Apadaz™ (immediate-release benzhydrocodone with acetaminophen) for the Treatment of Acute Pain

May 5, 2016
KemPharm, Inc.

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

Travis Mickle, Ph.D.
Co-Founder and Chief Executive Officer
KemPharm, Inc.
Apadaz is a Fixed-Dose IR Hydrocododone Combination Product

- Apadaz is composed of:
  - **Benzhydrocodone HCl [KP201]** (6.67 mg)
    - Prodrug: hydrocodone + benzoic acid
    - Equivalent to 7.5 mg hydrocodone bitartrate
  - **Acetaminophen [APAP]** (325 mg)
- Taken every 4-6 hours
Abuse-Deterrent Features of Apadaz Imparted Using a Novel Approach

- Historical approaches to deter abuse:
  - Agonist/antagonist
  - Aversive agents
  - Physical/chemical barriers

- Apadaz is a prodrug that imparts abuse-deterrence at molecular level
  - No impact of crushing or grinding on release profile
  - Abuse-deterrence does not affect analgesia
Apadaz Imparts Abuse-Deterrent Properties as Prodrug of Hydrocodone

- Intact prodrug is inert
- Ligand is naturally-occurring in berries

- Active hydrocodone cleaved from ligand through natural processes in GI tract
Summary of Clinical Pharmacology

- Bioequivalent to reference drugs to meet requirement of 505(b)(2) pathway
- Bioequivalent to Norco
- No clinically significant food effect
- No systemic exposure to prodrug when taken orally
## Similar Incidence of AEs for Both Products

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Apadaz (N=161)</th>
<th>Norco (N=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>21%</td>
<td>26%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Constipation</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

AEs with incidence ≥1% (Pooled from Studies 102, 104, S01)
## Apadaz Offers Protections Against Non-Oral Routes of Abuse

<table>
<thead>
<tr>
<th>Route of Abuse</th>
<th>Summary of Findings with Apadaz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Drug Liking similar to Norco, as expected</td>
</tr>
<tr>
<td>Intranasal</td>
<td>Lower hydrocodone exposure and lower Drug Liking compared to Norco at early time points; increased nasal adverse effects</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Cannot be efficiently extracted for IV injection; prodrug converts slowly to hydrocodone in blood</td>
</tr>
<tr>
<td>Smoking / Vaporizing</td>
<td>No release of hydrocodone</td>
</tr>
</tbody>
</table>
# Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Perspective</td>
<td><strong>Jeffrey Gudin, M.D.</strong></td>
</tr>
<tr>
<td></td>
<td>Director</td>
</tr>
<tr>
<td></td>
<td>Pain Management and Palliative Care</td>
</tr>
<tr>
<td></td>
<td>Englewood Hospital and Medical Center</td>
</tr>
<tr>
<td>Development Overview and Tampering Studies</td>
<td><strong>Travis Mickle, Ph.D.</strong></td>
</tr>
<tr>
<td></td>
<td>Co-Founder and Chief Executive Officer</td>
</tr>
<tr>
<td></td>
<td>KemPharm, Inc.</td>
</tr>
<tr>
<td>Clinical Abuse-Deterrence Studies</td>
<td><strong>Lynn Webster, M.D.</strong></td>
</tr>
<tr>
<td></td>
<td>Vice President, Scientific Affairs</td>
</tr>
<tr>
<td></td>
<td>PRA Health Sciences</td>
</tr>
<tr>
<td>Post-Market Surveillance Future Studies</td>
<td><strong>Travis Mickle, Ph.D.</strong></td>
</tr>
<tr>
<td>Benefit-Risk Profile</td>
<td><strong>Jeffrey Gudin, M.D.</strong></td>
</tr>
</tbody>
</table>
# Additional Experts

## Epidemiology

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon Budman, Ph.D.</td>
<td>Founder and Chief Strategy Officer</td>
<td>Inflexxion, Inc.</td>
</tr>
<tr>
<td>Theresa Cassidy, M.P.H.</td>
<td>Vice President, Health Analytics</td>
<td>Inflexxion, Inc.</td>
</tr>
</tbody>
</table>
Clinical Perspective

Jeffrey Gudin, M.D.
Director, Pain Management and Palliative Care
Englewood Hospital and Medical Center
Clinical Instructor, Anesthesiology
Icahn School of Medicine, Mt. Sinai
We at the Food and Drug Administration (FDA) continue to be deeply concerned about the growing epidemic of opioid abuse, addiction, and overdose—a epidemic directly related to the increasingly widespread misuse of powerful opioid pain medications.
Six approved ER/LA opioids with abuse-deterrent labeling:

