ADF Replacement (oxycodone hydrochloride) Abuse-Deterrent Immediate-Release Tablets

November 14, 2018
Mallinckrodt Pharmaceuticals
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Introduction

Martha Schlicher, PhD
Vice President
Research and Development, Generic Business Unit
Mallinckrodt Pharmaceuticals
"Transitioning from the current market, dominated by conventional opioids, to one in which most opioids have abuse-deterrent properties, holds significant promise for a meaningful public health benefit."

- FDA Statement, 2017
Mallinckrodt Requesting Approval for ADF Replacement

- Mallinckrodt immediate-release (IR) single-entity (SE) oxycodone tablets currently 15% of market
  - Roxicodone®
  - Generic oxycodone
- Requesting NDA approval for abuse-deterrent formulation (ADF) with label claims
  - Intranasal (IN)
  - Intravenous (IV)
- Mallinckrodt intends to replace all currently marketed IR SE oxycodone tablets with ADF Replacement (MNK-812)
ADF Replacement Characteristics

- Conventional solid dosage manufacturing process
  - Five strengths: 5, 10, 15, 20, 30 mg

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard, non-brittle tablet</td>
<td>Provide resistance to physical manipulation</td>
</tr>
<tr>
<td>Gelling agents</td>
<td>Produce viscous solution in small volumes of aqueous solvents to deter IV abuse</td>
</tr>
<tr>
<td>Aversive agents</td>
<td>Create nasal irritation to discourage IN abuse</td>
</tr>
</tbody>
</table>
# Components of ADF Replacement Tablets

<table>
<thead>
<tr>
<th>Proposed Function</th>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active pharmaceutical ingredient (API)</td>
<td>Oxycodone HCl</td>
</tr>
<tr>
<td>Abuse deterrence</td>
<td>Tartaric acid*</td>
</tr>
<tr>
<td></td>
<td>Citric acid</td>
</tr>
<tr>
<td></td>
<td>Effersoda*</td>
</tr>
<tr>
<td></td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td></td>
<td>Polyethylene oxide</td>
</tr>
<tr>
<td></td>
<td>Glucomannan</td>
</tr>
<tr>
<td></td>
<td>Sodium carboxymethyl cellulose</td>
</tr>
<tr>
<td></td>
<td>Hydroxypropylmethyl cellulose</td>
</tr>
<tr>
<td></td>
<td>Xanthan gum</td>
</tr>
<tr>
<td>Other</td>
<td>Butylated hydroxytoluene</td>
</tr>
<tr>
<td></td>
<td>Magnesium stearate</td>
</tr>
<tr>
<td></td>
<td>Opadry® coating materials</td>
</tr>
</tbody>
</table>

- Does not contain high molecular weight (HMW) PEO as used in Opana® ER
- HMW PEO in ADF Replacement similar to that in OxyContin® at > 20x lower amounts

- All excipients generally regarded as safe (GRAS) or in FDA-approved oral drug products

* Also functions as disintegrant
ADF Replacement is Bioequivalent to Roxicodone

- Submitted for FDA approval under the 505(b)(2) pathway
- Bioequivalence studies demonstrate ADF Replacement is therapeutically equivalent to Roxicodone
- Meets regulatory requirements for approval and would receive same indication as Roxicodone

...an opioid agonist indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
### Key Findings from Abuse Deterrence Studies Support Label Claims

<table>
<thead>
<tr>
<th>Intranasal (IN)</th>
<th>Intravenous (IV)</th>
</tr>
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<tbody>
<tr>
<td>- Resisted physical manipulation</td>
<td></td>
</tr>
<tr>
<td>- Reduced early positive effects</td>
<td></td>
</tr>
<tr>
<td>- Difficult to snort; aversive agents caused pain and burning</td>
<td></td>
</tr>
<tr>
<td>- Subjects did not express willingness to snort again</td>
<td></td>
</tr>
<tr>
<td>- Multiple gelling agents</td>
<td></td>
</tr>
<tr>
<td>- Resisted all common IV methods</td>
<td></td>
</tr>
<tr>
<td>- Multi-step procedure with advanced techniques required</td>
<td></td>
</tr>
<tr>
<td>- No evidence of overt toxicity from injection of extracts</td>
<td></td>
</tr>
</tbody>
</table>

