Demonstrates that Arymo ER Would be Difficult to Chew

- Hardness of Arymo ER and MS Contin assessed using conventional hardness tester
  - Arymo ER: >400 newtons
  - MS Contin: 63 newtons

- Average maximum human bite force is ~300-350 newtons*

- Arymo ER would be difficult to chew, posing potential safety risk to human subjects

* Takaki et al. Int Arch Otorhinolaryngol 2014;18(3).
# Categories 1 Assessments to Evaluate Common Routes of Abuse

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PSR = particle size reduction
Arymo ER Gelling Properties Impart Abuse Deterrence

Arymo ER

MS Contin

3 mL of IV Solvent A, Temperature A

Category 1
Less Morphine Recovered from Arymo ER in Small Volume IV Extraction

Mean % Morphine Recovered at 5 min [SD]

- **2 mL**: MS Contin (Tool B) - 52% ± 0.5%
  - Arymo ER (Tool F → Tool J) - 9%

- **5 mL**: MS Contin (Tool B) - 62% ± 9%
  - Arymo ER (Tool F → Tool J) - 9%

- **10 mL**: MS Contin (Tool B) - 66% ± 9%
  - Arymo ER (Tool F → Tool J) - 9%

N=3
Temperature B, Agitation A
“Gel Blob” Syringability Study with Long Extraction Times

- 12 extraction conditions evaluated
  - 4 and 24 hours of extraction
  - Injection solvents 1 and 2
  - 3 forms of Arymo ER
    - Intact
    - Tool F
    - Tool F → Tool J
“Gel Blob” Study: Limited Amounts of Morphine Were Recovered From Arymo ER

- 9 of 12 extractions conditions recovered <10% morphine
- 3 remaining conditions recovered 16-18% morphine
  - Required largest needle evaluated (Gauge D)
  - Extreme case, larger than those commonly used

Category 1
## Category 1 Assessments to Evaluate Common Routes of Abuse

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**PSR = particle size reduction**
Arymo ER Resists Extraction in Large Volumes of Solvents

Mean % Morphine Extracted at 30 min

- Solvent 5
  - Arymo ER 15 mg
  - Arymo ER 30 mg
  - Arymo ER 60 mg

- Solvent 11
  - Arymo ER 15 mg
  - Arymo ER 30 mg
  - Arymo ER 60 mg

≥80% at 30 minutes\(^1\)

Temperature A, Agitation B

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PSR = particle size reduction
No Evidence of Alcohol Dose Dumping

Mean % Morphine Released [SD]

Sampling Time (min)

Dissolution media: 0.1N HCl, replicates=12

Category 1
Abuse-Deterrent Studies for Arymo ER in Accordance with FDA Guidance

**Category 1**
*In Vitro Testing*
- Resistance to Physical & Chemical Manipulation

**Category 2**
*Clinical PK Studies*
- PK not converted to an immediate-release profile
  - $C_{\text{max}}$, $T_{\text{max}}$

**Category 3**
*Clinical Abuse-Deterrent Studies*
- Drug Liking
- Take Drug Again
- Positive Drug Effects

**Routes of Abuse**
- Oral
- Intranasal
- Intravenous

**Two Clinical Trials**
- EG-008 – Oral PK and HAP Study
- EG-009 – Intranasal PK and HAP Study
EG-009: Intranasal HAP Study

- Randomized, double-blind, double-dummy, 5-period crossover study
- Enrolled adult nondependent recreational opioid users experienced in nasal insufflation
Treatment Arms in Intranasal HAP Study Prepared by Site Pharmacy

- MS Contin, crushed IN (60 mg)
  - Tool B
- Arymo ER, manipulated IN (60 mg)
  - Tool F → Tool J
- Arymo ER, manipulated/sieved IN (60 mg)
  - Tool F → Tool J, then sieved
- Arymo ER, intact oral (60 mg)
- Placebo
Endpoints in Intranasal HAP Study