- OxyContin (oxycodone)
- Targiniq (oxycodone and naloxone)
- Embeda (morphine sulfate and naloxone)
- Hysingla ER (hydrocodone)
- Morphabond (morphine sulfate)
- Xtampza ER (oxycodone)

Abuse-deterrent properties can lower, but not eliminate ability to abuse opioid

All Opioid Products with Abuse-Deterrent Labeling are Extended-Release/Long-Acting
Currently No Approved IR Opioid with Abuse-Deterrent Labeling

- No IR opioids labeled for abuse-deterrence
- Hydrocodone IR combination products:
  - 90 million dispensed prescriptions in 2015
  - Most commonly prescribed analgesic
  - Often the first opioid abused
- Unmet need to prevent escalation and progression of opioid abuse
Goal: Prevention of Progression from Oral Route to More Dangerous Routes of Administration

Progression of Abuse

- Abusers progress to more dangerous routes as:
  - Opioid tolerance develops
  - Cost to maintain abuse patterns increases
Surveillance data are collected from drug abuse treatment centers

Drug abuse surveillance is useful for understanding opioid abuse:
  - Extent of abuse
  - Routes of administration
Hydrocodone IR Combination Products Are Commonly Abused

NAVIPPRO - ASI-MV Network
N=96,357 adults aged 18+
Surveyed between Jan ‘14 and Jun ‘15

Rate of Past 30-day Abuse per 100 Adult Assessments [95% CI]

- Hydrocodone IR Combination Products
- Oxycodone IR Combination Products
- Oxycodone IR Single-Entity Products
- All ADF ER/LA Opioids
- All non-ADF ER/LA Opioids

ASI-MV Database
Prevalence of Abuse of Hydrocodone IR Combination Products by Route and Age

% of Hydrocodone Abusers Reporting Route of Abuse in last 30 Days

- Oral: 90% (Adults), 81% (Adolescents)
- Intranasal: 23% (Adults), 43% (Adolescents)
- Smoking: 1% (Adults), 5% (Adolescents)
- Injection: 2% (Adults), 1% (Adolescents)

ASI-MV Database (Jan 12 – Jun 15; N=9,064)
CHAT Database (Jan 12 – Jun 15; N=468)
Hydrocodone IR Combinations are Often the First Opioid Abused by Young People

2015 Inflexxion Internet Survey (N=472)
REDUCE OPIOID ABUSE

- Patient and Family Education
- Physician Education
- Proper Prescribing
- Safe Storage and Disposal
- Prescription Monitoring
- Abuse-Deterrent Formulations
Development Overview

Travis Mickle, Ph.D.
Co-Founder and Chief Executive Officer
KemPharm, Inc.
Apadaz Abuse-Deterrence Program Followed FDA Guidance

**Category 1**
Lab-based *In Vitro* Manipulation and Extraction Studies

Evaluates the difficulty with which AD properties can be defeated or compromised

**Category 2**
Pharmacokinetic Clinical Trials

Evaluates *in vivo* properties by measuring PK profiles of AD drug vs a comparator

**Category 3**
Clinical Abuse Potential Studies

Assessment of potential PD effects of AD drug vs a comparator
Rationale for Tampering Studies

- As IR product, purpose of extraction is to remove acetaminophen and isolate hydrocodone to:
  - Reduce liver toxicity at high oral doses
  - Reduce insufflation volume
  - Prepare for injection
  - Prepare for freebasing/smoking
Abuse-deterrent Products Increase Time and Effort It Takes To Extract Active Product

- Goal of abuse-deterrent formulation
  - Make manipulation more difficult and less attractive to abusers
    - Increase time
    - Increase effort
Extraction with Common Ingestible Solvents

5 Common Ingestible Solvents
Evaluated up to 24 hours

Category 1
Extraction of Hydrocodone from Apadaz Was Ineffective with Common Ingestible Solvents

Max % Hydrocodone Extracted

<table>
<thead>
<tr>
<th>Ingestible Solvent</th>
<th>Max % Hydrocodone Extracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0%</td>
</tr>
<tr>
<td>B</td>
<td>0%</td>
</tr>
<tr>
<td>C</td>
<td>0%</td>
</tr>
<tr>
<td>D</td>
<td>0%</td>
</tr>
<tr>
<td>E</td>
<td>0%</td>
</tr>
</tbody>
</table>

Category 1
Extraction with Advanced Solvents

14 Advanced, Non-ingestible Solvents Evaluated up to 24 hours
Extraction of Hydrocodone from Apadaz Was Ineffective with Advanced Solvents