ADF Replacement can be expected to reduce abuse compared to products it would replace
Mallinckrodt Committed to Opioid REMS Requirements

- Medication Guide
- Elements to Assure Safe Use
  - Healthcare provider training
  - Independent continuing education activities
  - Tools on safe use, storage, and disposal of opioids
  - Encourage training on safe use and appropriate prescribing
- REMS assessments to FDA
Additional safety measures
  ▪ Enhanced pharmacovigilance, tailored AE questionnaire
  ▪ Web monitoring for safety signals

Additional intended vs. unintended use information
  ▪ Prescription rates / transition
  ▪ Street price data
  ▪ Drug user chat rooms
  ▪ Poison control center monitoring and product-specific inquiries

Physician focus groups to understand education needs on limitations of ADFs

Category 4 studies to evaluate effectiveness in reducing abuse
## Agenda

| Public Health Need for Abuse-Deterrent IR Opioid Analgesics | Richard Dart, MD, PhD  
Director, Rocky Mountain Poison & Drug Center  
Executive Director, RADARS® System |
| --- | --- |
| Category 1 *In Vitro* Studies | Edward Cone, PhD  
Principal Scientist, Drug Delivery & Abuse-Deterrent Drug Products  
Pinney Associates |
| Nonclinical Excipient Safety Studies | Mike Orr, PhD, DABT  
President/CEO  
Orr Nonclinical Consulting, LLC |
| IN Human Abuse Potential Study | Sandra Comer, PhD  
Professor of Neurobiology (in Psychiatry)  
Division on Substance Use Disorders  
Columbia University |
| Clinical Perspective | Jeff Gudin, MD  
Director, Pain Management & Palliative Care  
Englewood Hospital and Medical Center |
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
Pathways to Opioid Abuse

- Pain Patient
- Susceptible Individual
- Recreational User

Behaviors:
- Intact
- Crushed

Possible Adverse Outcomes:
- Addiction
- Overdose
- Death
ADFs Offer Potential to Deter Initiation to Non-Oral Routes of Abuse

Susceptible Individual

Possible Adverse Outcomes
- Addiction
- Overdose
- Death

Behaviors
- Intact
- Crushed

Guidelines
- Pain Patient
- Susceptible Individual
- Enforcement
- Recreational User

ADFs
- Crushed
- Intact

Enforcement
- PDMP

Recreational User

Pain Patient

Guidelines
Expectations and Limitations of ADFs

What ADFs CAN Do

- Reduce IN and IV abuse of specific product
- Make diversion less attractive
- Deter initiation to non-oral routes of abuse

What ADFs CANNOT Do

- Reduce IN and IV abuse of other opioids
- Reduce oral overconsumption
ADFs Can Impact Different Types of Individuals

**Patient with Pain**
- Makes their medication less attractive for misuse and diversion

**Novice / Recreational User**
- Deter initiation and progression of IN and IV abuse

**Persons with Severe Opioid Use Disorder**
- Make dangerous routes of abuse more difficult
IR Opioids Preferred Over ER Opioids for Abuse

- IR opioids abused and diverted more frequently than ER\(^1,2\)
  - 4.6-fold higher abuse
  - 6.1-fold higher diversion

- IR SE opioids preferred over ER opioids\(^2\)
  - Immediacy of high
  - Ease of snorting or injection
    - No abuse-deterrent properties
    - No acetaminophen or ibuprofen

Rate of Abuse of IR SE Oxycodone Greater than ER Oxycodone

Number of Individuals Reporting Abuse in Last 30 Days per 100 Assessments

IR SE Oxycodone: 5.2
ER Oxycodone: 2.5
IR SE Oxycodone Widely Abused via IN and IV Routes

Prevalence of IR SE Oxycodone Abuse (%)

- Oral: 50.2%
- IN: 49.9%
- IV: 24.6%

N=2,630

IV Route Poses Additional Risks for Serious Health Consequences

- 6% of new HIV diagnoses\(^1\)
- 9% of new AIDS diagnoses\(^1\)
- Hepatitis C\(^2\)
- Endocarditis\(^3\)
- Blood clots\(^3\)

