FDA Briefing Document

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

May 22, 2018

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 209-588, buprenorphine sublingual spray, submitted by INSYS Development, Inc., to this Advisory Committee to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

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

May 22, 2018

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DIVISION DIRECTOR MEMO

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: April 12, 2018

FROM: Sharon Hertz, MD
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TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the May 22, 2018 AADPAC/DSaRM Meeting to Discuss NDA 209588

At this joint meeting of AADPAC and DSaRM, we will be discussing a new drug application from Insys Development Company, Inc. for a sublingual spray formulation of buprenorphine with the proposed indication of the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The proposed tradename for this product is Buvaya. It is intended to be dosed at 0.125, 0.25, or 0.50 mg sprayed sublingually every 8 hours as needed for pain. The product is formulated as an aqueous solution in a single-use (unit-dose) device consisting of a glass vial inside a plastic spray apparatus. Buvaya was not formulated to include properties intended to deter abuse, nor is the Applicant requesting any such claims.

Buprenorphine is a partial mu-opioid agonist and a kappa-opioid antagonist, and is a Schedule III drug under the Controlled Substance Act. It is the active ingredient in an injectable formulation for acute pain, in sublingual and transdermal formulations for chronic pain, and in several formulations alone and in combination with naloxone as medication assisted therapy (MAT) for opioid addiction.

The Applicant relied in part on the Agency's prior findings of safety and efficacy for Buprenex (buprenorphine injection) and Subutex (buprenorphine hydrochloride sublingual tablets). However, because the most relevant reference product (Buprenex, also indicated for acute pain) has a different route of administration and a different pharmacokinetic profile, the Applicant was required to conduct a single adequate and well-controlled efficacy and safety study in the intended population, as well as pharmacokinetic studies to bridge their product to the products that were relied upon. The Applicant also conducted dose-finding and safety studies as part of the clinical development program.

The FDA presentations and background documents include findings from the FDA's review of the pharmacokinetics, efficacy and safety of Buvaya, drug utilization trends for buprenorphine products, and a review of the epidemiologic data on misuse and abuse of buprenorphine.

Because Buvaya is an immediate-release opioid analgesic expected to be used in the outpatient setting, FDA has determined that this product, if approved, will need a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits outweigh the risks and should be part of the shared system Opioid Analgesic REMS. The Agency's background document includes a description of this REMS.

We will ask you to discuss the Applicant's and Agency's findings with regard to this application, including any concerns you may have regarding the efficacy and safety of Buvaya in patients for whom it is prescribed as well as overall public health implications. We will also ask you to discuss whether the data supports the proposed indication, and whether the drug should be approved.

We request that you provide your expertise, your experience and your best insights in order to help us find a reasonable and responsible path forward. Your advice and recommendations will be essential in assisting us with addressing this application. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.

Draft Points to Consider

1. Does the Applicant's clinical program support the safe and effective use of Buvaya for the proposed indication?

2. Should Buvaya be approved for the proposed indication?

3. Do you have any concerns regarding the public health implications of this product entering the marketplace?

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: April 10, 2018

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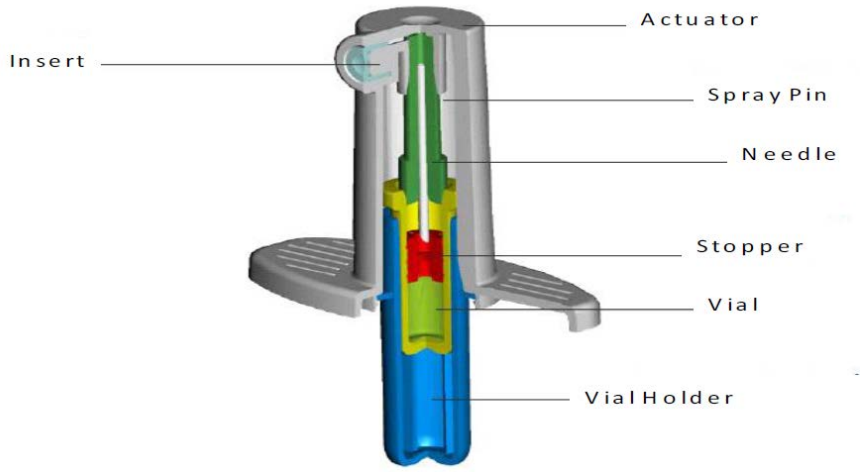
TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Summary of Clinical Data for Buprenorphine sublingual spray (Buvaya)

1 Background

Buprenorphine sublingual spray (BSS) (proposed tradename Buvaya) is a new formulation of buprenorphine (BPN) with a proposed indication of the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The proposed dosing regimen is 0.125, 0.25, and 0.50 mg sprayed under the tongue every 8 hours, as needed. Insys Development Company, Inc. ("Applicant") submitted a 505(b)(2) NDA for BSS relying in part on the Agency's previous findings of safety and efficacy for Buprenex (buprenorphine injection) and Subutex (buprenorphine hydrochloride sublingual tablets). BPN is an analgesic of the opioid class with a complex pharmacology. It is characterized as a partial mu-opioid agonist and a kappa-opioid antagonist. BPN is the active ingredient in a number of products approved for both acute and chronic pain and as medication assisted therapy (MAT) for opioid addiction. The molecule has been approved as the active ingredient in multiple dosage forms (injection, sublingual filmstrips, sublingual tablets, buccal film, transdermal system, depot injection, and subdermal implant). BPN is also approved in combination with naloxone, a mu-opioid antagonist, for the MAT indication. BSS is not intended to be an abuse-deterrent formulation.

BSS is formulated as an aqueous solution in a single-use (unit-dose) device consisting of a glass vial inside a plastic spray apparatus.



Source of diagram: Applicant

The device is to be packaged in an individually-sealed, child-resistant, opaque blister package. Scissors must be used to remove the device for use.

This background document will focus on five studies, the results of which are described in applicable sections below. Studies INS005-17-104 and INS005-17-104-105 are comparative bioavailability studies comparing BSS to Buprenex and Subutex. The Applicant conducted one adequate and well-controlled study (Study INS005-15-062 [Study 062]) to assess efficacy and provide safety data. The Applicant conducted two other studies that are relevant to this background document. Study INS-14-026 (Study 026) was a Phase 3 study that investigated doses as high as 1.0 mg TID in patients who had undergone a

bunionectomy. And, in response to concerns about high rates of nausea and vomiting observed in prior efficacy studies, the Applicant conducted an open-label study (Study INS005-17-111 [Study 111]) to further characterize this risk. Two other clinical pharmacology studies (dose proportionality and effects of drink temperature/pH) are briefly described.

2 Clinical Pharmacology

To rely in part on the Agency's previous findings for safety and effectiveness of other buprenorphine products, the Applicant was required to provide a scientific bridge to the buprenorphine-containing reference products. The Applicant conducted comparative bioavailability Studies INS005-17-104 and INS005-17-104-105 (Studies 104 and 105). Study 104 assessed the comparative bioavailability of 0.125 mg, 0.25 mg, and 0.5 mg sublingual spray given every 8 hours for 5 days plus one dose on Day 6 with 0.3 mg Buprenex IV injection given every 6 hours for 5 days plus one dose on Day 6, and 8 mg buprenorphine sublingual tablet given once every day for 6 days in a parallel group study. Study 105 assessed the comparative bioavailability of 0.125 mg, 0.25 mg, and 0.5 mg sublingual spray given every 8 hours for a total of 3 doses with 0.3 mg Buprenex IV injection given every 6 hours for a total of 4 doses, and a single dose of 8 mg buprenorphine sublingual tablet in a parallel group study.

Buprenorphine sublingual spray showed 40% to 49% absolute bioavailability, with similar Tmax values (~ 2 hours) to the sublingual tablet. At doses of up to 0.5 mg every 8 hours, buprenorphine Cmax and AUC values were lower than 0.3 mg Buprenex IV injection given every 6 hours or 8 mg sublingual tablet given once a day at steady state (Table 1) and after one-day dosing (Table 2).

The corresponding norbuprenorphine Cmax and AUC values for sublingual spray at doses up to 0.5 mg every 8 hours are lower than the sublingual tablet at steady state (Table 3) and after one day of dosing (Table 4). In comparison to Buprenex IV injection, 0.125 mg and 0.25 mg sublingual spray showed lower norbuprenorphine Cmax and AUC, but 0.5 mg sublingual spray showed greater norbuprenorphine exposure.