Max % Hydrocodone Extracted

Advanced Solvents

Category 1

0% for both products
Extraction with Advanced Buffers

7 Advanced Buffers of varying pH
Evaluated up to 24 hours
Extraction of Hydrocodone from Apadaz Was Inefficient with Advanced Buffers

Max % Hydrocodone Extracted

<table>
<thead>
<tr>
<th>Advanced Buffer</th>
<th>Apadaz</th>
<th>Norco</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>U</td>
<td>95%</td>
<td>0%</td>
</tr>
<tr>
<td>V</td>
<td>95%</td>
<td>0%</td>
</tr>
<tr>
<td>W</td>
<td>94%</td>
<td>0%</td>
</tr>
<tr>
<td>X</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Y</td>
<td>9%</td>
<td>94%</td>
</tr>
<tr>
<td>Z</td>
<td>72%</td>
<td>37%</td>
</tr>
</tbody>
</table>
Extraction of Hydrocodone with Heat and Continuous Agitation

20 solvents evaluated up to 24 hours
Extraction at Various Temperatures and Continuous Agitation Did Not Yield Abusable Hydrocodone

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Max % Hydrocodone Extracted</th>
<th>Time at Maximum Extraction</th>
<th>Solvent</th>
<th>Max % Hydrocodone Extracted</th>
<th>Time at Maximum Extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0%</td>
<td>-</td>
<td>N*</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>0%</td>
<td>-</td>
<td>O*</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>0%</td>
<td>-</td>
<td>R*</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>0%</td>
<td>-</td>
<td>T**</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>0%</td>
<td>-</td>
<td>U**</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>F*</td>
<td>0%</td>
<td>-</td>
<td>V**</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>G*</td>
<td>0%</td>
<td>-</td>
<td>W**</td>
<td>61%</td>
<td>24 hours</td>
</tr>
<tr>
<td>J*</td>
<td>0%</td>
<td>-</td>
<td>X**</td>
<td>60%</td>
<td>4 hours</td>
</tr>
<tr>
<td>K*</td>
<td>0%</td>
<td>-</td>
<td>Y**</td>
<td>63%</td>
<td>6 hours</td>
</tr>
<tr>
<td>L*</td>
<td>0%</td>
<td>-</td>
<td>Z**</td>
<td>46%</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

*Advanced non-ingestible solvents
**Advanced buffers

Category 1
Hydrolysis

Covalent bond between benzoic acid and hydrocodone has to be broken to release hydrocodone from Apadaz prodrug
Hydrolysis is Not a Feasible Way for Abusers to Tamper with Apadaz

- Fewer than 20% of samples tested released >50% of hydrocodone
  - Hydrolysis occurred only under specific conditions related to pH, with temperature modifications, over extended time
- Additional steps required to obtain abusable hydrocodone
Route-Specific Manipulations

Injection
Smoking
IV Preparation was Less Efficient for Apadaz Than Norco; Syringeability is Feasible

- Of 164 conditions tested:
  - 39 conditions yielded >70% hydrocodone from Norco
  - 1 condition yielded >70% benzhydrocodone from Apadaz
- Syringeability is feasible for both products
  - Only inactive prodrug can be extracted from Apadaz, and is less efficient than Norco
Common Extraction Method to Prepare IV Formulations is Inefficient for Apadaz

Apadaz

Norco

Common Extraction Method

36% yield of benzhydrocodone

68% yield of hydrocodone

>80% of APAP removed
Cloudy Mock IV Preparations Due to Undissolved Excipients and Acetaminophen

Apadaz

Norco
Why Would an Abuser Inject?

- Bypass first-pass metabolism
  - Cocaine and heroin
- Injection gets opioid into brain more quickly
- Faster exposures, faster highs
In Vitro Study: Stability of Apadaz in Whole Human Blood

Benzhydrocodone Remaining (%)

Time (min)

Whole Blood

Intestinal Fluid

Category 1
Smoking Simulation Study
Apadaz Did Not Release Hydrocodone in Smoking Simulation Study

- Freebasing Apadaz was not possible
- Vaporizing or smoking Apadaz or benzhydrocodone at any temperature did not produce any hydrocodone
Summary of Findings from Category 1 Evaluations of Apadaz

- Common ingestible solvents not effective in extracting Apadaz
- Harsh chemicals and heat typically required over 4-24 hours for moderate hydrocodone extraction
- Preparing Apadaz for IV injection was inefficient, and prodrug converts slowly in blood
- Smoking/freebasing Apadaz tablets not effective
Clinical Abuse-Deterrence Studies