ADFs Important, Yet Underutilized Component to Address Opioid Abuse in US

- Goal: produce safest product possible for each type of opioid
- ADFs offer mechanism to deter abuse by non-oral routes
- ADFs currently comprise very small portion of market
- FDA has advocated for transitioning market to ADF
  - Development and approval pathway clearly established
- All products should be in abuse-deterrent form
Category 1 Studies

Edward Cone, PhD
Principal Scientist, Drug Delivery & Abuse-Deterrent Drug Products
Pinney Associates
Category 1 Studies for ADF Replacement

- Evaluated physicochemical properties of ADF Replacement to make IN and IV abuse more difficult
- Designed in accordance with the FDA Guidance on ADFs\(^1\)
  - Incorporated feedback from FDA
- Roxicodone used as non-ADF comparator

Particle Size Reduction Studies

- IR products designed to release drug rapidly
- Particle size reduction does not change oral release profile
- Rationale: prepare usable form of drug for IN or IV use
Particle Size Reduction Studies Identified Methods to Achieve Smallest Particles

- Evaluated ability to crush, cut, grate, grind, and mill Roxicodone and ADF Replacement tablets
- 4 levels of manipulation formally evaluated
  - Tested until no further particle size reduction occurred
  - Most effective manipulation for each product used in human abuse potential study
ADF Replacement Difficult to Physically Manipulate

Mean Particles < 500 Microns [SD]

- Level 1: 68% ± 5%
- Level 2: 97% ± 4%
- Level 3: NP
- Level 4: 90% ± 2%

Roxicodone 30 mg
ADF Replacement 30 mg

Abuse-deterrent properties not defeated
- IN: unpleasant to snort
- IV: difficult to syringe ground material

NP = not performed
Small Volume Extraction and Syringeability

Rationale: determine conditions necessary to achieve high yield of syringeable oxycodone
Background on Selection of Methods and Interpretation of Small Volume Extraction Results

- ADFs are pain medications that must be bioavailable
- Can be overcome with sufficient time, effort, materials, and knowledge
  - Abuse-\textit{deterrent}, not abuse-\textit{proof}
- Goal of testing: determine whether extent of work required to overcome barriers can be expected to deter abuse
- Pretreatment conditions and advanced techniques selected to challenge abuse-deterrent properties
Small Volume Extraction Experiments to Understand IV Abuse Potential

- 1,836 combinations of conditions tested (> 5,000 samples)
- Iterative testing approach to challenge ADF Replacement

**Common Methods**
(288 combinations of conditions)
- Intact and ground Roxicodone and ADF Replacement
- Most frequently used solvent for IV abuse
- Various temperatures, needles, agitation, volumes, extraction times

**Advanced Methods**
(1,548 combinations of conditions)
- Intact and ground ADF Replacement
- Further evaluated with various pretreatments and other directly injectable solvents
## Common Methods Could Not Be Used to Prepare IV Solutions of ADF Replacement

<table>
<thead>
<tr>
<th>Yield of Syringeable Oxycodone</th>
<th>n (%) of Conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Roxicodone (N=144 Conditions)</td>
<td>ADF Replacement (N=144 Conditions)</td>
</tr>
<tr>
<td>&lt; 5%</td>
<td>0</td>
<td>141 (98%)</td>
</tr>
<tr>
<td>5% to 10%</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>&gt; 10% to 20%</td>
<td>0</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td>&gt; 20% to 40%</td>
<td>15 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 40% to 60%</td>
<td>73 (51%)</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 60% to 100%</td>
<td>56 (39%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Pre-Treatment Conditions Required to Challenge ADF Replacement Abuse-Deterrent Properties

Median Oxycodone Recovery [Range]

IV Pretreatment

0% 20% 40% 60% 80% 100%

[0 – 18] [0 – 9] [0 – 35] [0 – 60]