Table 1: Buprenorphine Pharmacokinetic Parameters at Steady State (Study INS005-17-104)

PK Parameters	Buprenorphine Sublingual Spray 0.5 mg (N=12)	Buprenorphine Sublingual Spray 0.25 mg (N=12)	Buprenorphine Sublingual Spray 0.125 mg (N=12)	Buprenex IV 0.3 mg (N=12)	Buprenorphine Sublingual Tablet 8 mg (N=12)
	(N=12)	(N=11)	(N=11)	(N=11)	(N=11)
T_{max} (h)	2.00 (1.00-4.00)	2.00 (1.00-3.00)	2.00 (1.00-2.00)	0.0500 (0.0500-0.0833)	2.00 (0.500-2.00)
C_{max} (ng/mL)	1.09 (20.2%)	0.543 (23.6%)	0.257 (22.1%)	5.62 (58.2%)	4.43 (44.6%)
AUC_{0-tau} (h*ng/mL)	5.85 (17.4%)	2.89 (20.2%)	1.42 (21.0%)	7.30 (29.8%)	35.3 (34.5%)
AUC_{0-24} (h*ng/mL)	17.5 (17.4%)	8.66 (20.2%)	4.25 (21.0%)	29.2 (29.8%)	35.3 (34.5%)

Source: CSR INS005-17-104, Synopsis Table 1

Table 2: Buprenorphine Pharmacokinetic Parameters after One Day Dosing (Study INS005-17-105)

PK Parameters	Buprenorphine Sublingual Spray 0.5 mg (N=12)	Buprenorphine Sublingual Spray 0.25 mg (N=12)	Buprenorphine Sublingual Spray 0.125 mg (N=12)	Buprenorphine Sublingual Tablet 8 mg (N=12)	Buprenex® IV 0.3 mg (N=12)
C_{max} (ng/mL)	1.04 (32.9%)	0.501 (31.7%)	0.218 (19.5%)	3.80 (51.3%)	23.5 (71.1%)
AUC_{0-24} (h*ng/mL)	11.9 (26.9%)	6.02 (29.9%)	2.73 (27.1%)	24.1 (46.3%)	23.7 (20.6%)
AUC_{last} (h*ng/mL)	18.5 (26.3%)	9.49 (33.1%)	3.39 (39.7%)	35.8 (41.0%)	30.4 (18.0%)
AUC_{inf} (h*ng/mL)	19.3 (27.6%)	9.94 (32.9%)	4.24[a] (29.7%)	37.0 (39.7%)	31.3 (17.7%)

Note: T_{max} presented as median (range); C_{max} and AUCs reported as mean (CV%).
[a]n=8

Source: CSR INS005-17-105, Synopsis Table 1

Table 3: Norbuprenorphine Pharmacokinetic Parameters at Steady State (Study INS005-17-104)

PK Parameters	Buprenorphine Sublingual Spray 0.5 mg (N=12)	Buprenorphine Sublingual Spray 0.25 mg (N=2)	Buprenorphine Sublingual Spray 0.125 mg (N=3)	Buprenex IV 0.3 mg (N=9)	Buprenorphine Sublingual Tablet 8 mg (N=12)
	(N=12)	(N=12)	(N=11)	(N=11)	(N=11)
T_{max} (h)	1.75 (0.500-8.00)	2.00 (0.250-8.00)	2.00 (0.00-6.00)	0.383 (0.217-5.92)	1.00 (0.500-2.00)
C_{max} (ng/mL)	0.419 (25.9%)	0.186 (49.9%)	0.114 (48.0%)	0.350 (70.8%)	3.93 (47.2%)
AUC_{0-tau} (h*ng/mL)	2.89 (25.8%)	1.33 (47.0%)	0.795 (49.5%)	1.79 (73.2%)	60.4 (52.5%)
AUC_{0-24} (h*ng/mL)	8.67 (25.8%)	4.00 (47.0%)	2.38 (49.5%)	7.16 (73.2%)	60.4 (52.5%)

Source: CSR INS005-17-104, Synopsis Table 2

Table 4: Norbuprenorphine Pharmacokinetic Parameters after One Day Dosing (Study INS005-17-105)

PK Parameters	Buprenorphine Sublingual Spray 0.5 mg (N=12)	Buprenorphine Sublingual Spray 0.25 mg (N=12)	Buprenorphine Sublingual Spray 0.125 mg (N=7)	Buprenorphine Sublingual Tablet 8 mg (N=12)	Buprenex® IV 0.3 mg (N=12)
T_{max} (h)	24.0 (11.9-24.1)	24.0 (11.9-48.2)	24.0 (9.00-48.0)	7.92 (1.00-48.0)	18.3 (12.3-24.0)
C_{max} (ng/mL)	0.0941 (38.6%)	0.0577 (28.5%)	0.0377 (33.9%)	0.870 (46.2%)	0.0789 (44.6%)
AUC_{0-24} (h*ng/mL)	1.20 (47.8%)	0.757 (30.7%)	0.394 (48.5%)	13.1 (40.4%)	1.03 (42.6%)
AUC_{last} (h*ng/mL)	6.61 (49.2%)	3.04 (54.2%)	1.17 (92.6%)	43.1 (49.3%)	3.62 (52.3%)
AUC_{inf} (h*ng/mL)	NC	NC	NC	48.4[a] (44.5%)	NC

Note: T_{max} presented as median (range); C_{max} and AUCs reported as mean (CV%).
NC = Not calculated; Due to n<2, no statistics are reported.
[a]n=10

Source: CSR INS005-17-105, Synopsis Table 2

Study INS005-16-076 assessed dose proportionality using a single spray of 0.0625, 0.125, 0.25, 0.5, and 1.0 mg sublingual spray in a parallel group study. Buprenorphine Cmax and AUC values were dose

proportional based on the analyses on log transformed parameters using a power model. The slopes of log-transformed Cmax, AUCt, and AUCinf values for buprenorphine were 0.9154, 1.0721 and 1.0543, respectively, and they fell within the range of 0.80 to 1.25. Therefore, dose proportionality is demonstrated over the range of 0.0625 mg to 1 mg for buprenorphine sublingual spray. Because the route of administration is sublingual and will bypass the stomach and intestine, food effect was not assessed.
Study INS005-16-069 assessed the effect of varying temperatures in the mouth due to hot and cold beverages, and of varying pH conditions in the mouth due to acidic and alkaline beverages on buprenorphine sublingual spray. Pretreatment with hot water increased buprenorphine AUC values by 16%, low beverage pH (such as Sprite) reduced buprenorphine Cmax by 10%, and high beverage pH (such as Essentia) increased buprenorphine AUC by 11%.

As noted briefly in the Background section of this document, compared to most medically useful opioids, buprenorphine has a complex pharmacology in that it is a partial mu-opioid agonist and kappa-opioid antagonist. As a partial agonist, BPN has affinity for the receptor but only partial activity at the mu-receptor. The affinity for BPN at the mu receptor is high with a slow duration that results in a long duration of action. Norbuprenorphine (NBPN), a metabolite of BNP, is a full agonist at the mu opioid receptor.

3 Clinical Efficacy

The Applicant submitted data from a single adequate and well-controlled study, Study 062, to provide substantial evidence of efficacy for BSS. Study 062 was a randomized, double-blind, placebo-controlled, parallel-group study of BSS at 0.125, 0.25, and 0.5 mg in patients with moderate-to-severe pain following bunionectomy.

Eligible patients were adults classified as P1 or P2 by the American Society of Anesthesiologists Physical Status Classification System who were scheduled to undergo primary, unilateral bunionectomy. Following informed consent, screening procedures, and surgery, patients were treated overnight with a continuous peripheral nerve blockade. Early (~3 AM) the following morning, the nerve block was discontinued and pain was monitored until a pain intensity of at least 4 out of 10 was reported. Patients were randomized to placebo or one of the three doses of BSS and the first dose of study drug was administered. A double-stopwatch assessment (DSA) was used. Two stopwatches were started to allow for measurement of first perceptible pain relief and first meaningful pain relief, and efficacy assessments of pain intensity were performed at close intervals for 48 hours following the first dose of study medication. Dosing was continued every 8 hours for a total of six doses. The allowed rescue analgesic medication was oral ibuprofen or intravenous ketorolac if the ibuprofen was inadequate.

Efficacy outcome measures included pain intensity using an 11-point numerical pain rating scale (NPRS), pain relief (5-point categorical scale), use of rescue analgesia, patient global evaluation of study drug, and the double-stopwatch assessment (DSA) as described above. Stopwatches were discontinued and patients censored from the DSA analysis if the patient did not stop the stopwatch either by the time of the second dose of study drug or the first use of rescue medication (whichever

occurred first). Safety data collected included hematology, serum chemistry, urinalysis, pregnancy testing, urine drug screen, ECG, vital signs, physical exams, including oral cavity, and adverse events.