Lynn Webster, M.D.
Vice President, Scientific Affairs
PRA Health Sciences
Apadaz Abuse-Deterrence Program Followed FDA Guidance

Category 1
Lab-based In Vitro Manipulation and Extraction Studies

Category 2
Pharmacokinetic Clinical Trials

Category 3
Clinical Abuse Potential Studies

Evaluates the difficulty with which AD properties can be defeated or compromised

Study A01: Oral abuse
Study A02: IN abuse
Study A03: IN abuse with APIs
Health Consequences of Intranasal Abuse of Hydrocodone Combination Products

- Nasal/facial pain
- Nasal obstruction
- Necrosis of nasal passages & soft palate
- Fungal rhinosinusitis
- Septal and palatal perforation

![Pre-debridement](image1)

Nasal Septal Injury from IN Hydrocodone-Acetaminophen Abuse

![Post-debridement](image2)

Why Does an Abuser Snort Opioids?

- Snorting gets opioids into circulation faster
  - Circumvents first-pass metabolism
  - Provides greater exposures and faster highs
How Do Abusers Snort Hydrocodone Combination Products?

1. Without manipulation (Study A02)

2. After removing APAP, using “Common Tampering Method” (Study A03)
   - Reduces snorting volume
   - Reduces potential for liver toxicity
Drug Liking $E_{\text{max}}$ is a Relevant Primary Endpoint to Evaluate Abuse-Deterrent ER Opioids

- Primary endpoint: difference in maximum Drug Liking ($E_{\text{max}}$)\(^1\)
  - Calculated as the average of every subject’s maximum liking, regardless of time it occurred
- Evaluates manipulated AD ER vs. non-AD IR product at high dose
- Lower $E_{\text{max}}$ expected if AD ER product does not dose dump

Differences between IR and ER in opioid quantity and timeframe of proper opioid delivery
  - ER products release more opioid slowly
  - IR products release less opioid quickly

Time course of Drug Liking, particularly at early time points, may be more relevant than $E_{\text{max}}$

Drug Liking $E_{\text{max}}$ does not account for time
Abuse Quotient
Rate of Rise in Drug Levels Evaluated Using Abuse Quotient

\[ AQ = \frac{C_{\text{max}}}{T_{\text{max}}} \]

Plasma Concentration (ng/mL)

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>2.5</th>
<th>3</th>
<th>3.5</th>
<th>4</th>
<th>4.5</th>
<th>5</th>
<th>5.5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQ</td>
<td></td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AQ = 50 \div 0.5 = 100

AQ = 30 \div 2 = 15
Abuse Quotient Simulation

\[ AQ = \frac{C_{\text{max}}}{T_{\text{max}}} \]

Plasma Concentration (ng/mL)

Time (hours)

\[ AQ = 50 \div 0.5 = 100 \]

\[ AQ = 50 \div 2 = 25 \]
Study A02: Intranasal Human Abuse Potential

Apadaz vs. Norco

Part A: Dose selection (2 tablets selected as largest volume that produced reliable Drug Liking scores)

Part B: Bioavailability and Drug Liking
Snorting Apadaz Does Not Accelerate Exposure to Hydrocodone

Mean ± SE HC Plasma Concentration (ng/mL)

Norco
- 2 Tablets - Snorted
- 2 Tablets - Oral

Apadaz
- 2 Tablets - Snorted
- 2 Tablets - Oral

Study A02: Intranasal HAP Study
Apadaz Has Lower Abuse Quotient Than Norco When Snorted

![Bar chart showing the mean abuse quotient (C_max/T_max) with 95% CI for Apadaz and Norco. Apadaz has a mean abuse quotient of 32 with a 95% CI, while Norco has a mean abuse quotient of 56.](image-url)
No Difference in Drug Liking $E_{\text{max}}$ in Study A02

<table>
<thead>
<tr>
<th>Drug Liking</th>
<th>Intranasal (2 Tablets)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apadaz</td>
<td>Norco</td>
</tr>
<tr>
<td>$E_{\text{max}}$, mean</td>
<td>75.9</td>
<td>79.0</td>
</tr>
<tr>
<td>P-value</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>
Snorting Apadaz Does Not Increase Drug Liking at Early Time Points

**Norco**

- **2 Tablets - Snorted**
- **2 Tablets - Oral**

**Apadaz**

- **2 Tablets - Snorted**
- **2 Tablets - Oral**

*Study A02: Intranasal HAP Study (N=42)*
Apadaz Associated with Lower Ease of Insufflation