More than 1 Hour to Perform

Specific Tool

Pretreatment

Large Extraction Volume

Long Extraction Time

Elevated Temperature

Large Needles

Large Injection Volume

Most frequently used solvent for IV abuse
### ADF Replacement Demonstrated Physical And Chemical Barriers to IN and IV Abuse

<table>
<thead>
<tr>
<th>Study</th>
<th>Relevant Route of Abuse</th>
<th>Key Findings for ADF Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical manipulation (particle size reduction)</td>
<td>IN, IV</td>
<td>▪ Difficult to crush ▪ Particle size reduction does not defeat IN or IV abuse-deterrent properties</td>
</tr>
<tr>
<td>Small volume extraction and syringeability</td>
<td>IV</td>
<td>▪ ADF Replacement difficult to syringe ▪ Creates substantial barrier to injection</td>
</tr>
</tbody>
</table>
Nonclinical Excipient Safety Studies

Mike Orr, PhD, DABT
Orr Nonclinical Consulting, LLC
Rationale for Performing Excipient Safety Studies

- All ADF Replacement excipients safe for oral use
- Concerns about repeated IV injection of HMW PEO in Opana ER\(^1\)
  - ADF Replacement does not contain this type of PEO
- General toxicology studies conducted to understand safety profile of all excipients via IV route

Design Elements of Nonclinical Excipient Safety Studies

- Sponsor designed studies in consultation with FDA
  - *In vitro* hemolytic potential, plasma compatibility, and platelet aggregation studies
  - *In vivo* multiple-dose IV toxicity study
- Test Article 1 and Test Article 2
  - Selected based on conditions achieving highest yields of syringeable oxycodone from two IV pretreatments
In Vitro Blood Compatibility Studies

- Hemolytic potential
- Plasma compatibility
- Platelet aggregation
No Evidence of *In Vitro* Hemolysis

<table>
<thead>
<tr>
<th>Condition in Human Blood</th>
<th>Hemoglobin (mg/dL)</th>
<th>Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative Control</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Test Article 1</td>
<td>9</td>
<td>Negative</td>
</tr>
<tr>
<td>Test Article 2</td>
<td>1</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive Control</td>
<td>5895</td>
<td>Positive</td>
</tr>
</tbody>
</table>

- Positive result defined as 500 mg/dL increase relative to negative control
No Evidence of Human Plasma Incompatibility or Increased Platelet Aggregation

- Human plasma incompatibility not observed with Test Articles
  - Test Article 1: no macro or micro observations
  - Test Article 2: cloudy appearance likely due to presence of finely suspended particles observed prior to mixing
  - Test Articles 1 and 2 both negative for protein flocculation
- Increased platelet aggregation not observed with Test Articles
  - Results similar to negative control and within normal reference range for healthy blood donors
In Vivo Multiple-Dose IV Toxicity Study

- Evaluated local and systemic effects of ADF Replacement extracts
Test Articles in Multiple-Dose *In Vivo* IV Toxicity Study in Rabbits

- 12 female rabbits randomized equally to receive once daily bolus injections (1 mL/kg) for 3 days
  - Test Article 1, N=4
  - Test Article 2, N=4
  - Control Article (0.9% sodium chloride), N=4
- Dose volume selected based on tolerability profile of oxycodone
- Dose volume in rabbit relative to human
  - ~10-fold higher based on body surface area
  - ~58-fold higher based on mL/kg
Multiple-Dose *In Vivo* IV Toxicity Study Methods

- Animals monitored ≥ 2x/day for abnormal findings
- Full panel of clinical pathology tests performed
  - Hematology, coagulation, clinical chemistry, urinalysis
  - Standard panel of tissues collected
  - Select organs evaluated microscopically
Summary of In Vivo Excipient Safety Study

- No evidence of overt toxicity or tissue damage
- Test Articles not associated with signs or symptoms of thrombotic microangiopathy
- Test Article 2: statistically significant increases in fibrinogen (1.5-fold) and increases in spleen weights (50%)
  - Not considered adverse by independent pathologist
- Minimal to slight microscopic pathology observations
  - Not considered adverse by independent pathologist
Intranasal Human Abuse Potential Study

