CLINICAL OVERVIEW
OF RBP-6000

NDA 209819
Name of drug: BUPRENNORPHINE-ATRIGEL ONE-MONTH DEPOT

FDA Presentation
Joint Meeting of the Psychopharmacologic Drugs Advisory Committee
and the Drug Safety and Risk Management Advisory Committee
October 31, 2017

Emily Deng, MD, MPH
Clinical Reviewer
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Outline

• Drug utilization data
• Pharmacokinetics of Phase 3 dosing regimens
• Efficacy
  – Opioid blockade study (13-0002)
  – Phase 3 pivotal, Double-Blind (DB), Placebo-Controlled (PC), 24 weeks study (13-0001)
• Safety
  – Phase 3 pivotal, DB, PC, 24 weeks study (13-0001)
  – Phase 3 Open-Label(OL), long-term, 48 weeks, safety study (13-0003)
• REMS
RBP-6000 overview

- Buprenorphine-ATRIGEL monthly depot injection in a prefilled syringe

- To be marketed dosing regimens
  - 300 mg monthly for the first 2 months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient

- Proposed Indication: treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. The product should be used as part of a complete treatment plan to include counseling and psychosocial support
Outpatient Patient Data

Nationally estimated number of patients who received buprenorphine* prescriptions dispensed from U.S. outpatient retail pharmacies, 2012-2016

Source: QuintilesIMS, Total Patient Tracker (TPT) Data Extracted August 2017.

*includes buprenorphine products labeled for medication assisted therapy (MAT) only

www.fda.gov
Outpatient Prescription Data

Nationally estimated number of buprenorphine* prescriptions dispensed from U.S. outpatient retail pharmacies by provider specialty, 2016

- FP/GP/IM: 39.4%
- Psychiatry: 20.6%
- Osteopathic Medicine: 14.4%
- All Other Specialties: 18.4%
- Emergency Medicine: 3.7%
- Anesthesiology: 3.6%

N = 12.2 M prescriptions


*includes buprenorphine products labeled for medication assisted therapy (MAT) only
PK parameters comparison (Study 12-0005)

<table>
<thead>
<tr>
<th>PK parameters</th>
<th>Subutex 24 mg daily (Run-in)</th>
<th>RBP 6000 300 mg (1st injection)</th>
<th>RBP 6000 300 mg (4th injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean $C_{avg\ ss}$ (ng/ml)</td>
<td>2.907</td>
<td>2.19</td>
<td>4.81*</td>
</tr>
<tr>
<td>Mean $C_{max\ ss}$ (ng/ml)</td>
<td>8.267</td>
<td>5.37</td>
<td>8.22</td>
</tr>
<tr>
<td>Mean $C_{min\ ss}$ (ng/ml)</td>
<td>1.543</td>
<td>1.25</td>
<td>3.35</td>
</tr>
</tbody>
</table>

* Data from cohort of Subutex 12 mg (Run-in) / RBP-6000 300 mg

Source: FDA backgrounder Tables 7, 8 and 9
PK parameters of Phase 3 dosing regimens

Table 14: Estimated Mean Buprenorphine PK Parameters after 6 Injections for 300/100-mg and 300/300-mg Dosing Regimens Calculated from Model-Based Individual PK Predictions in the Ph3DB Study

<table>
<thead>
<tr>
<th>RBP-6000 Regimen</th>
<th>Mean $C_{\text{avg}}$ (ng/mL)</th>
<th>Mean $C_{\text{min}}$ (ng/mL)</th>
<th>Mean $C_{\text{max}}$ (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300/100 mg</td>
<td>3.1</td>
<td>2.7</td>
<td>4.1</td>
</tr>
<tr>
<td>300/300 mg</td>
<td>6.3</td>
<td>5.1</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Source: Applicant backgrounder: Table 14
Blockade Study  
(RB-US-13-0002)  
Analysis and Issues

Alan Trachtenberg, MD, MPH  
Controlled Substance Staff  
Office of the Center Director  
Center for Drug Evaluation and Research, FDA

October 31, 2017  
Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
RBP-6000: Study #RB-US-13-0002