- Ease of Insufflation Score
  0 = Very Easy    100 = Very Difficult

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Difference (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apadaz</td>
<td>Norco</td>
</tr>
<tr>
<td>Ease of Insufflation (0-100 scale)</td>
<td>57 (36)</td>
<td>43 (33)</td>
</tr>
</tbody>
</table>
Apadaz Associated with More Adverse Nasal Effects When Snorted

- Nasal Effect Assessment Score
0=None   1=Mild   2=Moderate   3=Severe

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Difference (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apadaz</td>
<td>Norco</td>
</tr>
<tr>
<td>Burning</td>
<td>1.6 (1.0)</td>
<td>0.7 (0.7)</td>
</tr>
<tr>
<td>Pain</td>
<td>1.0 (1.0)</td>
<td>0.5 (0.8)</td>
</tr>
<tr>
<td>Blow</td>
<td>1.5 (0.9)</td>
<td>1.0 (0.9)</td>
</tr>
<tr>
<td>Irritate</td>
<td>1.5 (1.0)</td>
<td>0.7 (0.7)</td>
</tr>
<tr>
<td>Congestion</td>
<td>1.5 (1.0)</td>
<td>1.0 (0.8)</td>
</tr>
<tr>
<td>Discharge</td>
<td>1.4 (1.0)</td>
<td>0.8 (0.9)</td>
</tr>
</tbody>
</table>
**Apadaz Associated with Higher Frequency of Nasal-Related Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Apadaz Intranasal (N=44)</th>
<th>Norco Intranasal (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>66%</td>
<td>21%</td>
</tr>
<tr>
<td>Nasal discomfort</td>
<td>36%</td>
<td>5%</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>16%</td>
<td>5%</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>16%</td>
<td>9%</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td>Dry throat</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Upper-airway cough syndrome</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Study A02: Intranasal HAP Study (N=42)

Category 3
Study A03: Intranasal Bioavailability Study with Abuse Potential Assessments

Benzhydrocodone vs. Hydrocodone Bitartrate

- Subjects administered equivalent amounts of the API found in 2 tablets
Study A03: Intranasal Bioavailability Study with Abuse Potential Assessments

- No drug discrimination phase
- Lack of enrichment made it less likely to find differences in Drug Liking
Common Extraction Method Applied to Reduce Bulk for Snorting Is Inefficient for Apadaz

- Practical Extraction results:
  - >80% of APAP removed for both products
  - 68% yield of hydrocodone from Norco
  - 36% yield of benzhydrocodone from Apadaz

- Study A03 assumptions (assumes best case):
  - 100% of APAP removed
  - 100% yield of hydrocodone and benzhydrocodone
Intranasal Administration of Apadaz Prodrug Leads to Lower HC Release

![Graph showing mean ± SE hydrocodone concentration over time for Hydrocodone Bitartrate and Benzhydrocodone.](image)

**Mean ± SE Hydrocodone Concentration (ng/mL)**

**Time (hours)**

**Study A03: Intranasal Study of APIs (N=24)**
5-Fold Lower Abuse Quotient With Snorted Apadaz Prodrug

Study A03: Intranasal Study of APIs (N=24)

Mean Abuse Quotient ($C_{\text{max}}/T_{\text{max}}$) [95% CI]

<table>
<thead>
<tr>
<th>Category</th>
<th>2</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>17</th>
<th>87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzhydrocodone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone Bitartrate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Differences Observed in Drug Liking $E_{\text{max}}$ with APIs

<table>
<thead>
<tr>
<th>Drug Liking</th>
<th>Intranasal</th>
<th>Benzhydrocodone</th>
<th>Hydrocodone Bitartrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{\text{max}}$, mean</td>
<td></td>
<td>67.4</td>
<td>73.2</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

Study A03: Intranasal Study of APIs (N=51)
Differences in Drug Liking with APIs Over Time Mirrored PK Findings in Study A03

Study A03: Intranasal HAP Study of APIs (N=51)
Snorting Apadaz Prodrug Associated with Lower Ease of Insufflation than Hydrocodone API

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Difference (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benzhydrocodone</td>
<td>Hydrocodone Bitartrate</td>
</tr>
<tr>
<td>Ease of Insufflation</td>
<td>79 (20)</td>
<td>66 (26)</td>
</tr>
</tbody>
</table>

Category 3

Study A03: Intranasal HAP Study of APIs (N=51)
**Summary of Findings from Intranasal Clinical Abuse Potential Studies of Apadaz**