Sandra D Comer, PhD
Professor of Neurobiology (in Psychiatry)
Division on Substance Use Disorders
Columbia University
Rationale for Snorting IR Opioids is Faster Onset of Effects

- IN administration bypasses first-pass metabolism
  - Faster drug entry into bloodstream and brain
  - Faster onset of “positive effects” such as liking and high
- IN and oral administration of IR opioid have similar maximum positive effects\(^1-^3\)
- Motivation for snorting: faster onset of positive effects
  - Early timepoints are important

3. FDA Briefing Document for Avridi™.
Different Mechanisms of IN Abuse Deterrence

**Positive Effects**
- Drug Liking
- Drug High

**Negative Effects**
- Ease of Snorting
- Nasal Effects Assessment

ADF s can work by reducing positive effects

ADFs can work by creating negative effects

**Overall Experience**
- Overall Drug Liking
- Take Drug Again
Design: IN Human Abuse Potential (HAP) Study

- Randomized, double-blind, double-dummy, placebo-controlled, 4-period crossover study
  - Non-dependent, recreational opioid users
  - Recent IN experience with opioids
- Qualification Phase
  - Naloxone challenge test: not physically dependent on opioids
  - Drug discrimination test: able to discriminate IN 15 mg Roxicodone from placebo
- 38 subjects completed study
## IN HAP Study Treatments

- 72-hour washout period between treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Double-Dummy Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ADF Replacement (30 mg)</td>
<td>IN Roxicodone placebo</td>
</tr>
<tr>
<td>IN ADF Replacement (30 mg)</td>
<td>Oral ADF Replacement placebo</td>
</tr>
<tr>
<td>IN Roxicodone (30 mg)</td>
<td>Oral ADF Replacement placebo</td>
</tr>
<tr>
<td>Oral ADF Replacement placebo</td>
<td>IN Roxicodone placebo</td>
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</tbody>
</table>
## IN HAP Study Key Assessments

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Timing of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
</tr>
<tr>
<td>Drug Liking $E_{\text{max}}$</td>
<td>Max score 15 min to 12 hrs post dose</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
</tr>
<tr>
<td>Drug Liking</td>
<td>15 min to 12 hrs post dose</td>
</tr>
<tr>
<td>Drug High</td>
<td>15 min to 12 hrs post dose</td>
</tr>
<tr>
<td>Ease of Snorting Assessment</td>
<td>Within 5 min post dose</td>
</tr>
<tr>
<td>Nasal Effects Questionnaire</td>
<td>15 min to 12 hrs post dose</td>
</tr>
<tr>
<td>Overall Drug Liking</td>
<td>12 and 24 hrs post dose</td>
</tr>
<tr>
<td>Take Drug Again</td>
<td>12 and 24 hrs post dose</td>
</tr>
</tbody>
</table>

*All secondary assessments evaluated independently without any ranking assignment*
Pharmacokinetics
Lower Oxycodone Concentrations at Early Time Points for IN ADF Replacement

![Graph showing plasma concentration over time for different modes of administration.](image)

- **LS Mean Plasma Concentration (ng/mL) [95% CI]**
- **Time (Hours)**
- **Mean C\text{max}**
  - Oral ADF Replacement: 57.7
  - IN Roxicodone: 55.7
  - IN ADF Replacement: 55.0

\* p < 0.05 for IN ADF Replacement vs. IN Roxicodone
Pharmacodynamics: Positive Effects

- Drug Liking
- Drug High
Primary Endpoint Evaluated with Superiority Margin Per FDA Guidance

- Primary endpoint: maximum Drug Liking ($E_{max}$)
- Approved ADFs have needed to show statistically significant effect
  - Often referred to as “superiority”
- FDA Guidance requires use of superiority margin ($\delta^*$)
  - Requires that ADF show statistically significant effect by specific margin
  - Often referred to as “super-superiority”
- ADF Replacement study used 10% superiority margin
Primary Endpoint: Drug Liking $E_{\text{max}}$

Q: Do you like the drug effect you are feeling now?