Statistical Methodology

The Intent-to-Treat population, which included all randomized subjects, was used for the efficacy analyses. The primary efficacy endpoint was the summed pain intensity difference over 48 hours (SPID-48). This was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, site, and baseline pain. Baseline pain was measured prior to the first dose of blinded treatment after surgery. The Applicant planned a sequential closed testing approach to control the overall Type I error rate. First the 0.5 mg TID group would be compared to placebo at α=0.05. If that comparison showed statistical significance, then the 0.25 TID dose would be compared to placebo, and similarly the 0.125 dose would be compared to placebo last. There were no planned comparisons between the three dose groups of BSS.

Secondary endpoints included additional pain assessments, use of rescue medication, time to first use of rescue, and time to meaningful pain relief. There was no prespecified priority for testing any of the secondary endpoints, and no adjustment for multiplicity. Therefore, results for these endpoints were descriptive only.

Results

Patient Demographics and Patient Disposition

The patient demographics and baseline characteristics were typical for a bunionectomy study with a female predominance (79%) and mean age of 45. The baseline pain intensity averaged 6.5/10. Characteristics among the four treatment groups were balanced. All patients were opioid-naïve (defined as no opioid use in the prior 2 weeks excepting narcotics administered as pre-anesthesia). A total of 322 patients were randomized, approximately 80 per treatment group.

Efficacy

The primary efficacy endpoint was the SPID-48, a weighted average of the change in pain from baseline (post-surgery; prior to first dose of study treatment) to multiple timepoints at intervals through 48 hours after the first dose. Negative values for the SPID-48 represent negative change, i.e. worsening pain. Higher positive values represent greater improvement in pain. In the Applicant's primary analysis, missing data was not imputed for subjects who discontinued prior to 48 hours. Additional analyses with multiple imputation applied provided similar treatment effects and the same conclusions. The results of the primary analysis are presented in Table 5.

Table 5: Efficacy Analyses Results (Study 062)

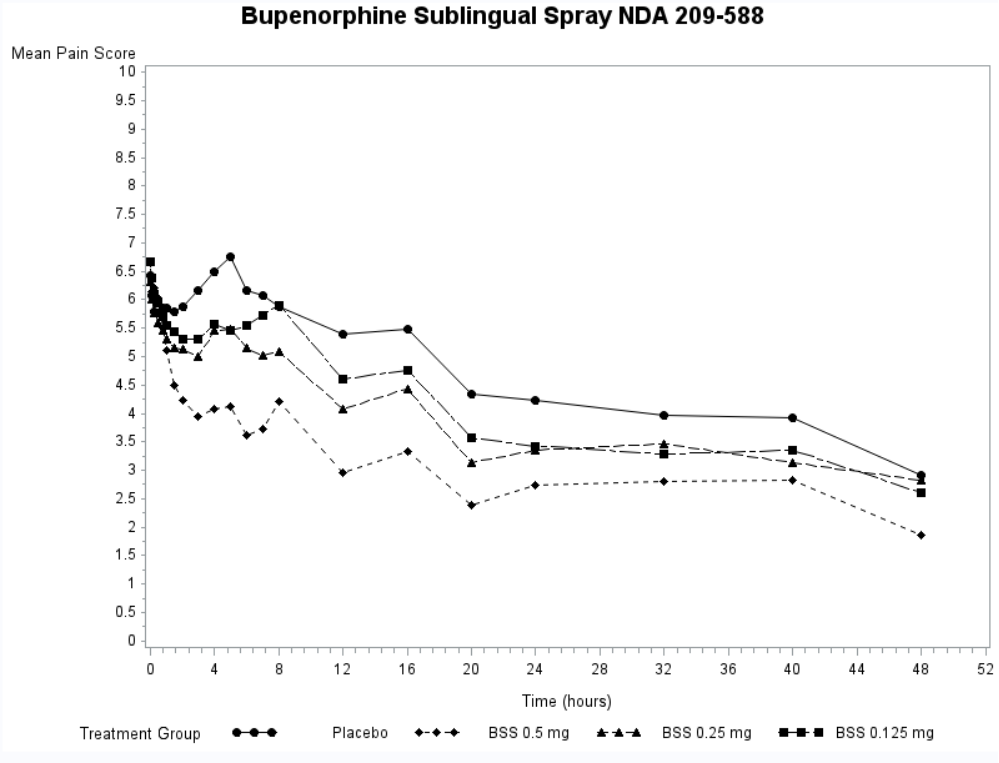
All Randomized (ITT)		**BSS 0.50 mg N=81**	**BSS 0.25 mg N=80**	**BSS 0.125 mg N=82**	**Placebo N=79**
Primary:					
SPID48	N	72	75	77	75
	Mean (SD)	183 (107.3)	126 (102.2)	136 (114.0)	93 (85.1)
	Range	-18 – 415	-56 – 319	-91 – 399	-78 – 378
	LS (adjusted) Mean (SE)	171 (10.3)	126 (10.1)	125 (9.9)	89 (10.1)
	LSM Diff. v. PBO	82	36	35	
	95% CI of Diff.	(54, 110)	(8, 64)	(8, 63)	
	2-sided p-value	<0.001	0.01	0.01	

BSS = Buprenorphine Sublingual Spray sprayed under the tongue every 8 hours as needed.
Least Squares Means (LSM) and between group comparisons from ANCOVA model with terms for treatment, site, and baseline pain (post-surgery; before first dose).
Data was not imputed for subjects who discontinued prior to 48 hours.
Source: Clinical Study Report Table 6, adpain.xpt SAS dataset

The primary analysis showed a statistically significant difference in SPID-48 for all three treatment groups with the largest treatment effect observed for the 0.5 mg dose group. The treatment effect size for patients treated with 0.125 and 0.25 mg were similar to each other. Secondary endpoint analyses of assessments of pain relief and the patient global assessment of study drug generally support the notion that patients treated with active drug had a benefit compared to placebo.

Pain intensity scores by time point and treatment group are summarized in the figure below (Figure 1). For the 0.5 mg dose the pain intensity curve separates from placebo throughout the entire 48-hour treatment period. The lowest two dose groups do not separate from placebo as clearly as the 0.5 mg group across the full 48-hour timeframe.

Figure 1: Pain Intensity Score by Time Point (Study 062)



Analyses of rescue medication use (Table 6) show that nearly the same number of patients treated with the two lower doses of BSS required rescue as patients treated with placebo, although the active groups used fewer doses of rescue than placebo.

Table 6: Summary of Use of Rescue Medication for Pain in Study 062 (ITT Population)

	Placebo N=79	Buprenorphine Sublingual Spray		
		0.5 mg N=81	0.25 mg N=80	0.125 mg N=82
Number (%) of subjects using rescue medication	77 (97.5)	45 (55.6)	70 (87.5)	72 (87.8)
Total Use of rescue medication (0-24 hours)				
N	77	41	68	71
Mean (SD)	3.8 (1.98)	2.2 (1.69)	2.6 (1.62)	2.9 (1.67)
Median	3	1	2	3
Total Use of rescue medication (0-48 hours)				
N	77	45	70	72
Mean (SD)	5.6 (3.60)	2.9 (2.81)	3.7 (2.68)	3.9 (2.69)
Median	5	2	3	3

ITT = intent-to-treat; SD = standard deviation

Note: Denominators for % are the number of subjects per treatment group in the ITT Population. Total use of rescue medication is the number of times a subject took rescue medication. Source: Modified from Applicant's Table 15 CSR

The Double-Stopwatch Assessment (DSA) data, specifically those for the 0.125 and 0.25 mg doses, do not support the effectiveness of BSS as an acute analgesic. In this verbatim transcription from the Applicant's Clinical Study Report from Study 062, the time to "onset of analgesia" is defined:

> Time to onset of analgesia was measured as time to first perceptible pain relief confirmed by meaningful pain relief. It was defined as the time when the first stopwatch was stopped given that the second stopwatch is stopped. If the second stopwatch was not stopped, time was censored at the time of the second dose of study drug or the use of rescue medication, whichever comes first. If both stopwatches were not stopped time was censored at the time of the second dose of study drug or the use of rescue medication whichever came first.

The preferred metric for reporting onset is time to meaningful pain relief based on the time recorded by the second stopwatch, not the first as was done here. The Applicant's primary analysis of the time to onset of analgesia data is shown in Table 7.

Table 7: Time to Onset of Analgesia Study 062 (ITT Population)

	Placebo N=79	Buprenorphine Sublingual Spray		
		0.5 mg N=81	0.25 mg N=80	0.125 mg N=82
Number (%) of subjects with onset of analgesia	27 (34)	53 (65)	37 (46)	36 (44)
Number (%) of subjects censored	52 (66)	28 (35)	43 (54)	46 (56)
Time (minutes) from first dose to onset of analgesia [a]				
25th percentile (95% CI)	5 (4, 83)	6 (5, 15)	13 (5, 29)	15 (6, 27)
Median (95% CI)	NE	43 (21, 64)	NE (43, NE)	NE (41,NE)
75th percentile (95% CI)	NE	NE (101, NE)	NE	NE

CI = confidence interval; ITT = intent-to-treat; NE = not estimable

[a] Quartile estimates and CIs are from a Kaplan-Meier analysis.