- With Apadaz, abusers do not achieve the rapid highs they seek from snorting
- Snorting with APAP (A02)
  - Unlike Norco, Apadaz produced nearly identical profiles for PK and Drug Liking compared to oral
- Snorting without APAP (A03)
  - Most common tampering method to remove APAP is half as efficient with Apadaz
  - Even at equimolar doses, benzhydrocodone produced lower hydrocodone exposure and Drug Liking
- Apadaz was harder to snort than Norco, with or without APAP
Post-Market Surveillance
Future Studies

Travis Mickle, Ph.D.
Co-Founder and Chief Executive Officer
KemPharm, Inc.
Epidemiologic Approach to Post-Market Surveillance and Evaluation of Abuse Profile

- Epidemiologic program evaluating abuse and routes of abuse
- Continued market surveillance
  - Specific for Apadaz
  - Generally related to entire opioid market
Several Sources of Post-Marketing Data

- Continuation of current market surveillance similar to pre-approval approach
- NAVIPPRO database
  - ASI-MV® Network (adults)
  - CHAT® (adolescents)
  - WIS®: Internet Monitoring
- Additional sources as needed for support
Surveillance Monitoring and Epidemiological Studies to Monitor Use and Abuse of Apadaz

- Surveillance monitoring for abuse
  - Initial abuse expected to be low
  - Monitoring tools to provide early assessment of abuse potential
- Post-market epidemiological studies
  - Primary study assessing rates and routes of abuse
  - Supportive study to monitor and assess discussion among recreational drug abusers
Benefit-Risk Profile

Jeffrey Gudin, M.D.
Director, Pain Management and Palliative Care
Englewood Hospital and Medical Center

Clinical Instructor, Anesthesiology
Icahn School of Medicine, Mt. Sinai
Epidemiologic Data Illustrate the Need for Abuse-Deterrent Hydrocodone IR Combination

**Hydrocodone IR Combination Products Are Commonly Abused**

- **NAVIPRO - ASI-MV Network**: N=96,357 adults aged 18+
  - Surveys between Jan '14 and Jun '15

  - Rate of Past 30-day Abuse per 100 Adult Assessments [95% CI]

**Prevalence of Abuse of Hydrocodone IR Combination Products by Route and Age**

- **ASI-MV Database (Jan 12 – Jun 15)**: N=64,168
- **CHAT Database (Jan 12 – Jun 13)**: N=68,684

  - % of Hydrocodone Users Reporting Route of Abuse in last 30 Days
    - **Oral**: 90%
    - **Intranasal**: 81%
    - **Smoking**: 43%
    - **Injection**: 1%

**Hydrocodone IR Combinations are Often the First Opioid Abused by Young People**

- 2015 IHS Inpatient Survey: N=472

  - % of Opioid Abusers
    - **First Abuse Was HC IR Combination**: 74%
    - **First Abuse of HC IR Combinations <18 Years of Age**: 63%

**Goal: Prevention of Progression from Oral Route to More Dangerous Routes of Administration**

- **Progression of Abuse**
  - Abusers progress to more dangerous routes as:
    - Opioid tolerance develops
    - Cost to maintain abuse patterns increases

**Images:**
- Oral
- Snorting
- Drinking
- Injection
## Apadaz: First Abuse-Deterrent Hydrocodone IR Combination Product

| Physical/Chemical Manipulations | • Prodrug: No impact of physical tampering on release  
| • Prodrug is very difficult to chemically manipulate |
| Smoking | • Apadaz cannot be smoked/vaporized to release HC |
| IV injection | • Extraction for injection is inefficient and expensive  
| • Slow conversion of inactive prodrug to HC in blood |
| Intranasal | **When Crushed and Snorted:**  
| | • Abusers don’t get more rapid exposure or faster highs  
| | • No advantage over oral administration  
| | • More nasal AEs, harder to snort  
| **When Crushed, APAP Extracted, and Snorted:** | • Extraction yields ½ as much API compared to Norco  
| | • Lower exposures and Drug Liking vs. Norco API  
| | • Harder to snort |
Apadaz Bioequivalent to Hydrocodone IR Combination Products; No Additional Risk

- Similar hydrocodone, hydromorphone and acetaminophen exposures to currently marketed products when taken as intended
- No clinically significant effect of food
- Safety of Apadaz in patients would be similar to existing products
  - No systemic exposure to prodrug
  - Ligand (benzoic acid) is naturally-occurring in berries
REDUCE OPIOID ABUSE

- Patient and Family Education
- Physician Education
- Proper Prescribing
- Safe Storage and Disposal
- Prescription Monitoring
- Abuse-Deterrent Formulations
Apadaz™
(immediate-release benzhydrocodone with acetaminophen) for the Treatment of Acute Pain

May 5, 2016
KemPharm, Inc.