Superiority $p = 0.0039$
Super-Superiority $p = 0.1409$

Based on FDA Analysis

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

- IN Roxicodone: 83
- IN ADF Replacement: 77
- Oral ADF Replacement: 84
- Placebo: 51

Strong Liking
Neither Like nor Dislike
Strong Disliking
Lower and Delayed Drug Liking for IN ADF Replacement at Early Time Points

**Q: Do you like the drug effect you are feeling now?**

- Placebo
- Oral ADF Replacement
- IN Roxicodone
- IN ADF Replacement

**LS Mean Drug Liking VAS Score [95% CI]**

- Difference in $\text{TE}_{\text{max}}$: 0.9 hours ($p = 0.018$)

* $p < 0.05$ for IN ADF Replacement vs. IN Roxicodone
Pharmacodynamics: Negative Effects

- Ease of Snorting
- Nasal Effects Questionnaire
ADF Replacement Significantly More Difficult to Snort Than Roxicodone

Q: Snorting this drug was?

LS Mean Ease of Snorting [95% CI]

- Roxicodone: 11
- ADF Replacement: 84

p < 0.001

Very Difficult

Very Easy
ADF Replacement Causes Adverse Nasal Effects

- IN ADF Replacement
  - 95% experienced at least 1 adverse nasal effect
  - 79% experienced moderate/severe nasal effect

Nasal Assessments:
- Facial Pain/Pressure
- Nasal Congestion
- Runny Nose/Nasal Discharge
- Need to Blow Nose
- Irritation
- Burning

Time (Hours) vs. Nasal Assessment – Moderate / Severe (% of Subjects)
Pharmacodynamics: Overall Drug Taking Experience

- Overall Drug Liking
- Take Drug Again
Significantly Lower Overall Drug Liking for IN ADF Replacement at 24 Hours

Q: Overall, my liking for this drug is:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Liking Score</th>
<th>LS Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN Roxicodone</td>
<td>71</td>
<td>71</td>
<td>[69, 73]</td>
</tr>
<tr>
<td>IN ADF Replacement</td>
<td>46</td>
<td>46</td>
<td>[44, 48]</td>
</tr>
<tr>
<td>Oral ADF Replacement</td>
<td>70</td>
<td>70</td>
<td>[68, 72]</td>
</tr>
<tr>
<td>Placebo</td>
<td>48</td>
<td>48</td>
<td>[46, 50]</td>
</tr>
</tbody>
</table>

$p < 0.001$
Significantly Lower Take Drug Again for IN ADF Replacement at 24 Hours

Q: Would you want to take the drug you just received again, if given the opportunity?

Mean Take Drug Again at 24 Hours [95% CI]

- IN Roxicodone: 71 (p < 0.001)
- IN ADF Replacement: 41
- Oral ADF Replacement: 72
- Placebo: 50

Definitely Would

Do Not Care

Definitely Would Not
ADF Replacement Can Be Expected to Reduce IN Abuse

**Positive Effects**
- Drug Liking $E_{\text{max}}$ significantly lower, but not super-superior to Roxicodone
- Significant decrease in Drug Liking and High at early timepoints

**Negative Effects**
- More difficult to snort than Roxicodone
- Aversive agents cause burning, irritation, and pain

**Overall Experience**
- Overall Drug Liking similar to placebo
- Subjects did not want to snort ADF again
Clinical Perspective

Jeffrey Gudin, MD
Director, Pain Management and Palliative Care
Englewood Hospital and Medical Center
Balancing Patient Need with Public Health Challenge

- Opioids remain needed treatment option for pain
- Clinicians typically feel comfortable evaluating patient’s potential risk of abuse
  - But cannot control diversion
- ADF safeguards against abuse intended for patients and anyone with access to medicine cabinet
FDA Questions for Joint Committee

- Can ADF Replacement be expected to deter abuse?
  - Nasal route
  - IV route
- Concerns regarding public health impact of ADF Replacement on misuse and abuse of opioids?
- Should ADF Replacement be approved?

Questions should be considered in light of replacing Mallinckrodt’s marketed non-ADF tablets
Can ADF Replacement Be Expected to Deter Abuse by Nasal Route of Administration?