Note: Denominator for % is the subjects per treatment group in the ITT Population. Time to onset of analgesia is the time when the first stopwatch is stopped given that the second stopwatch is stopped. If the second stopwatch was not stopped, time was censored at the time of the second dose of study drug or the use of rescue medication. If neither were stopped, time was censored at time of second dose of study drug or the use of rescue medication.

Source: Modified from Applicant's Table 14 CSR

Less than 50% of patients treated with the two lower doses stopped the second stopwatch before the next dose of study drug (8 hours) or the use of rescue. Even for the high dose group, in which a median time to analgesia was estimable, it is important to note that more than one third of patients did not experience onset of analgesia. The Applicant's Time to Meaningful Pain Relief analysis (analysis of second stopwatch data) also indicates a long latency to clinically meaningful benefit. The median time to pain relief was 92, 122, and 166 minutes in the high, mid, and low-dose groups, respectively (Table 8).

Table 8: Time to Meaningful Pain Relief Study 062 (ITT Population)

	Placebo N=79	Buprenorphine Sublingual Spray		
		0.5 mg N=81	0.25 mg N=80	0.125 mg N=82
Number (%) of subjects with meaningful pain relief	27 (34)	53 (65)	37 (46)	36 (44)
Number (%) of subjects censored	52 (66)	28 (35)	43 (54)	46 (56)
Time (minutes) from first dose to onset of meaningful pain relief [a]				
25th quartile (95% CI)	64 (12, 121)	60 (40, 66)	71 (44, 90)	60 (29, 87)
Median (95% CI)	238 (121, NE)	92 (79, 120)	122 (90, 227)	166 (87, 240)
75th quartile (95% CI)	NE (238, NE)	255 (120, NE)	NE (189, NE)	NE (240, NE)

CI = confidence interval; ITT = intent-to-treat; NE = not estimable

[a] Quartile estimates and CIs are from a Kaplan-Meier analysis.

Note: Denominator for % is the number of subjects per treatment group in the ITT Population. Time to meaningful pain relief is the time when the subject stops the second stopwatch.

Source: Modified from Applicant's Table 19 CSR

Although assessments of pain intensity, pain relief and the patient global assessment show a benefit from treatment with BSS, the analyses of the use of rescue medication and the time to onset of action cast doubt on the appropriateness of BSS for the treatment of acute pain.

Discussion

Study 062 is an adequate and well-controlled study of three doses of BSS in patients with moderate-to-severe pain following bunionectomy. The study meets criteria for success in that the Applicant showed a statistically significant difference, favoring all active groups, over placebo on the primary endpoint. Furthermore, secondary analyses of pain intensity, pain relief, and patient global assessment data also imply a benefit with BSS treatment compared to placebo.

However, for analgesics intended to treat acute pain, there is an expectation that meaningful pain relief will be experienced soon after taking the first dose of drug (generally within one hour). More than half of the patients treated with 0.125 and 0.25 mg BSS never experienced meaningful analgesia. Furthermore, the median time to onset of meaningful pain relief was 92 minutes for patients treated with 0.5 mg of BSS. It is important to note that, while enough high-dose patients experienced meaningful analgesia to estimate a median, over one third of patients in that group either were redosed with study drug or received rescue prior to experiencing analgesia. The concern around a delay in onset of pain relief is that, in seeking adequate analgesia, patients may redose with BSS or use another opioid medication before the next dosing time, which poses the increased risk of adverse opioid-related events or potentially opioid overdose.

The rates of rescue analgesia use in patients receiving BSS, which closely approximate the rate in placebo for the 0.125 and 0.25 mg doses, also raise doubt whether this drug product will be useful in patients with acute pain.

4. Clinical Safety

Exposure and Demographics

In the Phase 2 and 3 postoperative pain studies, a total of 323 subjects were exposed to BSS with 161 subjects exposed to the 0.5 mg dose or higher. There were more female subjects (81%) consistent with bunionectomy surgery and breast augmentation. Most patients were White (67%) with the next most common race Black or African American (27%). The mean age of the subjects, ranged from 41 years-old in the 1 mg (TID) group to 48 years-old in the 0.125 mg (TID) group.

Adverse Events:

There were no deaths in the BSS development program and there were a small number of serious adverse events that did not appear related to study drug. These included atrial fibrillation, angioedema and incision site hematoma. In all of the Phase 2 and 3 studies, 33 subjects (10%) discontinued BSS due to an adverse event. The most common adverse events resulting in discontinuation were nausea and vomiting in 14 patients each, hypoxia in six patients, somnolence in four patients (two at higher doses than currently proposed) and dizziness in two patients. Summary statistics for adverse events leading to discontinuation for the relevant doses of BSS are shown following (Table 9).

Table 9: Selected Adverse Events Requiring Drug Discontinuation for 0.5, 0.25 and 0.125 mg doses in Phase 2 and 3 Postoperative Pain Studies[1] (Safety Population)

System Organ Class Preferred Term	Buprenorphine Sublingual Spray			Placebo N=89 n (%)	Standard Narcotic Therapy N=50 n (%)
	0.125 mg N=82 n (%)	0.25 mg N=80 n (%)	0.5 mg N=140 n (%)		
Subjects with ≥ 1 AE	1 (1.2)	4 (5.0)	26 (18.6)	0	4 (8.0)
Total Number of AEs	1	6	38	0	4
Gastrointestinal disorders	1 (1.2)	4 (5.0)	17 (12.1)	0	0
Nausea	0	3 (3.8)	11 (7.9)	0	0
Vomiting	1 (1.2)	3 (3.8)	10 (7.1)	0	0
Nervous system disorders	0	0	4 (2.9)	0	1 (2.0)
Dizziness	0	0	2 (1.4)	0	1 (2.0)
Somnolence	0	0	2 (1.4)	0	0
Respiratory disorders					
Hypoxia	0	0	6 (4.3)	0	2 (4.0)

[1] Studies 14-026, 15-062, 17-111

Source: Modified from Applicanat's Table 4-76 ISS

Study 062

In Study 062, the treatment period was limited to 48 hours, in relatively healthy (ASA P1 and P2) patients. As shown below, patients treated with the 0.5 mg dose of BSS experienced an extraordinarily high rate of adverse events.

Table 10: Overall Summary of Treatment-Emergent Adverse Events Study 062 (Safety Population)

	Placebo N=79 n (%)	Buprenorphine Sublingual Spray		
		0.5 mg N=81 n (%)	0.25 mg N=80 n (%)	0.125 mg N=82 n (%)
Number of subjects with:				
Any TEAE	38 (48)	76 (94)	67 (84)	57 (70)
Any serious TEAE	0	1 (1)	0	0
Any TEAE leading to withdrawal of study drug	0	8 (10)	4 (5)	1 (1)
Any TEAE related to study drug	27 (34)	73 (90)	66 (83)	49 (60)
Total Number of TEAEs reported	95	461	296	219

AE = adverse event; TEAE = treatment-emergent adverse event Note: For each category, subjects are included only once, even if they experienced multiple events in that category. Denominators for percentages are the number of subjects per treatment group in the Safety Population. Source: Modified from Applicant's Table 40 CSR

The most common adverse events were nausea, vomiting, and dizziness that showed a clear dose dependence (Table 11).

Table 11: Selected Common Treatment-Emergent Adverse Events Study 062 (Safety Population)

Preferred Term	Placebo N=79 n (%)	Buprenorphine Sublingual Spray		
		0.5 mg N=81 n (%)	0.25 mg N=80 n (%)	0.125 mg N=82 n (%)
Any TEAE	38 (48)	76 (94)	67 (84)	57 (70)
Nausea	13 (17)	68 (84)	47 (59)	36 (44)
Vomiting	**4 (5)**	**59 (73)**	**33 (41)**	**24 (29)**
Dizziness	7 (9)	44 (54)	26 (33)	18 (22)
Headache	9 (11)	13 (16)	23 (29)	15 (18)
Somnolence	0	11 (13)	6 (8)	6 (7)

TEAE = treatment-emergent adverse event
Note: Adverse events are coded using MedDRA version 19.0. For each preferred term subjects are counted only once even if they experienced multiple events.
Source: Modified from Applicant's Table 41

The severity of nausea, vomiting, and dizziness is summarized following (Table 12).