- Non-treatment Seeking Adults w/Mod-Severe OUD; Male & Female
- SQ Depot Buprenorphine, 300mg/month x 2 to Block Effect of
- 1 Daily IM Hydromorphone (HM) Challenge of
- 18mg, 6mg, or Placebo (0mg), In Random Order, over the
- Last 3 Days of Each Week x 12 Weeks (+2 prior 3 Day Sets)

Day -18, Admission

Qualification Phase (Days -18 to -15)
- HM, 0 mg, or 6 mg or 18 mg, One each, random, Once/Day x 3 days
- Baseline Hydromorphone (HM) Challenge, IM x 3 (1st Prior Challenge, W/O Bup)

Stabilization Phase, w/SL Buprenorphine (Days -14 to -1), then Pre-treatment Challenge
- Induction (Day -14/-13 to -9)
- Stabilization (Day -9 to -1)

First Injection RBP-6000 Day 1

Randomization

Week -1 HM Challenge (Day -3 to -1)

Pre-Treatment HM Challenge On SL Bup (2nd Prior Challenge)
**RBP-6000: Study #RB-US-13-0002**

**Treatment Phase**

**Day 1- 1st injection**
RBP-6000- 300 mg

**Day 29- 2nd Injection**
RBP-6000- 300 mg

<table>
<thead>
<tr>
<th>Sequence of 12 weeks, each w/3-day HM Challenge, one IM q AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

**Challenge Days** - Subjects are randomized to receive, on the days numbered below, a daily IM injection (HM: 0 mg, or 6 mg, or 18 mg), on each morning of the *last 3 days of each 1 week period*, randomly sequenced.

| 5-7 | 12-14 | 19-21 | 26-28 | 33-35 | 40-42 | 47-49 | 54-56 | 61-63 | 68-70 | 75-77 | 82-84 |

On these days, PD measures are taken: Drug Liking (VAS, **Unipolar** scale) and 5 other secondary scales, every 15 minutes for a period of up to 5 hours. Also daily buprenorphine levels, to correlate w/PD.
The need for FDA post-hoc re-analysis:

• The Sponsor’s primary statistical analysis of “Drug Liking” Visual Analog Scale (VAS) differences was atypical:
  – Instead of the recommended comparison of Peak Drug Liking $E_{\text{max}}$ values, they compared $E_{\text{mean}}$, the average drug liking over the full 5 hours post-injection, diluting peak differences, and possibly biasing toward a finding of blockade.
  – Drug Liking was measured on a Unipolar scale, and differences tested against a non-inferiority (NI) margin of 11. But, this margin had been standardized and established with data from Bipolar scales (Chen & Bonson, 2013).
  – Use of this Bipolar NI margin, may be too stringent a limit to compare values from a Unipolar scale. Applying this margin would have deemed the study as “failed.”

• Details will now be presented on the re-analyses that resulted in a valid & significant “lack of difference” finding, to support opioid blockade by 300 mg of RBP-6000.
Blockade Study: Statistical Analysis and Issues

Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Qianyu Dang, PhD
Lead Statistician
Division of Biostatistics VI, Office of Biostatistics
October 31, 2017
Blockade: Noninferiority (NI)

- Blockade defined as noninferiority in Emax Drug Liking for hydromorphone compared to placebo
- Isn’t what it sounds like
- Isn’t what it is in efficacy trials
- Just means we think the liking of hydromorphone is not higher than placebo if the test drug (RBP-6000) is useful
Noninferiority Margin

- Defined in terms of Emax Drug Liking (The peak Drug Liking scores)
- Defined on a certain scale
- Peak effect on that scale should be less than the test margin with confidence
Drug Liking: Emax vs. Average

- Emax is more important than average over several hours
- Peak 11 ≠ average 11
Visual Analogue Scales (VAS) can be Bipolar or Unipolar

- **Unipolar scales:** 0 = “no response” and 100 = “maximum response”

<table>
<thead>
<tr>
<th>Do you like the drug?</th>
<th>None</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

- **Bipolar scales:** Neutral text anchor in the middle (50) between opposite effects

