RoxyBond™
(oxycodone hydrochloride)
Immediate-Release Tablets

April 5, 2017

Inspirion Delivery Sciences
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Introduction

Stefan Aigner, MD
Co-Founder and Chief Executive Officer
Inspirion Delivery Sciences
Proposed RoxyBond Indication

RoxyBond is an opioid agonist indicated for management of pain severe enough to require the use of an opioid analgesic and for which alternative treatments are inadequate.
RoxyBond: Abuse-Deterrent Immediate-Release Single-Entity Oxycodone Product

- Formulated with SentryBond™ Technology
  - Used in FDA approved MorphaBond ER™ (morphine ER), which has abuse-deterrent label claims
- Physical and chemical barriers to deter intranasal and IV abuse
  - Abuse-**deterrent**, not abuse-**proof**
  - Not expected to deter oral abuse
- Intended to replace easily abusable IR single-entity oxycodone products (e.g., Roxicodone)
Current State of Abuse Deterrence for Opioid Products

- Opioid analgesics
  - Important treatment option for pain
  - At risk of diversion, misuse, and abuse
- FDA encourages development of abuse-deterrent opioids
  - 9 approved abuse-deterrent ER/LA opioids
  - No approved abuse-deterrent IR opioids
- IR profile poses challenge for abuse deterrence
Challenge of Abuse Deterrence for Immediate-Release Opioids

- ER opioids intended to release drug slowly
- Goals of manipulation/extraction with ER opioids:
  - Convert ER into IR
  - Transform into abusable form for snorting or injecting
- Most abuse-deterrent ER products resist manipulation and conversion into IR form
- IR products already have profile desired by abusers
RoxyBond Formulated with Physical and Chemical Barriers to Deter IN/IV Abuse

**RoxyBond**

Unique Approach to Immediate-Release Abuse Deterrence

- Difficult to manipulate or extract
- LOWER and SLOWER release when not taken as intended
- Difficult to snort or prepare for IV abuse
RoxyBond Regulatory Pathway and Dosage Strengths

- Used 505(b)(2) regulatory pathway
  - Roxicodone as reference listed drug (RLD)
- Dosage strengths same as Roxicodone: 5, 15, and 30 mg
RoxyBond Expected to Have Same Efficacy and Safety as Roxicodone

- RoxyBond demonstrated comparable bioavailability to Roxicodone
- RoxyBond strengths are dose proportional
- No clinically significant effect of food
Abuse-Deterrent Studies Designed in Accordance with FDA Guidance

- **Category 1** studies evaluated physical manipulation, chemical extraction, and syringeability
- **Category 2/3** study evaluated intranasal human abuse potential
RoxyBond expected to be incorporated into existing Opioid Analgesics REMS program

**Category 4** studies to evaluate real-world impact
  - Monitor utilization of RoxyBond relative to comparators
  - Monitor abuse of RoxyBond including:
    - Route-specific abuse outcomes
    - Internet forums
    - Spontaneous adverse event reporting
  - Conduct formal observational studies

Inspirion Committed to Fulfilling Post-Approval Requirements
## Agenda

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<th>Public Health Need for Abuse-Deterrent IR Opioid Analgesics</th>
<th>Richard Dart, MD, PhD</th>
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<td>Director, Rocky Mountain Poison &amp; Drug Center</td>
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<td>Executive Director, RADARS® System</td>
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<th>Robert Bianchi</th>
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<td>Prescription Drug Research Center</td>
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<th>Intranasal Human Abuse Potential Study</th>
<th>Lynn Webster, MD</th>
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<th>Clinical Perspective</th>
<th>Jeffrey Gudin, MD</th>
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<tr>
<td></td>
<td>Director, Pain Management Center</td>
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<td>Englewood Hospital and Medical Center</td>
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Public Health Need for Abuse-Deterrent IR Opioid Analgesics

Richard C. Dart, MD, PhD
Director, Rocky Mountain Poison & Drug Center
Professor of Emergency Medicine, University of Colorado School of Medicine
Executive Director, RADARS® System
Development of Prescription Opioid Abuse

Pain Patient

Susceptible Person

Recreational User

Behaviors

Intact

Crushed

Possible Adverse Outcomes

Addiction

Overdose

Death

Theoretical Roles of Opioids with Abuse-Deterrent Properties

How Can ADFs Make Positive Impact on Different Types of Individuals?