Table 12: Selected Treatment-emergent Adverse Events by Severity in Study 062 (Safety Population)

AE	Severity	Placebo (n/%)	0.125 mg (n/%)	0.25 mg (n/%)	0.50 mg (n/%)
Nausea	Mild	10 (12.7)	27 (32.9)	34 (42.4)	42 (51.9)
	Moderate	3 (3.8)	8 (9.8)	11 (13.8)	24 (29.6)
	Severe	0	1 (1.2)	2 (2.5)	2 (2.5)
Vomiting	Mild	1 (1.3)	13 (15.9)	17 (21.3)	29 (35.8)
	Moderate	2 (2.5)	10 (12.2)	10 (12.5)	23 (28.4)
	Severe	1 (1.3)	1 (1.2)	6 (7.5)	7 (8.6)
Dizziness	Mild	7 (8.9%)	14 (17.1)	24 (30.0)	32 (39.5)
	Moderate	0	4 (4.9)	1 (1.3)	12 (14.8)
	Severe	0	0	1 (1.3)	0

Source: CSR Study 062, Table 14.3.6

Thirty-seven percent of patients receiving the 0.5 mg dose of BSS experienced moderate-to-severe vomiting. The use of antiemetic drugs was permitted. A total of 4 (5%) patients treated with placebo required at least one dose of antiemetic drug compared to 17/82 (21%) of patients treated with 0.125 mg BSS, 32 (40%) patients treated with 0.25 mg BSS, and 55 (68%) patients treated with 0.5 mg BSS. The maximum number of doses of antiemetic drug in any single patient was three, four, four, and eight in placebo, low, mid, and high dose groups, respectively.

The remainder of the adverse event data from Study 062 are typical for an opioid. In addition, the available data to not show any local toxicity to the oral mucosa or sublingual area.

Other Studies in Patients

The finding of high rates of nausea and vomiting are not limited to Study 062. Prior to starting Study 062 in January 2016, the applicant conducted Study 026 which ran for 24 days (February 24, 2015 to March 19, 2015). Study 026 was a randomized, double-blind, placebo-controlled, parallel-group study comparing BSS at 0.5 mg TID, 1.0 mg BID, and 1.0 mg TID to placebo. The study was similar in design and conduct to Study 062 and used a population of patients status post bunionectomy. The planned study size was 312 patients and the study was stopped after 40 patients. While 82.5% of patients enrolled were able to complete the study, the available adverse event again show high rates of nausea, vomiting, and dizziness (Table 13).

Table 13: Treatment-Emergent Adverse Events for the GI and Nervous Systems by SOC and PT for Study 026 (Safety Population)

System Organ Class Preferred Term	Buprenorphine Sublingual Spray			Placebo N=10 n (%)
	0.5 mg TID N=9 n (%)	1.0 mg BID N=11 n (%)	1.0 mg TID N=10 n (%)	
Any TEAEs	9 (100)	11 (100)	9 (90)	7 (70)
Gastrointestinal disorders				
Nausea	7 (78)	10 (91)	7 (70)	3 (30)
Vomiting	**6 (67)**	**8 (73)**	**8 (80)**	**0**
Constipation	0	3 (27)	2 (20)	0
Diarrhea	0	0	0	2 (20)
Dry mouth	1 (11)	2 (18)	1 (10)	0
Nervous system disorders				
Dizziness	7 (78)	5 (46)	5 (50)	0
Headache	1 (11)	4 (36)	1 (10)	4 (40)
Somnolence	4 (44)	3 (27)	4 (40)	0

TID = 3 times daily; BID = twice daily
Note: The denominator for the percentages is the number of subjects in each treatment group. Subjects experiencing more than one TEAE were counted only once for each preferred term. All TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.1.
Source: Modified from Applicant's Table 14 CSR

A total of one (10%), six (67%), 10 (91%), and seven (70%) patients in the placebo, 0.5 mg TID, 1.0 mg BID, and 1.0 mg TID groups, respectively, required one or more doses of antiemetic drugs at some point following the first dose of study drug. The maximum number of doses of antiemetic drug in any single patient was one, eight, four, and 10 in the placebo, low, mid, and high dose groups, respectively.

The Applicant also conducted Study 111, a randomized, open-label study in ASA P1 and P2 patients undergoing bunionectomy, breast augmentation, or abdominoplasty. Eligible patients were randomized to 0.5 mg of BSS TID or "standard postoperative narcotic therapy" (intravenous morphine, 4 mg TID for 24 hours followed by 10 mg oral oxycodone, TID). Patients were treated for up to 7 days. Patients received nausea and vomiting prophylaxis consisting of single doses of dexamethasone and ondansetron perioperatively. The rescue medication for pain was acetaminophen (inpatients and outpatients) or ketorolac (inpatients only). At the discretion of the clinician, ondansetron, 4 mg IV or as orally disintegrating tablets were administered. No data on pain intensity were collected.

A total of 100 patients were randomized, 50 per arm. The summary safety data showed imbalances in the adverse events, favoring standard opioid therapy over BSS as summarized below (Table 14).

Table 14: Summary of Selected Treatment-emergent Adverse Events in Study 111

Parameter	Standard Opioid Therapy (n/%)	BSS (n/%)
Any AE	33 (66)	47 (94)
Mild TEAEs	13 (26)	7 (14)
Moderate TEAEs	20 (40)	29 (58)
Severe TEAEs	0	1 (2)
Nausea	17 (34)	39 (78)
Vomiting	**6 (12)**	**26 (52)**
Dizziness	5 (10)	11 (22)
Hypoxia	**3 (6)**	**14 (28)**

Source: CSR, Study 111, Table 13

A total of 39 (78%) patients required at least one dose of antiemetic drug at some point after the first dose of 0.5 mg BSS compared to 12 (24%) patients treated with the standard opioid regimen. The maximum number of doses of antiemetic drug in any single patient was 16 in the BSS group and 9 in the standard opioid group.

Pulse Oximetry Data:

Study 111 showed an imbalance in the adverse event term of "hypoxia" when BSS was compared to a standard opioid regimen (28% vs. 6%), as noted in the table above. "Hypoxia" was defined as oxygen saturation levels ≤ 92% on room air. Respiratory depression is a well-known risk for opioids. In Study 062, all patients were continuously monitored for decrease in oxygen saturation. No serious, non-mild events of hypoxia were observed. Investigators used the terms of "hypoxia" and "oxygen saturation decrease" to report decreases in oxygen saturation. As opposed to the stringent definition of "hypoxia," "oxygen saturation decreased" was reported based on any decrease in oxygen saturation down to, but not exceeding 92% regardless of whether medical intervention was required.

In Study 062, "oxygen saturation decrease" was reported in 25 subjects (four in the placebo group, six in the 0.125 mg group, eight in the 0.25 mg group, and seven in the 0.5 mg group), and "hypoxia" was reported in four subjects (one in the 0.125 mg group and three in the 0.5 mg group). Of these 29 cases, 26 were administered supplemental oxygen via nasal cannula and all resolved without clinically significant sequelae.

Other Safety Data:

Data for other vital signs, hematology, serum chemistry, and ECG did not show any signals of concern.

Discussion

The safety data from the BSS clinical development program show no evidence that the formulation or route of administration are associated with any local toxicity. Qualitatively, the adverse event profile for BSS is typical for an opioid.

However, in all three clinical trials of BSS in post-surgical patients, very high rates of nausea, vomiting, and dizziness (NVD) were observed. While NVD are expected adverse reactions for the opioid class of drugs, an open-label, randomized trial in patients showed that BSS, at 0.5 mg TID, is associated with higher rates of NVD, and hypoxia than the morphine/oxycodone opioid regimen selected by Insys as a comparator. The active-controlled trial also showed much higher use of antiemetic drugs in the BSS arm compared to the comparator. Potential explanations for the high adverse event rates for BSS include the pharmacokinetics of this specific product, the patient population (specifically opioid-naïve pain patients), formulation, route of administration, or the intrinsic pharmacologic properties of the active drug.

Key data from the BSS clinical development program and other, approved BPN-containing drugs are summarized in Table 16 to assess whether the unusually high rate of vomiting in BSS studies may be related to a unique pharmacokinetic profile. Unfortunately, data for all pharmacokinetic (PK) parameters are not available in the public domain for all products and, for the most part, the table contains cross study comparisons of heterogeneous populations and study designs.