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Backup Slides Shown
## Drug Liking Study A02

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intranasal</th>
<th>Oral</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apadaz</td>
<td>Norco</td>
<td>Apadaz</td>
<td>Norco</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>AUE(_{0-0.5})</td>
<td>30.2</td>
<td>6.3</td>
<td>30.8</td>
<td>3.9</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.1244</td>
<td>0.4689</td>
</tr>
<tr>
<td>AUE(_{0-1})</td>
<td>63.5</td>
<td>12.6</td>
<td>63.7</td>
<td>11.7</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.4689</td>
<td>11.6</td>
</tr>
<tr>
<td>AUE(_{0-2})</td>
<td>129.8</td>
<td>26.6</td>
<td>131.7</td>
<td>26.3</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0079</td>
<td>0.9896</td>
<td></td>
<td>25.1</td>
</tr>
<tr>
<td>AUE(_{0-4})</td>
<td>249.6</td>
<td>53.3</td>
<td>249.5</td>
<td>47.5</td>
</tr>
<tr>
<td>P-value</td>
<td>0.1219</td>
<td>0.8270</td>
<td></td>
<td>41.2</td>
</tr>
<tr>
<td>AUE(_{0-8})</td>
<td>467.0</td>
<td>83.2</td>
<td>456.2</td>
<td>70.2</td>
</tr>
<tr>
<td>P-value</td>
<td>0.4112</td>
<td>0.7991</td>
<td></td>
<td>71.9</td>
</tr>
<tr>
<td>AUE(_{0-24})</td>
<td>1294</td>
<td>187.0</td>
<td>1264</td>
<td>83.1</td>
</tr>
<tr>
<td>P-value</td>
<td>0.5847</td>
<td>0.9610</td>
<td></td>
<td>127.2</td>
</tr>
</tbody>
</table>
Earlier Exposure to Abuse of Hydrocodone IR Combination Products Associated with Non-Oral Routes of Abuse

Age at first abuse of hydrocodone IR combination products:
- ≤ 18 years
- >18 years

<table>
<thead>
<tr>
<th>Route of Abuse</th>
<th>≤ 18 years</th>
<th>&gt;18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallow whole</td>
<td>86%</td>
<td>83%</td>
</tr>
<tr>
<td>Snorting</td>
<td>75%</td>
<td>47%</td>
</tr>
<tr>
<td>Smoking</td>
<td>31%</td>
<td>23%</td>
</tr>
<tr>
<td>Injection</td>
<td>31%</td>
<td>19%</td>
</tr>
</tbody>
</table>

% of Abusers
Figure 25: Mean Drug Liking in First Two Hours of Study A02
Lower Early HC Exposure with Apadaz with Intranasal Administration

\[C_{\text{max}}\]
\[\text{AUC}_{0-0.5}\]
\[\text{AUC}_{0-1}\]
\[\text{AUC}_{0-2}\]
\[\text{AUC}_{0-4}\]
\[\text{AUC}_{0-8}\]
\[\text{AUC}_{0-24}\]
\[\text{AUC}_{\text{last}}\]
\[\text{AUC}_{\text{inf}}\]

Percent Mean Ratios (Apadaz vs Norco)

[90% CI]

Category 2

Study A02: Intranasal HAP Study (N=42)
Significantly Lower Drug Liking for Intranasal Administration of Apadaz vs. Norco at Early Time Points

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>LS Mean Difference [95% CI]</th>
<th>Favors Apadaz</th>
<th>Favors Norco</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>-10</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15</td>
<td>-10</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30</td>
<td>-10</td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>60</td>
<td>-10</td>
<td></td>
<td></td>
<td>0.201</td>
</tr>
<tr>
<td>90</td>
<td>-10</td>
<td></td>
<td></td>
<td>0.355</td>
</tr>
<tr>
<td>120</td>
<td>-10</td>
<td></td>
<td></td>
<td>0.646</td>
</tr>
</tbody>
</table>

Study A02: Intranasal HAP Study (N=42)
# Enzyme Hydrolysis Study of Benzhydrocodone