- Physical and chemical properties
- IN HAP study
- Precedent set by FDA-approved IR ADF (RoxyBond™)
# ADF Replacement Has Physical and Chemical Properties to Deter IN Abuse

<table>
<thead>
<tr>
<th>Properties</th>
<th>ADF Replacement</th>
<th>Current Roxicodone and Generic</th>
</tr>
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<tbody>
<tr>
<td>Physical</td>
<td>- Difficult to manipulate</td>
<td>- Easily manipulated with simple tools</td>
</tr>
<tr>
<td></td>
<td>- Required most advanced level of manipulation</td>
<td></td>
</tr>
<tr>
<td>Chemical</td>
<td>- Difficult to snort</td>
<td>- Easy to snort</td>
</tr>
<tr>
<td></td>
<td>- Aversive agents cause pain and burning</td>
<td>- No agents to discourage IN abuse</td>
</tr>
</tbody>
</table>
### IN HAP Study Demonstrates ADF Replacement Can Be Expected to Deter IN Abuse

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Mean for IN Administration</th>
<th>Difference (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Roxicodone</td>
<td>ADF</td>
</tr>
<tr>
<td><strong>Drug Liking $E_{max}$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADF Replacement</td>
<td>83</td>
<td>77</td>
</tr>
<tr>
<td>RoxyBond</td>
<td>83</td>
<td>71</td>
</tr>
<tr>
<td><strong>Take Drug Again $E_{max}$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADF Replacement</td>
<td>77</td>
<td>46</td>
</tr>
<tr>
<td>RoxyBond</td>
<td>82</td>
<td>62</td>
</tr>
</tbody>
</table>

Lack of willingness to snort again consistent with aversive effects

Statistics based on FDA Briefing Documents for ADF Replacement and RoxyBond.
Can ADF Replacement Be Expected to Deter Abuse by IV Route of Administration?

- Physical and chemical properties
- Category 1 studies
- Precedent with FDA-approved IR ADF (RoxyBond)
# ADF Replacement Has Physical and Chemical Properties to Deter IV Abuse

<table>
<thead>
<tr>
<th>Properties</th>
<th>ADF Replacement</th>
<th>Current Roxicodone and Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical</strong></td>
<td>▪ Difficult to manipulate</td>
<td>▪ Easily manipulated with simple tools</td>
</tr>
<tr>
<td></td>
<td>▪ Required most advanced level of manipulation</td>
<td></td>
</tr>
<tr>
<td><strong>Chemical</strong></td>
<td>▪ Multiple gelling agents make injection difficult</td>
<td>▪ No barriers to injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Category 1 Studies Demonstrate ADF Replacement Can Be Expected to Deter IV Abuse

<table>
<thead>
<tr>
<th>IV Abuse Assessment</th>
<th>Roxicodone</th>
<th>ADF Replacement</th>
<th>RoxyBond¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult to syringe?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Low yields in vast majority of conditions?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Required advanced conditions for IV abuse?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Worst-case yield with pretreatment</td>
<td>n/a</td>
<td>60%</td>
<td>66%</td>
</tr>
</tbody>
</table>

- Complex, multi-step processes (> 1 hr)
- Abuse-deterrent, not abuse-proof

---

1. Inspirion Delivery Sciences, LLC Slides for April 5, 2017 Advisory Committee.
Concerns Regarding Public Health Impact of ADF Replacement on Misuse And Abuse of Opioids?
# Benefit-Risk Analysis for Public Health Concerns

<table>
<thead>
<tr>
<th>ADF Public Health Concern</th>
<th>Benefit-Risk Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low uptake or limited public health impact</td>
<td>▪ Replacing currently marketed branded and generic tablets</td>
</tr>
</tbody>
</table>
| Can send false sense of security to prescribers | ▪ Approval of ADFs have not increased prescribing  
▪ ADF Replacement will not be promoted |
| Cannot deter initiation to dangerous routes | ▪ Contains aversive agents to discourage IN abuse |
| Should not push individuals to IV abuse | ▪ Extensive multi-step process required |
| Injected excipients may cause serious health consequences | ▪ No evidence of overt toxicity from excipient safety studies  
▪ Most dangerous ingredient for injection is oxycodone |
Should ADF Replacement be Approved?
ADFs Part of More Comprehensive Plan to Address Prescription Opioid Epidemic