Table 16: PK Parameters and Selected Adverse Events with Approved Buprenorphine Products

Tradename	Indication	Dose	Route	Tmax (hr)	Cmax (ng/mL)	AUC (ng*hr/ mL)	Nausea (%)	Vomiting (%)	Dizziness (%)	Comments
BSS	Acute pain	0.50 mg	SL	2	1.1	21.4	78-84	52-73	22-78	PK from Study 104, AE rates from clinical trials
Buprenex	Acute pain	0.3 mg	IV	0.05	5.6	28.2	5-10	2-10	5-10	PK from Study 104. AE rates from the PI. Vomiting rate estimated from "hypotension/nausea/ vomiting and vomiting/hypoventilation"
Subutex	MAT	8 mg	SL	2	4.4	76.7	14	8	4-6	PK from Study 104. AEs for 16 mg dose from the PI (dizziness from moderate & high dose 16-week study)
Belbuca	Chronic pain	0.3 mg	Buccal				17	7	5	Opioid-experienced
Belbuca	Chronic pain	0.3 mg	Buccal	2.5	0.5	2	50	8	6	Opioid-naïve PK for 300 mcg dose
Sublocade	MAT	300 mg	SC depot		10.1		8-9	6-9	2-3	Opioid-experienced
Butrans	Chronic pain	10 mcg/hr	Trans-dermal system				14	<5	5	Opioid-experienced
Butrans	Chronic pain	11 mcg/hr	Trans-dermal system		0.2	2.7	23	7	10	Opioid-naïve PK for 10 mcg/hr steady state
Probuphine	MAT	320 mg	Sub-dermal implant	12		19.6	6	6	4	Opioid-experienced

The PK data do not show that the PK profile of BPN from BSS is substantially different from the other products to explain to the high rates of NVD observed. Specifically, Study 104 directly compared Buprenex, an IV formulation, with BSS. The PK data are consistent with the respective routes of administration with rapid Tmax and high relative Cmax and AUC for the injection. However, based on adverse event rates from the package insert, Buprenex has NVD rates similar to the other products. In Study 104, which included Buprenex, the study participants were treated with naltrexone, rendering opioid-related adverse event data unreliable.

Most of the approved BPN-containing products are used in patients who are opioid-experienced, tolerant, and/or dependent. In contrast, patients being treated for acute pain are often opioid-naïve as was the case in the BSS program. It is possible that opioid-naïve patients tolerate BPN poorly compared to experienced individuals. However, the Belbuca and Butrans development programs included studies in opioid-naïve and opioid-experienced patients. As shown in Table 16, opioid-naïve patients had numerically higher rates of NVD than opioid-experienced patients although some differences were probably not clinically important. These findings are also consistent with the general principle that opioid-induced nausea and vomiting improves with continued dosing. There is a lack of consistency in the data though; Buprenex appears to be equally tolerable in opioid-naïve patients as the products that are used in opioid-experienced populations.

BSS is formulated in an aqueous solution containing water, co-solvents, antioxidants, pH adjustment agents, and a flavoring agent. The excipients themselves, at the concentrations used, are unlikely to cause the adverse event profile seen. With regard to route of administration, Subutex is also administered via the sublingual route and has an unexceptional safety profile so there is no reason to believe that route of administration alone plays a significant role in the NVD seen with BSS.

With regard to whether the poor tolerability may be an intrinsic quality of the BPN molecule, the literature does not clearly inform this issue.

> Fullerton et al (1991), described a randomized, double-blind crossover study in 4 (20 were planned) healthy volunteers who received single doses of morphine (10 mg), meperidine (100 mg), BPN (0.3 mg), or saline intravenously. After the first four subjects experienced significant, prolonged nausea and vomiting, the blind was broken and BPN was found to the culprit drug in all cases. “Other treatment arms produced either mild or no side effects.” The investigators terminated the study early. Fullerton hypothesizes that BPN-induced nausea and vomiting have a prominent vestibular component because his subjects’ symptoms were worse on being upright or ambulating.
>
> White et al (2017) conducted a meta-analysis of 28 RCTs to assess differences between BPN and morphine in the treatment of acute pain. These authors showed no difference between BPN and morphine for nausea and vomiting.
>
> Schnabel et al (2017) published a meta-analysis of studies evaluating whether the addition of BPN to the local anesthetic affects the safety and efficacy of local anesthetic blocks. Briefly, Schnabel found that adding BPN extended the duration of analgesia (mean difference 8.4 hours) although the BPN group was associated with a significantly higher risk of nausea and vomiting (relative risk 5.0 [1.12-22.27]).

van Beek et al (2017) reported a randomized, double-blind, placebo-controlled study to assess whether adding BPN to a femoral nerve block prolongs analgesia in patients status post total knee arthroscopy. The treatment groups were ropivacaine alone perineurally, ropivacaine + BPN perineurally, and BPN, 0.3 mg subcutaneously. The investigators found no difference between treatment groups in their primary outcome measure (time to first rescue analgesic) and the rates of nausea were similar in all three arms (~30%). However, the rates of vomiting were 19.0%, 9.5%, and 28.6% for the combination, ropivacaine alone, and subcutaneous BPN groups.

Data from the BSS development program suggest that BSS may be associated with a risk of hypoxia. Study 062 showed small imbalances in cases of hypoxia compared to placebo which is not unexpected. However, Study 111 showed a substantial imbalance in hypoxia favoring the morphine/oxycodone regimen used by the Applicant. Paradoxically, BPN is generally thought to have a ceiling effect for respiratory depression. Most of the data supporting the concept of a ceiling effect were generated in opioid-experienced or opioid-tolerant individuals. If opioid-naïve patients, the likely patient population for BSS, experience clinically significant respiratory depression, the unique pharmacology of the drug may exacerbate that clinical scenario. Due to the high-affinity of binding to the mu-opioid receptor and slow dissociation, standard doses of naloxone are not sufficient to reverse BPN-induced respiratory depression [van Dorp, Gal]. If emergency responders are not aware that high dose naloxone, followed by a naloxone infusion are necessary, poor clinical outcomes could ensue.

In conclusion, the Applicant's efficacy data demonstrate superiority of BSS over placebo for all doses tested, however time to onset of analgesia is later than is optimal for a drug intended to treat acute pain and the need for rescue analgesic was high. From a safety perspective, there is an unexpectedly high rate of nausea, vomiting and dizziness for BSS. And the Applicant showed in a comparative safety study that rates for BSS are markedly higher than rates for other opioids (morphine and oxycodone) used in similar acute pain settings. The totality of data submitted by the Applicant does not support the use of this product in an acute pain setting, based on both efficacy and safety findings.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Utilization Review

Date:	April 10, 2018
Reviewer(s):	LCDR Jennie Wong, Pharm.D. Drug Utilization Data Analyst Division of Epidemiology II
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Subject:	Utilization Patterns of Buprenorphine-Containing Products
Drug Name(s):	Buprenorphine sublingual spray, 0.125 mg, 0.2 5mg, and 0.5 mg
Application Type/Number:	NDA 209588
Applicant/sponsor:	Insys Development Company, Inc
OSE RCM #:	2017-2643

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

CONTENTS

EXECUTIVE SUMMARY

On May 22, 2018, a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee Advisory Committee (DSaRM) will be held to discuss New Drug Application (NDA 209588) for buprenorphine sublingual spray with the proposed indication for the management of moderate-to-severe acute pain where the use of an opioid analgesic is appropriate. The committee will discuss the safety and efficacy of this product that contains an opioid analgesic with no abuse-deterrent properties. To provide context and background information, this review examines U.S. outpatient retail utilization of buprenorphine (single-ingredient and in combination with naloxone) products from 2013 through 2017.

The utilization of buprenorphine products increased from 10 million prescriptions in 2013 to 14 million prescriptions dispensed through outpatient retail pharmacies in 2017. Prescriptions dispensed for buprenorphine products labeled with indications for the management of pain (such as transdermal buprenorphine) increased to approximately 701,000 prescriptions dispensed in 2017. Of the products indicated for pain management, 87% of prescriptions were dispensed for the transdermal patch formulation of buprenorphine, while 13% of prescriptions were dispensed for the buccal film formulation. Based on office-based physician survey data in 2017, buprenorphine-containing products labeled for opioid dependence (such as buprenorphine-naloxone) are also being mentioned for pain management; however, reported mentions were low at approximately 5% of the total buprenorphine products labeled for opioid dependence.

1 INTRODUCTION

1.1 BACKGROUND

The new drug application in discussion is a buprenorphine sublingual spray formulation with no abuse-deterrent properties. The proposed indication is for the management of moderate-to-severe acute pain where an opioid analgesic is appropriate. As of 2017, there are three single-ingredient buprenorphine products with FDA-approved labeling indicated for the treatment of pain – Belbuca (buccal film), Buprenex (injection), and Butrans (transdermal patch). The purpose of this Advisory Committee meeting is to discuss the risks, benefits, and approvability of this product in the current opioid analgesic market. In preparation for this upcoming meeting, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has requested Division of Epidemiology II (DEPI II) to provide overall utilization data for buprenorphine-containing products to provide informational context and background information; particularly, to ascertain the extent of use of these products for pain management.

1.2 PRODUCT INFORMATION[i]

Buprenorphine is a sublingual spray designed to be available in the following strengths, 0.125mg, 0.25mg, and 0.5mg. There are currently no buprenorphine products available in a sublingual spray formulation in the market. The proposed indication is for the management of moderate-to-severe acute pain where an opioid analgesic is appropriate.