Pain Patient
- Decrease likelihood of crushing drug to increase effects
- Deter transition to intranasal and IV abuse

Novice / Recreational Abuser
- Deter dangerous routes of intranasal and IV abuse

Advanced Abuser
- Make dangerous routes of abuse more difficult with that ADF product
Most Oral Opioid Prescriptions Are Immediate Release; None Abuse Deterrent

Number of Oral Prescriptions in 2016 (in millions)

Immediate Release: 151.4
Extended Release: 17.9 million
IR SE Oxycodone

Symphony Health Solutions PHAST™ PRESCRIPTION Database.
Population-Adjusted Rates of Abuse and Diversion Higher with IR than ER Opioids

Population-adjusted rate in Q4 2015 (per 100,000) [95% CI]

4.6-fold difference (P<0.001)

6.1-fold difference (P<0.001)

IR Opioids are Preferred Over ER Opioids for Abuse

Most people who abuse prescription opioids initiate with IR opioids

Rate of Abuse of IR SE Oxycodone Greater than ER Oxycodone

Number of Individuals Reporting Abuse in Last 30 days per 100 Assessments [95% CI]

NAVIPPRO Addiction Severity Index-Multimedia Version (ASI-MV) [Q1 2015 - Q4 2016].
IR SE Oxycodone Widely Abused via Intranasal and IV Routes

Prevalence of Abuse (%) [95% CI]

- Oral: 48%
- Intranasal: 52%
- Intravenous: 28%

NAVIPPRO Addiction Severity Index-Multimedia Version (ASI-MV) [Q1 2015 - Q4 2016].
IV and Intranasal Abuse of Prescription Opioids Associated With Serious Outcomes

<table>
<thead>
<tr>
<th>Route of Abuse</th>
<th>Relative Risk of Death or Major Effect</th>
<th>Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compared to Oral Ingestion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intranasal</td>
<td>2.2 [1.7, 3.0]</td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>2.6 [2.0, 3.4]</td>
<td></td>
</tr>
</tbody>
</table>

RADARS System Poison Center Program, 2015 Data on File.
IV Route Poses Additional Risks for Serious Health Consequences

- 6% of HIV diagnoses and 10% of AIDS cases attributed to IV drug use in 2015\(^1\)
- Other health risks of injection
  - Hepatitis C\(^2\)
  - Endocarditis\(^3,4\)
  - Blood clots\(^5\)

1. CDC. HIV Surveillance Report, 2015;27.
Unmet Need For Abuse-Deterrent IR Opioid Analgesics

- IR opioids much more commonly prescribed, abused, and diverted than ER opioids
- IR SE oxycodone is commonly abused by high-risk intranasal and IV routes
  - Dangerous routes of abuse associated with serious health consequences
- Abuse-deterrent formulations designed to:
  - Complement other strategies
  - Replace easily abusable products
In Vitro Physical Manipulation and Chemical Extraction Studies

Robert Bianchi
President and Chief of Scientific and Technical Affairs
Prescription Drug Research Center
Comprehensive Category 1 Testing for Intranasal and IV Abuse

- Consistent with FDA’s Guidance on Abuse-deterrent Opioids\(^1\)
- Iterative testing approach with FDA
- Roxicodone used as non-abuse-deterrent comparator

Overview of Category 1 Studies

- Particle Size Reduction
  (with and without pre-treatment)
- Large Volume Extraction
- Small Volume Extraction
- Syringeability
Rationale for Reducing Particle Size of IR Opioids is to Get Drug in Abusable Form

<table>
<thead>
<tr>
<th>Rationale for Particle Size Reduction</th>
<th>ER Opioids</th>
<th>IR Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convert ER into IR</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Transform into abusable form for snorting or injection</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- RoxyBond: Formulated for lower and slower release of oxycodone when manipulated for non-oral route compared to intact administration

Particle Size Reduction ≠ Defeat of RoxyBond ADF Properties

Category 1
Roxicodone Easily and Quickly Turned Into Abusable Form

- Roxicodone easily manipulated with Tool E
  - 100% of particles < 2000 microns
  - No further tools evaluated
  - Easily reduced to fine powder that could be snorted or prepared for IV abuse
Pre-treatments did not substantially increase yield of small particles

Most effective tools used in subsequent studies
- **Roxicodone**: Tool E
- **RoxyBond**: Tool G