- **Primary**: Maximum ($E_{\text{max}}$) Drug Liking
- **Secondary**
  - Overall Drug Liking
  - Take Drug Again
  - Drug Effects Questionnaire
- **Pharmacokinetics (PK)**
  - $C_{\text{max}}$
  - $T_{\text{max}}$
  - AUC
Significantly Lower Maximum Drug Liking for Arymo ER Compared to MS Contin after Snorting

Mean $E_{\text{max}}$ Drug Liking [95% CI]

- MS Contin, Crushed IN: 78
- Arymo ER, Manipulated IN: 66
- Arymo ER, Manipulated/Sieved IN: 60
- Arymo ER, Intact Oral: 69
- Placebo: 55

$p < 0.0001$
Take Drug Again and Overall Drug Liking for Arymo ER Similar to Placebo

Study EG-009: Intranasal HAP Study (N=46)
Arymo ER Associated with Lower VAS Scores on Drug High and Good Effects

Study EG-009: Intranasal HAP Study (N=46)
Lower Morphine Concentrations after Snorting Arymo ER Compared to MS Contin

Study EG-009: Intranasal HAP Study (N=46)
EG-008: Oral HAP Study

- Randomized, double-blind, triple-dummy, 4-period crossover study
- Enrolled adult nondependent recreational opioid users
- Chewing has been most common manipulation in oral HAP studies
- Chewing Arymo ER would not provide effective PSR and poses potential safety risk
Treatment Arms in Oral HAP Study
Prepared by Site Pharmacy

- Crushed MS Contin (60 mg)
  - Tool B
- Manipulated Arymo ER (60 mg)
  - Tool F
- Intact Arymo ER (60 mg)
- Placebo
Endpoints in Oral HAP Study

- **Primary:** Maximum ($E_{\text{max}}$) Drug Liking
- **Secondary**
  - Overall Drug Liking
  - Take Drug Again
  - Drug Effects Questionnaire
- **Pharmacokinetics (PK)**
  - $C_{\text{max}}$
  - $T_{\text{max}}$
  - AUC
Significantly Lower Maximum Drug Liking with Manipulated Oral Arymo ER

Study EG-008: Oral HAP Study (N=38)

Mean $E_{\text{max}}$ Drug Liking [95% CI]

- **MS Contin, Crushed**: 73
- **Arymo ER, Manipulated**: 68
- **Arymo ER, Intact**: 63
- **Placebo**: 53

$p = 0.0069$
Lower Mean Drug Liking for Manipulated Arymo ER at Early Time Points

Study EG-008: Oral HAP Study (N=38)
Key Secondary Endpoints in Oral HAP Study

**Take Drug Again**

- MS Contin, Crushed: 70
- Arymo ER, Manipulated: 63
- Arymo ER, Intact: 55
- Placebo: 51

- \( p = 0.054 \)

**Overall Drug Liking**

- MS Contin, Crushed: 70
- Arymo ER, Manipulated: 65
- Arymo ER, Intact: 56
- Placebo: 52

- \( p = 0.128 \)

Study EG-008: Oral HAP Study (N=38)
Significant Differences Observed in Drug High VAS and Good Effects VAS

Study EG-008: Oral HAP Study (N=38)
Arymo ER Does Not Exhibit IR Profile after Manipulation for Oral Abuse

---

**Study EG-008: Oral HAP Study (N=38)**

- **MS Contin, Crushed**
- **Arymo ER, Manipulated**
- **Arymo ER, Intact**

**Mean Morphine Plasma Concentration (ng/mL) [95% CI]**

- **Time (hours):** 0, 1, 2, 3, 4, 5, 6

---

Category 2
Category 1 and 2/3 Development Program Support Abuse Deterrence

Resistant to Particle Size Reduction

**INTRA VENOUS**
- Gels in solution
- Difficult to extract
- Difficult to draw into syringe

**NASAL**
- Difficult to reduce to snortable powder
- Met primary endpoint for Category 2/3
- Statistically significant for all secondary PD measures
- PK consistent with PD results