1.3 MOLECULES INCLUDED

Table 1 provides the list of all buprenorphine and buprenorphine-naloxone products indicated for the treatment of opioid dependence or pain management. For this drug utilization review, we only focused on non-injectable buprenorphine formulations.

Buprenorphine Single-Ingredient Products				
Brand Name	**Dosage Form/Route**	**Indications**	**Strengths**	**Initial U.S Approval**
Belbuca	Film/Buccal	Pain	▪ 75mcg ▪ 150mcg ▪ 300mcg ▪ 450mcg ▪ 600mcg ▪ 750mcg ▪ 900mcg	October 23, 2015
(Buprenex)	Injectable/Injection	Pain	▪ 0.3mg/mL	December 29, 1981
Butrans and generics*	Extended-Release Film/Transdermal	Pain	▪ 5mcg/hr ▪ 7.5mcg/hr ▪ 10mcg/hr ▪ 15mcg/hr ▪ 20mcg/hr	June 30, 2010
(Probuphine)	Implant/Implantation	Opioid Dependence	▪ 80mg/implant	May 26, 2016
(Sublocade)	Solution, Extended-Release/Subcutaneous	Opioid Dependence	▪ 100mg/0.5mL ▪ 200mg/1mL	November 30, 2017
Subutex	Tablet/ Sublingual	Opioid Dependence	▪ 2mg ▪ 8mg	October 8, 2002
Buprenorphine generics	Tablet/ Sublingual	Opioid Dependence	Multiple	Multiple
	Injectable/Injection	Pain	Multiple	
Buprenorphine-Naloxone Combination Products				
Brand Name	**Dosage Form/Route**	**Indications**	**Strengths**	**Initial U.S Approval**
Bunavail	Film/Buccal	Opioid Dependence	▪ 2.1mg/0.3mg ▪ 4.2mg/0.7mg ▪ 6.3mg/1mg	June 6, 2014
Suboxone	Film/Buccal, Sublingual	Opioid Dependence	▪ 2mg/0.5mg ▪ 4mg/1mg ▪ 8mg/2mg ▪ 12mg/3mg	August 30, 2010
Zubsolv	Tablet/Sublingual	Opioid Dependence	▪ 0.7mg/0.18mg ▪ 1.4mg/0.36mg ▪ 2.9mg/0.71mg ▪ 5.7mg/1.4mg ▪ 8.6mg/2.1mg ▪ 11.4mg/2.9mg	July 3, 2013
Buprenorphine-Naloxone generics	Tablet/Sublingual	Opioid Dependence	Multiple	Multiple

* Authorized generic[1] of Butrans enter the market in May 2017[ii]

Note that the following buprenorphine-containing products in parenthesis were NOT included in this review:

†Buprenex and Sublocade were injectable products not included in our analyses .

††Probuphine (buprenorphine) implant is indicated for treatment of OUD. Only available under a restricted distribution program, therefore it is not included in our analyses.[iii]

[1] The term "authorized generic" drug is most commonly used to describe an approved brand name drug that is marketed without the brand name on its label. Other than the fact that it does not have the brand name on its label, it is the exact same drug product as the branded product. An authorized generic may be marketed by the brand name drug company, or another company with the brand name company's permission. In some cases, even though it is the same as the brand name product, a company may choose to sell the authorized generic at a lower cost than the brand name drug.

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Detailed description and limitation of the databases are included in Appendix 2.

2.1 DATA SOURCES USED

The IQVIA, National Sales Perspectives™ (NSP) database was used to determine the retail, non-retail, and mail-order channels of distribution for buprenorphine-containing products.

The IQVIA, National Prescription Audit™ (NPA) database was used to obtain nationally estimated number of prescriptions dispensed for buprenorphine-containing products, stratified by labeled indications for either pain management or treatment of opioid dependence, from U.S. outpatient retail pharmacies, from 2013-2017, annually.

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel, a U.S. office-based physician survey database was used to obtain diagnoses codes associated with the use of buprenorphine-containing products. Diagnoses data by number of drug use mentions[2] were captured based on International Classification of Diseases (ICD-10-CM) codes and 95% confidence intervals were applied to the estimates.

3 RESULTS

3.1 SETTINGS OF CARE

Sales data for 2017 indicated that 93% of buprenorphine products (single-ingredient buprenorphine and combination buprenorphine-naloxone) excluding injectable were distributed to outpatient retail pharmacies[iv]. Thus, only outpatient retail pharmacy utilization patterns were examined. Mail-order/specialty pharmacy and non-retail pharmacy settings data were not included in this analysis.

In the same year, sales data indicated that the majority (76% of vials/ampules sold) of injectable buprenorphine-containing products were distributed to the miscellaneous/other channels which include prisons, universities, and others. As a result, our analysis did not include injectable buprenorphine-containing products because the current proprietary drug utilization databases available to the Agency do not have comprehensive capture or visibility into those settings of care.

3.2 PRESCRIPTION DATA

Table 3.2.1 in Appendix 1 provide the nationally estimated number of prescriptions dispensed for total buprenorphine products (single-ingredient and combination buprenorphine-naloxone), stratified by labeled indication for pain management or treatment of opioid dependence, from U.S. outpatient retail pharmacies, from 2013 through 2017, annually. The total number of prescription dispensed for buprenorphine products increased 41%, from 10 million prescriptions in 2013 to 14 million prescriptions dispensed in 2017.

In 2017, of the total buprenorphine products, about 5% of dispensed prescriptions were for products indicated for pain management, while most prescriptions dispensed were still for products indicated for

[2] A "drug use mention" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

treatment of opioid dependence. Of the products indicated for pain management, approximately 87% of prescriptions were dispensed for the transdermal patch formulation of buprenorphine. Approximately 13% of prescriptions were dispensed for the buccal film formulation of buprenorphine.

3.3 DIAGNOSIS DATA

Table 3.3.1 in Appendix 1 provides the diagnosis codes (ICD-10) in terms of drug use mentions[3] associated with the utilization of buprenorphine-containing products, stratified by labeled indication for pain management or treatment of opioid dependence, as reported by a U.S. office-based physician survey database. In 2017, of the buprenorphine products indicated for treatment of opioid dependence, most the diagnoses were associated with opioid related disorders with approximately 91% of drug use mentions, followed by diagnoses associated with pain (i.e., neoplasms, diseases of the musculoskeletal system etc.) at approximately 5% of drug use mentions.

In the same year, of the buprenorphine products indicated for pain management, approximately 57% of drug use mentions were for various diagnoses associated with pain, followed by approximately 34% of drug use mentions for diagnoses associated with opioid related disorders.

4 DISCUSSION

The focus of this drug utilization analysis is to provide an analysis of utilization patterns in support of the upcoming advisory committee meeting to discuss an NDA for buprenorphine sublingual spray with no abuse-deterrent properties. Of note, there are currently no buprenorphine products that are available as a sublingual spray formulation in the market.

Prescriptions dispensed for buprenorphine products increased 41% over the 5-year study period. The steady increase in the overall utilization of these products may be attributed to multiple factors such as 1) an increased prevalence of individuals addicted to opioids, 2) increasing admissions into opioid treatment facilities/programs, and 3) multiple regulatory actions from the federal, state, and local level in response to the continuing opioid epidemic in the nation. However, this review did not assess the reasons behind the trends in utilization.

U.S. office-based physician survey data was used to describe the indications of use for buprenorphine by prescribers, specifically the products labeled for treatment of opioid dependence. Of note, not all prescribers can prescribe buprenorphine for treatment of opioid dependence. On October 17, 2000, Congress passed the Drug Addiction Treatment Act (DATA) which permitted qualified physicians to treat opioid dependence with schedules III-V narcotic controlled substances that have been approved by the Food and Drug Administration (FDA) for that indication.[v] Qualified physicians are permitted to dispense or prescribe buprenorphine for the treatment of opioid dependence in outpatient settings. In the past, medication-assisted treatments (MATs) were only available in opioid treatment facilities (OTF) such as methadone clinics. However, a physician can prescribe buprenorphine for pain management off-label and not be certified by the Drug Enforcement Agency (DEA). Recent literature reviews have shown that there is off-label use of buprenorphine products for chronic pain management.[vi,vii] Our analysis of survey data indicates that most mentions for buprenorphine products labeled for treatment of opioid dependence were associated with diagnoses of mental and behavioral disorders while approximately 5% of mentions were

[3] The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

for diagnoses associated with pain. It appears that prescribers may use buprenorphine products labeled for treatment of opioid dependence for pain management; however, the use is infrequent based on the low number of drug use mentions reported. In general, survey data are best used to identify the typical uses for the products reported by physicians in an office-based setting and thus may not represent other settings where buprenorphine may be prescribed, such as opioid treatment clinics, pain clinics, and hospitals.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that buprenorphine-containing products are distributed primarily to the outpatient retail pharmacy setting based on the IQVIA, National Sales Perspectives™ sales data in 2017. As a result, we focused our analysis only on the outpatient retail pharmacy settings; thus, these estimates may not apply to other settings of care in which these products are used (i.e., mail-order pharmacies, clinics, non-federal hospitals, etc.)