  At this moment, my liking for this drug is

  ![Bipolar Scale Diagram]

  - Unipolar 11 ≠ bipolar 11
  - Unipolar 20 ≈ bipolar 11
Mean Difference of Emax (in Unipolar Scales) between Hydromorphone and Placebo over Weeks (NI=20)
Conclusion

- The test product (RBP-6000) showed blockade effect for hydromorphone (6 mg and 18 mg).
Blockade Study: Pharmacokinetic-Pharmacodynamic Analyses of Drug Liking

Michael Bewernitz, PhD
Pharmacometrics Reviewer
Division of Pharmacometrics
Office of Clinical Pharmacology
Office of Translational Sciences, CDER, FDA
Motivation for PK/PD Analyses

• Provide additional context for issues raised during review of the blockade study (13-0002)
  – Explore potential effect of changes in buprenorphine concentration on drug liking

• Provide supportive evidence of effectiveness of opioid blockade

• Inform dosing and support results observed in efficacy trial
PK and PD Data from Blockade Study

- N=38 subjects
- PK Data: buprenorphine concentrations
  - Collected immediately before hydromorphone challenge
- PD Data: “Drug Liking” VAS Score (0 to 100)
  - 0 = no liking, 100 = strongest liking
  - Used peak subjective effect ($E_{\text{max}}$) during hydromorphone challenge
  - Scores were placebo-corrected by subtracting $E_{\text{max}}$ during corresponding placebo challenge
Buprenorphine Concentration By Time

![Buprenorphine Concentration By Time Graph](image-url)
Placebo-Corrected Drug-Liking By Time and Hydromorphone Dose Level
Placebo-Corrected Drug-Liking vs. Associated Buprenorphine Concentration (Response to 18 mg Hydromorphone Challenge)
Representative Individual with Abrupt Changes in Drug-Liking Between Weeks of Study

Approximately ½ of subjects express such abrupt changes in drug-liking score from week-to-week
Observations and Conclusions

• PK/PD data provide supportive evidence of opioid blockade
  – Trend of drug-liking reduction with increasing buprenorphine exposure
  – Higher buprenorphine concentration required to reduce drug-liking after 18 mg than for 6 mg hydromorphone

• Drug-liking score can undergo abrupt changes that do not correlate with the PK profile
  – It is likely that other, unknown factors influence the drug-liking score
CLINICAL AND STATISTICAL REVIEW OF RBP-6000

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Emily Deng, MD, MPH
Clinical Reviewer
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Feng Li, PhD
Statistic Reviewer
Division of Biometrics II
Pivotal Ph3DB study: 13-0001

- Adult subjects seeking MAT

- DSM-5 OUD (mod-severe)

- **Open-Label Run-in Phase**
  - SUBOXONE® film induction (3 d)
  - 4- to 11-day OL run-in dose-adjustment period to achieve a dosage range between 8 to 24 mg
Double-blind Treatment Phase

• Regimen #1: RBP-6000 300 mg SC every 28 days (± 2) × 6 doses
• Regimen #2: RBP-6000 300 mg SC every 28 days (± 2) × 2 doses followed by RBP-6000 100 mg SC every 28 days (± 2) × 4 doses
• Placebo Regimen #1: Volume-matched to Regimen #1
• Placebo Regimen #2: Volume-matched to Regimen #2
• Subjects also received manual-guided behavior counselling/individual drug counselling (IDC) at least once per week
• Major efficacy outcome measurements: weekly UDS and TLFB
Phase 3 DB study overview

• A total of 33 study sites randomized subjects
  • One site was excluded from efficacy analysis due to compliance issues

• A total of 1187 subjects were screened and 665 subjects entered the OL run-in phase

• A total of 504 subjects (~75%) were randomized into study

• Patients were blindly switched to active or placebo injections
  – Protocol was amended to include a open-label Suboxone taper for both arms to prevent ↑ withdrawal/dropout in placebo arm (~1/3 patients treated after this amendment)
Demographics and Baseline Characteristics

- Most subjects in the study were white males with an average age of approximately 40 years.
- Age, Sex and Race of the populations were evenly distributed across the RBP-6000 treatment arms and placebo arms.
- More than 40% of subjects reported a history of injection drug use.
- More than 50% of subjects reported a history of multiple substance uses.
- More than 10% of subjects reported PMH of hepatitis C.