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**RoxyBond Difficult to Get Into Abusable Form with Most Tools**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Time (sec)</td>
<td>300</td>
</tr>
<tr>
<td>Manipulation Difficulty (1-10)</td>
<td>10</td>
</tr>
<tr>
<td>Mean % Particles &lt; 2000 Microns</td>
<td>0%</td>
</tr>
</tbody>
</table>
Overview of Category 1 Studies

- Particle Size Reduction (with and without pre-treatment)
- Large Volume Extraction
- Small Volume Extraction
- Syringeability
Large Volume Extraction Does Not Speed Oral Absorption for IR Oxycodone

<table>
<thead>
<tr>
<th>Oxycodone Parameter</th>
<th>Mean ± SD</th>
<th>Roxicodone Liquid Concentrate 15 mg / 15 mL Oral Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22 ± 8</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>1.4 ± 0.7</td>
<td>1.9 ± 1.5</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td></td>
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</table>

- Large volume extraction for IR oxycodone does not speed absorption over intact oral administration
- Resistance to physical manipulation and/or extraction not expected to deter oral abuse
RoxyBond Difficult to Extract in Large Volumes of Ingestible and Non-ingestible Solvents

Oxycodone Released (%)

Roxicodone (1 min)
- Intact
- Manipulated - Tool E

RoxyBond (30 min)
- Intact
- Manipulated - Tool G

Volume C, Temperature A, Agitation B, Tablet Form A
Overview of Category 1 Studies

- Particle Size Reduction (with and without pre-treatment)
- Large Volume Extraction
- Small Volume Extraction
- Syringeability
Small Volume Extraction and Syringeability Experiments

- Small volume extraction in injectable volumes of solvent
- Used smallest needle gauge able to syringe liquid
- Difficulty to syringe measured on 1-10 scale
  - 1 = “very easy to syringe”
  - 10 = “impossible”
Multiple Needle Gauges Used to Evaluate Syringeability
RoxyBond Forms Viscous Material When Manipulated and Subjected to Liquid Environment

Volume A, Solvent A, Temperature A, Agitation B, Tablet Form A
RoxyBond Resistant to Small Volume Extraction and Syringeability

Oxycodone Recovered (%)

- Roxicodone, Manipulated, 1 min: 98%
- Time (min): 0% (1), 6% (1), 7% (30), 2% (30), 8% (30), 19% (30)

Median Difficulty:
- Roxicodone - Tool E, Gauge A: 1
- RoxyBond - Intact, Gauge A: 1
- RoxyBond - Tool G, Gauge C: 9
- RoxyBond - Tool C, Gauge C: 9
Extreme Temperature Modification Did Not Appreciably Increase Yield of Oxycodone from RoxyBond

![Graph showing the recovery of Oxycodone over different times and conditions.]

- **Roxicodone, Manipulated, 1 min**: 89%
- **1 min**: 1%
- **18%**: 7%
- **21%**: 10%
- **30 min**: 22%

**Median Difficulty**
- RoxyBond - Tool E, Gauge A: 1
- RoxyBond - Intact, Gauge A: 4
- RoxyBond - Tool G, Gauge C: 8
- RoxyBond - Tool C, Gauge C: 8

**Conditions**: Volume A, Solvent A, Temperature B, Agitation A, Tablet Form A

**Category 1**
Complex, Multi-Step Process Required to Prepare RoxyBond Solution for IV Abuse

- Volume B, Temperature A, Agitation B, Tablet Form A (unless specified), Pre-Treatment D

Oxycodone Released at 30 min (%)
- 66% Intact, Gauge A
- 34% Tool G, Gauge C
- 31% Tablet Form B, Gauge A

Required Steps for Abuse
- Pre-Treatment D
- Large IV Volume B
- Extreme Solvent H
- Agitation B
- Extended Time Point
- Neutralize Solvent

Category 1
RoxyBond Demonstrated Physical and Chemical Abuse-Deterrent Properties

- Difficult to convert into abusable form for intranasal or IV abuse
- Particle size reduction did not defeat abuse-deterrent properties
- All extraction experiments produced considerably lower and slower oxycodone release compared to Roxicodone
- Manipulated RoxyBond was difficult to syringe
Intranasal Human Abuse Potential Study

Lynn Webster, MD
Vice President, Scientific Affairs
PRA Health Sciences
Study 002: Intranasal HAP Study

- Randomized, double-blind, double-dummy, placebo-controlled, 4-period crossover study
- Enrolled recreational, nondependent opioid users experienced in nasal insufflation
- 31 subjects entered treatment phase
- 29 subjects completed study
Treatments in Intranasal HAP Study