**ORAL** (chewed / manipulated)
- Difficult to chew
- Met primary endpoint for Category 2/3
- All secondary PD measures supportive
- PK consistent with PD results
Clinical Relevance of Arymo ER Abuse-Potential Data

Nathaniel Katz, M.D., M.S.
CEO, Analgesic Solutions
Adjunct Associate Professor
Tufts University School of Medicine
Two Primary Questions for Today’s Advisory Committee Meeting

- Should Arymo ER be approved for the treatment of chronic pain?
- Should Arymo ER be labeled as an abuse-deterrent product?
  - IV route
  - Nasal route
  - Oral route (chewed / manipulated)
Arymo ER Has Met Regulatory Standard for Approval

- Arymo ER is bioequivalent to MS Contin
- No clinically significant effect of food
- No acceleration of release with alcohol (i.e., no alcohol dose-dumping)
Two Ways to Assess Clinical Relevance of Pre-Marketing Abuse-Deterrent Studies

- Compare route-specific laboratory results to real-world outcomes
- Determine *Clinically Important Difference* associated with change in drug-taking behavior
In Vitro Syringeability Findings Predict Real-World IV Abuse Deterrence

In Vitro Findings

OxyContin OP

“When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.”

OxyContin® Label

Arymo ER

Real-world Evidence from Epidemiologic Studies

Butler et al. J Pain. 2013

Havens et al. Drug Alcohol Depend. 2014
Intranasal Human Abuse Potential Findings Predict Real-World Nasal Abuse Deterrence

**Intranasal HAP Studies**

**OxyContin OP**

<table>
<thead>
<tr>
<th></th>
<th>Mean E$_{\text{max}}$</th>
<th>Drug Liking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crushed OxyContin (original)</td>
<td>94.0</td>
<td></td>
</tr>
<tr>
<td>Crushed OxyContin OP</td>
<td>80.4</td>
<td>13.6</td>
</tr>
</tbody>
</table>

**Arymo ER**

<table>
<thead>
<tr>
<th></th>
<th>Mean E$_{\text{max}}$</th>
<th>Drug Liking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crushed MS Contin</td>
<td>77.7</td>
<td></td>
</tr>
<tr>
<td>Manipulated Arymo ER</td>
<td>65.5 (not sieved)</td>
<td>12.2</td>
</tr>
<tr>
<td>77.7</td>
<td>59.6 (sieved)</td>
<td>18.1</td>
</tr>
</tbody>
</table>

**Real-world Evidence from Epidemiologic Studies**


- Pre-period: 53%
- Post-period: 25%


- Pre-period: 39%
- Post-period: 5%
Arymo ER Would be Difficult or Impossible to Chew

- Chewing is most common form of manipulated oral abuse for ER morphine*

- Arymo ER hardness > 400 N

- Average maximum human bite force in literature is ~300-350 N†

† Takaki et al. Int Arch Otorhinolaryngol 2014;18(3).
Two Ways to Assess Clinical Relevance of Pre-Marketing Abuse-Deterrent Studies

- Compare route-specific laboratory results to real-world outcomes
- Determine *Clinically Important Difference* leading to change in drug-taking behavior
8- to 10-Point Reduction in $E_{\text{max}}$ Drug High is Clinically Important

- Estimated clinically important difference (CID) for $E_{\text{max}}$ Drug High is 8-10 mm

5-Point Reduction in $E_{\text{max}}$ Drug Liking is Clinically Important

- Meta-analysis of multiple human abuse potential studies across molecules
- Compared to “non-medical use” (NMU) rates in NSDUH and DAWN using multiple regression
- For ER morphine ADF, 5-point reduction in $E_{\text{max}}$ Drug Liking predicted 20% reduction in lifetime NMU

NSDUH = National Survey of Drug Use and Health
DAWN = Drug Abuse Warning Network
# Arymo ER Reductions in Drug High and Drug Liking are Clinically Important