Source: FDA backgrounder: Table 11 and Table 21
<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>RBP-6000 300mg/100mg+IDC (N=203)</th>
<th>RBP-6000 300mg/300mg+IDC (N=201)</th>
<th>Placebo+IDC (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Randomised</td>
<td>504</td>
<td>203 (100.0)</td>
<td>201 (100.0)</td>
<td>100 (100.0)</td>
</tr>
<tr>
<td>Randomised and treated</td>
<td>504</td>
<td>203 (100.0)</td>
<td>201 (100.0)</td>
<td>100 (100.0)</td>
</tr>
<tr>
<td>Completed</td>
<td>288</td>
<td>125 (61.6)</td>
<td>129 (64.2)</td>
<td>34 (34.0)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>216</td>
<td>78 (38.4)</td>
<td>72 (35.8)</td>
<td>66 (66.0)</td>
</tr>
<tr>
<td>Reasons for discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>61</td>
<td>26 (12.8)</td>
<td>23 (11.4)</td>
<td>12 (12.0)</td>
</tr>
<tr>
<td>Subject withdrew consent to participate</td>
<td>59</td>
<td>20 (9.9)</td>
<td>21 (10.4)</td>
<td>18 (18.0)</td>
</tr>
<tr>
<td>Other(^a)</td>
<td>30</td>
<td>17 (8.4)</td>
<td>6 (3.0)</td>
<td>7 (7.0)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>26</td>
<td>3 (1.5)</td>
<td>5 (2.5)</td>
<td>18 (18.0)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>18</td>
<td>6 (3.0)</td>
<td>10 (5.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>7</td>
<td>2 (1.0)</td>
<td>5 (2.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Withdrawal symptoms</td>
<td>5</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Noncompliance with study drug</td>
<td>4</td>
<td>2 (1.0)</td>
<td>0 (0.0)</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Subject was withdrawn by the investigator</td>
<td>4</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>2</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Death(^b)</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
EFFICACY RESULTS
# Primary Efficacy Results

P-values < 0.0001 for each active injection compared with placebo

<table>
<thead>
<tr>
<th>Percentage of Negative Drug Use</th>
<th>RBP-6000 100 mg (N=194)</th>
<th>RBP-6000 300 mg (N=196)</th>
<th>Placebo (N=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0%</td>
<td>194 (100)</td>
<td>196 (100)</td>
<td>99 (100)</td>
</tr>
<tr>
<td>≥10%</td>
<td>139 (72)</td>
<td>126 (64)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>≥20%</td>
<td>115 (59)</td>
<td>111 (57)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>≥30%</td>
<td>101 (52)</td>
<td>101 (52)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>≥40%</td>
<td>90 (46)</td>
<td>90 (46)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>≥50%</td>
<td>86 (44)</td>
<td>82 (42)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>≥60%</td>
<td>78 (40)</td>
<td>70 (36)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>≥70%</td>
<td>66 (34)</td>
<td>67 (34)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>≥80%</td>
<td>55 (28)</td>
<td>57 (29)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>≥90%</td>
<td>41 (21)</td>
<td>48 (24)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>100%</td>
<td>25 (13)</td>
<td>23 (12)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>
Drug Use Results for Individual Subjects
CDF of Percentage of Negative Drug use by Tapering Status

With tapering

Without tapering
CDF of Percentage of Negative Drug Use by Injection Drug Use

Injection Drug User

Not Injection Drug User
Efficacy Summary

• Superiority over placebo demonstrated
  – RBP-6000 300/100 mg and RBP-6000 300 mg/300 mg

• Similar efficacy observed between two dose regimens
Phase 3, OL, long-term safety study (13-0003)

• 2 weeks run-in period with Suboxone film to achieve a dosage range between 8-24 mg