- Prescription Drug Monitoring
- Physician & Patient Education
- Approach to Address Opioid Epidemic
- Appropriate Prescribing
- Substance Abuse Treatment
- Safe Disposal
- Abuse-Deterrent Formulations
**ADF Replacement in Interest of Patients and Public Health**

- FDA has advocated for transitioning market to ADFs
  - Meaningful public health benefit expected from providing safeguards against abuse
- Approval of ADF Replacement would allow for transition

Mallinckrodt’s IR SE oxycodone products without safeguards against abuse would no longer be available

- Millions of prescriptions replaced by ADF that
  - Is therapeutically equivalent
  - Discourages snorting
  - Makes IV injection difficult
ADF Replacement (oxycodone hydrochloride) Abuse-Deterrent Immediate-Release Tablets

November 14, 2018
Mallinckrodt Pharmaceuticals
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
BACK-UP SLIDES
Figure 7: Oxycodone Plasma Concentrations for 3 Subjects with $T_{\text{max}}$ Values of 6-8 Hours in Fed Bioequivalence Study Following Administration of ADF Replacement 15 mg Tablets

All subjects had oxycodone concentrations similar to $C_{\text{max}}$ values by start of 4-6-hour dosing interval.
Figure 1: Bioequivalence of ADF Replacement to Roxicodone 15 mg Tablets in Fasted and Fed States

Note: Yellow shaded area indicates pre-specified bioequivalence bounds of 80% to 125%.
# Respiratory AEs Driven by Aversive Agents

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term, N (%)</th>
<th>Intact Oral MNK-812 N=41</th>
<th>Intranasal MNK-812 N=40</th>
<th>Intranasal Oxycodone (IR) N=42</th>
<th>Placebo N=42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects at least 1 AE</td>
<td>32 (78)</td>
<td>29 (72.5)</td>
<td>24 (57.1)</td>
<td>12 (28.6)</td>
</tr>
<tr>
<td>Respiratory, Thoracic, Mediastinal Disorders</td>
<td>6 (14.6)</td>
<td>21 (52.5)</td>
<td>4 (9.5)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (7.3)</td>
<td>11 (27.5)</td>
<td>1 (2.4)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>Nasal Discomfort</td>
<td>0</td>
<td>10 (25.0)</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>1 (2.4)</td>
<td>2 (5.0)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Hiccups</td>
<td>2 (4.9)</td>
<td>1 (2.5)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>1 (2.4)</td>
<td>1 (2.5)</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Paranasal Sinus Discomfort</td>
<td>0</td>
<td>1 (2.5)</td>
<td>1 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Nasal Pruritus</td>
<td>0</td>
<td>1 (2.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary Congestion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>
## HMW PEO in Opana ER Not Present in ADF Replacement

<table>
<thead>
<tr>
<th></th>
<th>ADF Replacement</th>
<th>OxyContin</th>
<th>Opana ER (Reformulated)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of HMW PEO</strong></td>
<td>Similar to OxyContin</td>
<td>4 million</td>
<td>7 million</td>
</tr>
<tr>
<td><strong>% HMW PEO in Tablet</strong></td>
<td>&lt; 2%</td>
<td>≥ 65%</td>
<td>&gt; 60%</td>
</tr>
</tbody>
</table>
# No Rationale for Needle / Dose Sharing with ADF Replacement

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<td>&gt; 60%</td>
</tr>
<tr>
<td>API</td>
<td>oxycodone</td>
<td>oxycodone</td>
<td>oxymorphone</td>
</tr>
<tr>
<td>Oral Bioavailability</td>
<td>85%</td>
<td>85%</td>
<td>10-15%</td>
</tr>
<tr>
<td>IV Dose Potency Relative to Oxycodone</td>
<td>1x</td>
<td>1x</td>
<td>10-20x more potent</td>
</tr>
<tr>
<td>Single Tablet Suitable for Sharing IV</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prescriptions in 2017</td>
<td>-</td>
<td>3.4 million</td>
<td>306,000</td>
</tr>
</tbody>
</table>