- 4 treatment arms
  - Roxicodone, manipulated [Tool E] (IN)
  - RoxyBond, manipulated [Tool G] (IN)
  - RoxyBond, intact (oral)
  - Placebo
- Active treatments used 30 mg dosage strength
Endpoints Intranasal HAP Study

- Primary Endpoint
  - Drug Liking $E_{\text{max}}$
- Key Secondary Endpoints
  - Take Drug Again $E_{\text{max}}$
  - Overall Drug Liking $E_{\text{max}}$
  - Drug Effects Questionnaire
  - Ease of Snorting Assessment
Lower Oxycodone Concentrations for Manipulated IN RoxyBond

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

Roxicodone, Manipulated IN
RoxyBond, Manipulated IN
RoxyBond, Intact Oral

Time (hours)

Study 002: Intranasal HAP Study
Significantly Lower Maximum Drug Liking for Manipulated RoxyBond

Study 002: Intranasal HAP Study

Category 3
Lower Drug Liking for Manipulated RoxyBond At Early Time Points

Study 002: Intranasal HAP Study

Category 3
Significantly Lower Take Drug Again for Manipulated RoxyBond

Study 002: Intranasal HAP Study
Significantly Lower Overall Drug Liking for Manipulated RoxyBond

Study 002: Intranasal HAP Study
Significantly Lower Drug High for Manipulated RoxyBond

Study 002: Intranasal HAP Study
RoxyBond Significantly More Difficult to Snort than Roxicodone

Study 002: Intranasal HAP Study
Clinical Relevance of HAP Results
Meta-Analysis: Reduction in Overall Drug Liking Associated with Decrease in Non-Medical Use

- 5 mm reduction in Overall Drug Liking $E_{\text{max}}$ for ADF ER oxycodone
  $\rightarrow$ \~10.1% reduction in non-medical use

- 17 mm reduction in Overall Drug Liking $E_{\text{max}}$ for RoxyBond likely to lead to reductions in abuse

Literature Provides Support for Clinical Significance of RoxyBond HAP Study

- Determined clinically important difference in Drug High $E_{\text{max}}$ in treatment setting\(^1\)
- 8-10 mm differences in Drug High $E_{\text{max}}$ led to clinically significant changes in drug-taking behavior
- 28 mm lower Drug High $E_{\text{max}}$ for RoxyBond supports lower IN abuse potential

RoxyBond Can Be Expected to Deter Intranasal Abuse

- Met primary endpoint with statistically significantly lower Drug Liking $E_{\text{max}}$
- Met secondary endpoints
  - Less likely to Take Drug Again
  - Lower Overall Drug Liking
  - Lower Drug High
  - More difficult to snort
- PK consistent with PD
- Results consistent with clinical significance in literature
Clinical Perspective

Jeffrey Gudin, MD
Director
Pain Management and Palliative Care
Englewood Hospital and Medical Center
Questions for Joint Advisory Committee

- Should RoxyBond be approved for the proposed indication, management of pain severe enough to require an opioid analgesic?
- Whether there are sufficient data to support a finding that RoxyBond has properties that can be expected to deter:
  - Intranasal route of abuse
  - Intravenous route of abuse
RoxyBond Expected to Have Same Efficacy and Safety as Roxicodone

- Comparable bioavailability
  - Equivalent efficacy and safety expected
- Available in commonly prescribed oxycodone strengths and dosing schedule
- Can be taken without regard to food
- No new risks compared to existing products
Questions for Joint Advisory Committee

- Should RoxyBond be approved for the proposed indication, management of pain severe enough to require an opioid analgesic?
- Whether there are sufficient data to support a finding that RoxyBond has properties that can be expected to deter:
  - Intranasal route of abuse
  - Intravenous route of abuse
Most Nonmedical Opioid Users Obtain Drug from Friend or Family

- Difficult to ascertain risk of diversion
- ADFs benefit patients and individuals with access to their medicine cabinet

Important Real-World Considerations for Abuse Deterrence

- Most abusers start with IR products\(^1-3\)
  - RoxyBond is opportunity to intervene earlier, deter progression to more dangerous routes
- ADFs are abuse deterrent, not abuse proof
  - Can be defeated with enough knowledge, time, and effort
- Clinically relevant questions for ADFs:
  - *Does it make abuse more difficult?*
  - *Does it make the experience less rewarding?*