• Actual treatment period (N=669)
  – De novo patients (N=412):
    • an initial dose of 300 mg
    • followed by up to 11 additional injections (Flex dose)
    • a total of 12 injections
  – Roll-over patients (N=257):
    • an initial dose of 300 mg
    • followed by up to 5 additional injections (Flex dose)
    • a total of 6 injections
# Exposure summary

<table>
<thead>
<tr>
<th>Duration of exposure (Cumulative)</th>
<th>RBP-6000 300/Flex mg</th>
<th>RBP-6000 300/300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 24 weeks</td>
<td>542 (63.9%)</td>
<td>460 (54.2%)</td>
</tr>
<tr>
<td>≥ 48 weeks</td>
<td>320 (37.7%)</td>
<td>187 (22.1%)</td>
</tr>
</tbody>
</table>

*Source: Updated exposure summary provided by Applicant*
Identified risks of RBP-6000

• Systemic effects of buprenorphine
  – CNS effects: headache, somnolence, sedation
  – GI effects: constipation, nausea, vomiting
  – Hepatic effects: elevated liver enzymes

• Injection site reactions: injection site pain, injection site pruritus, injection site erythema

• Common TEAEs leading to drug discontinuations and dose reductions in the RBP-6000 group included:
  – Abnormal liver function tests, sedation, constipation, injection site reactions, somnolence
# Dose dependent effects (13-0001)

<table>
<thead>
<tr>
<th>Effects</th>
<th>RBP 300/300 mg</th>
<th>RBP 300/100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs leading to drug discontinuation</td>
<td>5.0%</td>
<td>3.5%</td>
</tr>
<tr>
<td>TEAEs related to injection site reactions</td>
<td>18.9%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Abnormal LFT values (post baseline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT ≥ 3X ULN</td>
<td>12.44%</td>
<td>5.42%</td>
</tr>
<tr>
<td>AST ≥ 3X ULN</td>
<td>11.44%</td>
<td>7.88%</td>
</tr>
</tbody>
</table>

Source: Applicant backgrounder: Table 22, 25, 27 and 29  
FDA backgrounder: Table 34
Safety Overview

- The safety database for RBP-6000 was adequate
- The safety population is an adequate representation of the target treatment population of patients with OUD
- One death occurred in RBP-6000 300/300 mg group due to homicide gunshot
- A total of 50 non-fatal SAEs occurred among 42 subjects in Phase 3 studies and the majority of SAEs were not drug related
- No Hy’s law case was identified in the clinical development program
- No SAEs related to injection site reactions
- The overall safety experience is consistent with the safety profile of transmucosal buprenorphine products indicated for the treatment of OUD
- The local injection tolerability is acceptable
Clinical Conclusion

• The efficacy data provide evidence that both dosing regimens of RBP-6000 are effective in treating patients with opioid use disorder.

• The safety database did not identify major new safety issues compared to the established safety profile of transmucosal buprenorphine, despite higher plasma exposures.

• RBP-6000 is intended to be administered by a health care provider in a clinical setting.

• The Applicant has proposed REMS.
Proposed Risk Evaluation and Mitigation Strategies (REMS) for RBP-6000

October 31, 2017

Somya Dunn, MD
Commander, United States Public Health Service
Risk Management Analyst
Center for Drug Evaluation and Research
Division of Risk Management
Overview

• Background on Risk Evaluation and Mitigation Strategies (REMS)
• Prescribing requirements for buprenorphine products indicated for Medication-Assisted Treatment (MAT)
• Potential serious risks of RBP-6000
• Risk management options:
  – Applicant’s proposal
  – FDA’s proposal
Risk Evaluation and Mitigation Strategy (REMS)*

• REMS is a required risk management plan that uses risk mitigation strategies beyond FDA-approved labeling.

• FDA can require a REMS
  – if determined necessary to ensure the benefits outweigh the risks
  – at the time the medication is initially approved or after approval if a new safety concern arises

• REMS provide a way for patients to have access to medications with particular serious risks that would otherwise be unavailable or would be removed from the market.

• Applies to NDAs, BLAs, and ANDAs

• REMS are enforceable.