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>%-Release of Hydrocodone After 2 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Chymotrypsin</td>
<td>0%</td>
</tr>
<tr>
<td>Amylase</td>
<td>0%</td>
</tr>
<tr>
<td>Bromelain</td>
<td>0%</td>
</tr>
<tr>
<td>Esterases</td>
<td>100%</td>
</tr>
<tr>
<td>Papain</td>
<td>0%</td>
</tr>
<tr>
<td>Pepsin</td>
<td>0%</td>
</tr>
<tr>
<td>Protease</td>
<td>0%</td>
</tr>
<tr>
<td>Trypsin</td>
<td>0%</td>
</tr>
<tr>
<td>Commercial Digestive Enzyme Cocktail</td>
<td>0%</td>
</tr>
</tbody>
</table>

Data Not Reviewed by FDA
## Coefficient of Variation for PK Parameters for All PK Studies with Therapeutic Doses

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>$C_{\text{max}}$</th>
<th>$AUC_{\text{last}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td>KP201 (1x5 mg)</td>
<td>29.97</td>
<td>24.6</td>
</tr>
<tr>
<td>101</td>
<td>KP201 (2x5 mg)</td>
<td>26.04</td>
<td>25.6</td>
</tr>
<tr>
<td>101</td>
<td>Norco (10 mg)</td>
<td>31.55</td>
<td>26.43</td>
</tr>
<tr>
<td>102</td>
<td>Apadaz</td>
<td>24.63</td>
<td>25.67</td>
</tr>
<tr>
<td>102</td>
<td>Norco</td>
<td>25.24</td>
<td>26.36</td>
</tr>
<tr>
<td>103</td>
<td>Apadaz (Day 1)</td>
<td>24.77</td>
<td>24.8</td>
</tr>
<tr>
<td>103</td>
<td>Apadaz (Day 4)</td>
<td>23.49</td>
<td>27.42</td>
</tr>
<tr>
<td>104</td>
<td>Apadaz (fasted)</td>
<td>25.24</td>
<td>28.98</td>
</tr>
<tr>
<td>104</td>
<td>Apadaz (fed)</td>
<td>22.49</td>
<td>21.38</td>
</tr>
<tr>
<td>104</td>
<td>Norco (fed)</td>
<td>36.49</td>
<td>22.38</td>
</tr>
<tr>
<td>105</td>
<td>Apadaz</td>
<td>21.02</td>
<td>25.79</td>
</tr>
<tr>
<td>105</td>
<td>Vicoprofen</td>
<td>18.11</td>
<td>20.02</td>
</tr>
<tr>
<td>106</td>
<td>Apadaz</td>
<td>28.33</td>
<td>24.61</td>
</tr>
</tbody>
</table>
Extraction of Hydrocodone from Apadaz Was Ineffective with Ingestible Solvents

Max % Benzhydrocodone Extracted

- A: 53%
- B: 81%
- C: 93%
- D: 56%
- E: 87%
Hydrocodone Exposures at Supratherapeutic Doses Similar Between Products

Category 2

Study A01: Oral HAP Study (N=62)
Benzoic Acid Is Safe for Injection

- Ammonul® (sodium phenylacetate and sodium benzoate [BzONa]) for acute hyperammonemia in adult and pediatric patients (250 mg/kg of BzONa in loading phase)
- Used as preservative in some drug injections (e.g., Diazepam Injection, USP)
Benzoic Acid in Benzhydrocodone

- 27.7% of benzhydrocodone mass is benzoic acid
- 1.85 mg of benzoic acid per tablet
- Naturally occurs in berries and some fruits
- 1 cup of cranberries contains about 50 mg benzoic acid
- Used as preservative in fruit juice, soda, salad dressing, etc.
- 75–100% of oral doses up to 160 mg/kg excreted as hippuric acid within 6 hours
- Estimated intake of benzoic acid in U.S.
  - Average consumer: 161 mg/day/day
  - High consumers: 511 mg

Intranasal Administration of Apadaz Prodrug Leads to Lower HC Release

Mean ± SE Hydrocodone Concentration (ng/mL) vs. Time (hours)

- Orange line with markers: Hydrocodone, Intranasal
- Blue line with markers: Apadaz, Oral (Study 103)
- Dashed blue line: Apadaz Prodrug, Intranasal

Study A03: Intranasal Study of APIs (N=24)
Clarification of Sponsor Solvent X and FDA Solvent G

**Sponsor Solvent X**
- Advanced buffer
- 4 hours under stress conditions to extract 60% hydrocodone
- Stress +/- 4 hours reduced percent extracted
- Turned black in color
- FDA banned as food additive

**FDA Solvent G**
- Advanced laboratory equipment required to maintain stress temperature
- 3 hours under stress condition #2 required for effective hydrolysis