RoxyBond Can Be Expected to Deter Intranasal and IV Abuse

Slows release and resists extraction of oxycodone when manipulated compared to intact oral administration

**Intranasal Abuse Deterrence**
- Difficult to get into abusable form
- More difficult to snort than Roxicodone
- Lower and slower absorption
- Significantly lower Drug Liking and Take Drug Again

**IV Abuse Deterrence**
- Resistant to particle size reduction
- Difficult to extract
- Forms viscous material when manipulated
- Resists syringeability

Significant improvement over non-abuse-deterrent products
ADFs One Component to Address Prescription Opioid Epidemic

- Full impact cannot be realized until all opioids are abuse-deterrent
- FDA’s goal: ADFs for all major opioids
RoxyBond™
(oxycodone hydrochloride)
Immediate-Release Tablets

April 5, 2017

Inspirion Delivery Sciences

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Back-up Slides
Gastric pH When Taking PPI Similar to Gastric pH After a Meal

- PPI pH at steady state, median (min, max)$^1$
  - Esomeprazole – 4.8 (2.5, 5.8)
  - Tenatoprazole – 5.0 (2.3, 5.8)
- Effect of food on pH, median (interquartile range)$^2$
  - Fasted – 1.7 (1.4, 2.1)
  - Fed – 5.0 (4.3, 5.4)

No clinically significant effect of food on oxycodone bioavailability with RoxyBond

Similar Food Effects with RoxyBond and Roxicodone

- RoxyBond (fed vs. fasted)
  - 23% increase in AUC
  - 18% increase in $C_{\text{max}}$
  - $T_{\text{max}}$ delay from 1.8 to 2 hrs

- Roxicodone (fed vs. fasted)
  - 27% increase in AUC
  - $T_{\text{max}}$ delay from 1.25 to 2.54 hrs

- Inspirion agrees with FDA conclusion that “a food restriction should not be recommended for RoxyBond (FDA briefing book; p. 55)”
RoxyBond Produced Significantly More Adverse Nasal Effects

<table>
<thead>
<tr>
<th>$E_{\text{max}}$ Parameter</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Irritation</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Burning</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Runny Nose / Nasal Discharge</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Facial Pain / Pressure</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>&lt;0.0001</td>
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Study 002: Intranasal HAP Study

Category 3
Lower Drug Liking for Manipulated RoxyBond At Early Time Points

Mean Drug Liking [95% CI]

RoxyBond, Intact Oral
Roxicodone, Manipulated IN
RoxyBond, Manipulated IN

Time (hours)

Strong Liking
Neutral
Disliking

Study 002: Intranasal HAP Study (N=29)
RoxyBond Expected to Have Same Efficacy and Safety as Roxicodone

- Strengths are dose proportional
- No clinically significant effect of food

Comparative PK Results (30 mg)
RoxyBond : Roxicodone

- $AUC_{0-t}$
- $AUC_{\text{inf}}$
- $C_{\text{max}}$

Note: Gray shaded area reflects bioequivalence range of 80% to 125%

LS Mean Ratios (%) [90% CI]
Electric Tool G Produced the Largest Percentage of Small Particles

Tablet Weight (%)

- > 2000 µm
- > 425 µm
- > 150 µm
- > 53 µm
- < 53 µm

Smallest Percentage of Very Large Particles

Tool G
### Table 11: Treatment Emergent Adverse Events - Intranasal HAP Study O-ARIR-002

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Manipulated Roxicodone Intranasal (N = 30)</th>
<th>RoxyBond Manipulated Intranasal (N = 30)</th>
<th>RoxyBond Intact Oral (N = 31)</th>
<th>Placebo (N = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Pruritus</td>
<td>23.3%</td>
<td>6.7%</td>
<td>12.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13.3%</td>
<td>13.3%</td>
<td>6.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.7%</td>
<td>10.0%</td>
<td>6.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.0%</td>
<td>0.0%</td>
<td>12.9%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

HAP = human abuse potential; N = number of subjects.
Figure 7: Particle Size Distribution Results for Varying Use Times with Tool G
RoxyBond Manipulated with Tool G
Individual PK Curves

![Graph showing individual PK curves for Crushed RoxyBond and Intact RoxyBond](image_url)

- **Crushed RoxyBond**
- **Intact RoxyBond**

Y-axis: Oxycodone Concentrations (ng/mL)
X-axis: Time (hours)