Components of a REMS

A REMS can include

- Medication Guide or Patient Package Insert
- Communication plan for healthcare providers (HCPs)*
- Elements to assure safe use (ETASU)
- Must include a timetable for submission of assessments*

* Does not apply to ANDAs (generics)
Elements to Assure Safe Use (ETASU)

- Certification and/or specialized training of HCPs who prescribe the drugs
- Certification of pharmacies or other dispensers of the drug
- Dispensing/administration of drug in limited settings e.g., hospitals
- Drug is dispensed/administered only with evidence of safe-use conditions
- Each patient using the drug is subject to certain monitoring
- Enrollment of treated patients in registries
ETASU
Can be Restrictive or Non-restrictive

Restrictive

- REMS elements that can be linked to distribution/dispensing the drug
  - certification/training of prescribers
  - certification of pharmacies and/or healthcare settings
  - documentation of safe use conditions (e.g., pregnancy test)

Non-Restrictive

- REMS elements that need not be linked to distribution/dispensing the drug
  - training is made available to prescribers
  - documentation of safe use conditions (e.g., recommended tool/checklist for counseling)
Buprenorphine Products Indicated for MAT with Approved REMS

- **Suboxone/Subutex REMS**
  - Suboxone (buprenorphine and naloxone) sublingual tablets and sublingual film
  - Subutex (buprenorphine) sublingual tablets and generics

- **Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS**
  - Generic versions of Suboxone and Subutex sublingual tablets
  - Bunavail (buprenorphine and naloxone) buccal film
  - Zubsolv (buprenorphine and naloxone) sublingual tablets

- **Probuphine REMS** (buprenorphine implant)
Suboxone/Subutex and BTOD REMS

Goals
• Mitigate the risks of accidental overdose, misuse, and abuse.
• Inform prescribers, pharmacists, and patients of the serious risks associated with buprenorphine-containing products.

Elements
• Medication Guide
• Appropriate Use Checklist, assessment of compliance (non-restrictive ETASU)
Goal is to mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of Probuphine and the risks of accidental overdose, misuse and abuse.
Probuphine REMS

Objectives:

a) Ensuring that healthcare providers are educated on the following:
   - proper insertion and removal of Probuphine
   - risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of Probuphine
   - risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin

b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with insertion and removal, as well as the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.
Probuphine REMS

REMS Elements

• Medication Guide

• ETASU – HCP certification and patient monitoring (restrictive ETASU)
  – Healthcare providers who prescribe Probuphine must be specially certified.
  – Healthcare providers who insert Probuphine must be specially certified.
  – Each patient is subject to certain monitoring for removal of Probuphine.
Overview

• Background on Risk Evaluation and Mitigation Strategies (REMS)

• **Prescribing requirements for buprenorphine products indicated for Medication-Assisted Treatment (MAT)**

• Potential serious risks of RBP-6000

• Risk management options:
  – Applicant’s proposal
  – FDA’s proposal

- Expands medication-assisted opioid dependency treatment beyond opioid treatment programs (OTP) (i.e. methadone clinics)
- DATA 2000 waiver enables prescribers to dispense or prescribe buprenorphine for MAT in settings other than OTPs

*http://www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management/qualify-for-physician-waiver*
Who can Prescribe Buprenorphine for MAT?

- Prescribers that are DATA 2000 waived
  - In office based settings
- Non DATA 2000 waived prescribers
  - In opioid treatment programs (OTP)
  - Inpatients admitted for other medical conditions
  - Emergency addiction treatment for up to 3 days

*https://www.samhsa.gov/medication-assisted-treatment/legislation-regulations-guidelines/special-circumstances-providing-buprenorphine*
Overview

• Background on Risk Evaluation and Mitigation Strategies (REMS)
• Prescribing requirements for buprenorphine products indicated for Medication-Assisted Treatment (MAT)

**Potential serious risks of RBP-6000**

• Risk management options:
  – Applicant’s proposal
  – FDA’s proposal
Safety Concerns for RBP-6000

The Agency has concerns about abuse and misuse if this product was dispensed directly to patients and self-administered IV