<table>
<thead>
<tr>
<th>Arymo ER Condition</th>
<th>E(_{\text{max}}) Drug High</th>
<th>E(_{\text{max}}) Drug Liking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment Difference</td>
<td>Clinically important? (8-10 mm(^*))</td>
</tr>
<tr>
<td>Nasal Manipulated</td>
<td>33.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Nasal Manipulated/sieved</td>
<td>45.2</td>
<td>Yes</td>
</tr>
<tr>
<td>Manipulated Oral</td>
<td>13.1</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Treatment differences in HAP studies do not reflect the fact that Arymo ER was more difficult to manipulate than MS Contin

Totality of Data Support Broad Abuse-Deterrent Profile of Arymo ER

**Intravenous**

- Resists small volume extraction to 24 hours
- Difficult to draw into a needle

**Nasal**

- Low yield of particles amenable for snorting
- Less liking than non-ADF comparator

**Oral**

- Difficult or impossible to chew
- Less liking than non-ADF comparator after optimal manipulation
Arymo™ ER (morphine sulfate) Extended-Release Tablets for the Treatment of Chronic Pain

August 4, 2016
Egalet Corporation
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Backup Slides Shown
Large Volume Extraction – Arymo ER 60mg at 1 Hour

Mean % Morphine Extracted at 1 Hour [SD]

Temperature A, Agitation B, 200 mL

Manipulated Arymo ER (Tool F -> Tool J); N=3
Figure 20: Morphine Extraction in Large Volumes of Ingestible and Non-Ingestible Solvents at Temperature A and Agitation B with Maximal Manipulation at 30 Minutes
Development Process to Identify Optimal PSR for Arymo ER

**Exploratory Phase**
- 25 tools
- Representative of cutting, crushing, grating, grinding

**Screening Phase**
- 10 tools (mechanical and electrical)
- MS Contin crushed to fine powder
- *Arymo ER tested 5 x longer* to identify tools effective for Arymo ER

**Single- and Multi-Tool PSR**
- MS Contin crushed to fine powder with Tool B
  - Does not require multi-tool process
- Arymo ER single tool result: Tool F & Tool J (< 5% particles < 500 microns)
- Arymo ER challenged with sequential multi-tool procedure (F → J)
  - No significant changes in PSR
  - Increasing time resulted in plateau effect on PSR
Arymo ER Particle Size Reduction: Tool F vs Tool F → J

N = 6
Arymo ER Particle Size Reduction: Tool F at 3 and 5 Minutes

Mean % Particles [SD]

- Arymo ER 60mg (Tool F) 3 minutes N=6
  - <212: 0, 0
  - 212-499: 1, 1
  - 500-999: 10, 9
  - ≥1000: 89, 90

- Arymo ER 60mg (Tool F) 5 minutes N=3

Particle Size
Morphine Extraction from Arymo ER Over Time

Mean % Morphine Extracted [SD]

Solvent 5

Solvent 11

Temperature A, Agitation B, 200 ml, N=3

Category 1
Arymo ER 60 mg
Solvent 18

Mean % Morphine Extracted [SD]

Time (hrs)

Temperature A, Agitation B, 200 ml, N=3
Arymo ER 100 mg
Solvent 18

Mean % Morphine Extracted

Time (hrs)

Temperature A, Agitation B, 50 ml, N=1
Arymo ER Resists Extraction in Large Volumes of Solvents 9 and 10

Temperature B, Agitation B

Category 1
Morphine Extraction from Arymo ER and MS Contin Over Time

Category 1

**Temperature A, Agitation B, 200 ml, N=3**

*FDA has not reviewed MS Contin data*
Figure 31: Ease of Snorting VAS Scores in Intranasal HAP Study EG-009

![Bar chart showing mean ease of snorting scores for different conditions.

- MS Contin, Manipulated IN: 77
- Arymo ER, Manipulated IN: 17
- Arymo ER, Manipulated/Sieved IN: 75
- Placebo: 74

Scale: 0 to 100, with "Very Easy" at the top and "Very Difficult" at the bottom.]