- IV injection may be associated with potential:
  - Overdose of buprenorphine*
  - Venous occlusion or embolus
- Proposed indicated population is at risk for abusing/misusing the drug intravenously
  - Formulation of drug is readily injectable
  - More than 40% in clinical program had history of IV drug abuse

*Doses range from 100 to 300 mg, formulations do not contain naloxone
Overview

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Applicant’s Proposed Labeling

Under the Dosing and Administration Section

– For subcutaneous injection only
– Should only be prepared and administered by a healthcare provider
– Must not be administered intravenously or intramuscularly
Applicant’s Proposed REMS

Goals
- Mitigate risks of accidental overdose, misuse and abuse
- Inform HCPs and patients about serious risks and long-acting nature of the product
Applicant’s Proposed REMS

Non-restrictive Elements

Safe Use and Monitoring using:
- Appropriate Use Checklist
- Patient Alert Card
- HCP provider brochure
Applicant’s Proposed REMS

Restrictive Elements

• Administration limited to certain healthcare settings using current applicable laws:
  • Office based setting - *DATA 2000 Waiver Required*
  • Hospitals, integrated health systems, long-term care facilities, DOD, prisons - *DEA Registration required*
  • Federally approved Opioid Treatment Programs (OTPs) - *DATA 2000 waiver is not required*
• Contract with specialty pharmacies and specialty distributors to ensure that RBP-6000 is only dispensed to the above healthcare settings
  • Applicant indicated that the specialty distributors would take responsibility to require pharmacies ordering RBP-6000 to certify that they will not dispense the product directly to patients
• RBP-6000 will not be distributed to patients by retail pharmacies
Applicant’s Proposed Distribution

**Applicant—all orders received in centralized customer service dept**

- **Specialty Pharmacies**
  - DATA 2000-waivered prescribers on a named-patient basis
    - HCP office based setting

- **Specialty Distributors (buy and bill)**
  - OTPs or Facilities/Clinics (DEA registrants)
    - HCP office based setting
    - IHS, DOD, VA, other large healthcare facilities
Limitations of Applicant’s REMS Proposal

• The REMS proposal does not ensure that all sites that order RBP-6000 will put policies and procedures in place to make certain that RBP-6000 is not dispensed directly to the patient
  – Some settings have both outpatient and inpatient pharmacy services.
  – The proposal to have specialty distributors certify sites is not specific about the site type or who at the site makes the agreement.
Overview

• Background on Risk Evaluation and Mitigation Strategies (REMS)
• Prescribing requirements for buprenorphine products indicated for Medication-Assisted Treatment (MAT)
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• Risk management options:
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  – FDA’s proposal
FDA’s Proposed REMS

Goal: To mitigate potential adverse consequences due to intravenous self-administration by:

- Ensuring that RBP-6000 is only dispensed and administered in certain healthcare settings by an HCP
FDA’s Proposed REMS

• Agree with Applicant’s proposal to limit RBP-6000 administration by a HCP only in certain healthcare settings

• FDA also proposes a one-time certification of healthcare settings that order and dispense:
  • Certification to include an agreement to put systems into place that prevent RBP-6000 from being dispensed directly to the patient
Potential Burden of FDA’s Proposal

• Distribution of RBP-6000 requires one-time certification of healthcare settings
  • Requires the setting to develop internal policies and procedures to ensure that RBP-6000 is not dispensed directly to the patient

• Distributors would be required to verify healthcare setting certification of facilities before distribution
BACK-UP SLIDES SHOWN
SENSITIVITY ANALYSES FOR HANDLING DROPOUTS
Sensitivity Analysis 1
Observed in study data with no imputation

P-values < 0.0001 for each active injection compared with placebo
Sensitivity Analysis 2
Placebo based on observed in study data with no imputation

P-values < 0.0001 for each active injection compared with placebo
Sensitivity Analysis 3
Missing data due to lack of efficacy imputed positive

P-values < 0.0001 for each active injection compared with placebo
Sensitivity Analysis 4
Missing data imputed negative except for lack of efficacy

P-values < 0.0001 for each active injection compared with placebo
Tipping Point Analysis for Comparing Responder Rate

Responder: ≥80% Negative Drug Use