5 CONCLUSIONS

In preparation for the upcoming Advisory Committee meeting to discuss a new application for a sublingual spray formulation of buprenorphine, this review provides the current drug utilization patterns of buprenorphine and buprenorphine-naloxone products currently marketed in the U.S. with labeled indications for either pain management or treatment of opioid dependence to provide context to generate discussions. Prescriptions dispensed for buprenorphine products with labeled indication for pain management has increased through the examined time-period to approximately 701,000 prescriptions in 2017. Of the products indicated for pain management, approximately 87% of prescriptions were dispensed for the transdermal patch formulation of buprenorphine, while approximately 13% of prescriptions were dispensed for the buccal film formulation.

6 APPENDICES

6.1 APPENDIX 1: TABLES AND FIGURES

Table 3.2.1

Nationally estimated number of prescriptions dispensed for buprenorphine-containing products, stratified by labeled indications for pain management or treatment of opioid dependence, from U.S. outpatient retail pharmacies

	2013		2014		2015		2016		2017	
	TRx	Share	TRx	Share	TRx	Share	TRx	Share	TRx	Share
Total Buprenorphine Market	**9,986,243**	***100.0%***	**11,247,647**	***100.0%***	**12,053,458**	***100.0%***	**12,902,510**	***100.0%***	**14,118,387**	***100.0%***
Pain	**497,697**	***5.0%***	**613,086**	***5.5%***	**643,634**	***5.3%***	**696,025**	***5.4%***	**701,103**	***5.0%***
Buprenorphine	497,697	*100.0%*	613,086	*100.0%*	643,634	*100.0%*	696,025	*100.0%*	701,103	*100.0%*
Belbuca	0	*0.0%*	0	*0.0%*	0	*0.0%*	50,575	*7.3%*	90,133	*12.9%*
Butrans	497,697	*100.0%*	613,086	*100.0%*	643,634	*100.0%*	645,450	*92.7%*	504,164	*71.9%*
Buprenorphine generics transdermal	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	106,806	*15.2%*
Opioid Dependence	**9,488,546**	***95.0%***	**10,634,561**	***94.5%***	**11,409,824**	***94.7%***	**12,206,485**	***94.6%***	**13,417,284**	***95.0%***
Buprenorphine	1,616,849	*17.0%*	1,954,812	*18.4%*	2,071,403	*18.2%*	2,189,411	*17.9%*	2,386,356	*17.8%*
Subutex	240	*0.0%*	196	*0.0%*	75	*0.0%*	60	*0.0%*	71	*0.0%*
Buprenorphine generics	1,616,609	*100.0%*	1,954,616	*100.0%*	2,071,328	*100.0%*	2,189,351	*100.0%*	2,386,285	*100.0%*
Buprenorphine-Naloxone	7,871,697	*83.0%*	8,679,749	*81.6%*	9,338,421	*81.8%*	10,017,074	*82.1%*	11,030,928	*82.2%*
Bunavail	0	*0.0%*	2,734	*0.0%*	66,348	*0.7%*	109,402	*1.1%*	86,095	*0.8%*
Suboxone	6,988,212	*88.8%*	6,837,764	*78.8%*	7,030,215	*75.3%*	7,492,005	*74.8%*	7,751,898	*70.3%*
Zubsolv	23,482	*0.3%*	264,941	*3.1%*	521,271	*5.6%*	576,836	*5.8%*	555,851	*5.0%*
Buprenorphine-Naloxone generics	860,003	*10.9%*	1,574,310	*18.1%*	1,720,587	*18.4%*	1,838,831	*18.4%*	2,637,084	*23.9%*

Source: IQVIA, National Prescription Audit™ (NPA). January 2013- December 2017. Data extracted March 2018.

Table 3.3.1

Diagnoses (ICD-10) in terms of drug use mentions* associated with the use of buprenorphine-containing products as reported by office-based physician surveys, 2017

	2017		
	Uses	Share (%)	95% CI
Buprenorphine products labeled for opioid dependence	5,546,000	*100.0%*	5,106,000 — 5,986,000
F11 Opioid related disorders	5,054,000	*91.1%*	4,633,000 — 5,474,000
M54 Dorsalgia	201,000	*3.6%*	117,000 — 285,000
F19 Other psychoactive substance related disorders	102,000	*1.8%*	42,000 — 161,000
R52 Pain, unspecified	54,000	*1.0%*	11,000 — 97,000
G89 Pain, not elsewhere classified	40,000	*0.7%*	2,000 — 77,000
Z79 Long term (current) drug therapy	34,000	*0.6%*	0 — 69,000
K04 Diseases of pulp and periapical tissues	16,000	*0.3%*	0 — 40,000
O99 Oth maternal diseases classd elsw but compl preg/chldbrth	14,000	*0.3%*	0 — 36,000
E13 Other specified diabetes mellitus	14,000	*0.3%*	0 — 36,000
M16 Osteoarthritis of hip	8,000	*0.1%*	0 — 25,000
F10 Alcohol related disorders	6,000	*0.1%*	0 — 21,000
D86 Sarcoidosis	4,000	*0.1%*	0 — 15,000
Buprenorphine products labeled for pain management	407,000	*100.0%*	288,000 — 526,000
F11 Opioid related disorders	128,000	*31.5%*	61,000 — 195,000
M54 Dorsalgia	68,000	*16.6%*	19,000 — 116,000
C67 Malignant neoplasm of bladder	33,000	*8.2%*	0 — 67,000
O99 Oth maternal diseases classd elsw but compl preg/chldbrth	21,000	*5.1%*	0 — 47,000
M79 Oth and unsp soft tissue disorders, not elsewhere classified	19,000	*4.7%*	0 — 45,000
M16 Osteoarthritis of hip	14,000	*3.5%*	0 — 37,000
Z01 Encntr for oth sp exam w/o complaint, suspected or reprtd dx	14,000	*3.5%*	0 — 37,000
M12 Other and unspecified arthropathy	14,000	*3.5%*	0 — 37,000
M50 Cervical disc disorders	14,000	*3.4%*	0 — 36,000
M51 Thoracic, thoracolum, and lumbosacral intvrt disc disorders	11,000	*2.8%*	0 — 31,000
M47 Spondylosis	11,000	*2.8%*	0 — 31,000
M48 Other spondylopathies	10,000	*2.5%*	0 — 29,000
G89 Pain, not elsewhere classified	8,000	*2.1%*	0 — 26,000
F19 Other psychoactive substance related disorders	8,000	*2.0%*	0 — 25,000
R51 Headache	6,000	*1.4%*	0 — 20,000
Z96 Presence of other functional implants	5,000	*1.3%*	0 — 19,000
M96 Intraop and postproc comp and disorders of ms sys, NEC	5,000	*1.2%*	0 — 18,000
M17 Osteoarthritis of knee	4,000	*1.1%*	0 — 16,000
C50 Malignant neoplasm of breast	4,000	*0.9%*	0 — 15,000
C18 Malignant neoplasm of colon	3,000	*0.8%*	0 — 14,000
G90 Disorders of autonomic nervous system	3,000	*0.8%*	0 — 14,000
S32 Fracture of lumbar spine and pelvis	2,000	*0.5%*	0 — 10,000

Source: Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel, 2017. Data extracted March 2018.

*The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

IQVIA, National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IQVIA National Prescription Audit™

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 – 75% (varies by class and geography) of mail service pharmacies and approximately 70 – 85% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

Syneos Health Research & Insights, LLC., TreatmentAnswers™

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialist physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns. Given that statistical accuracy increases as the projected number of records increase, data below 100,000 projected mentions or occurrences may not represent national level trends, because results below this threshold represent insufficient raw physician responses prior to applied projection factors. Data below 100,000 (mentions or occurrences) do not represent sufficient portion of the population and is not representative of actual physician prescribing habits at a national level.

6.3 REFERENCES

[i] DARRTS NDA 209588, New/NDA; Form 3674; User Fee/Coversheet, Supporting Document 1/eCTD0000, dated 9/28/2017.

[ii] Food and Drug Administration. (2017, December 29). FDA List of Authorized Generic Drugs. Retrieved from https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm126391.htm

[iii] U.S. Food and Drug Administration: Probuphine Prescribing Information and REMs Program Accessed March 2, 2018. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/rems/Probuphine_2017-04-19_Full.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204442Orig1s000lbl.pdf.

[iv] IQVIA, National Sales Perspectives™ (NSP). Year 2017. Data extracted April 2018.

[v] Drug Enforcement Administration. "DEA Requirements for DATA Waived Physicians (DWPs)." *DEA Diversion Control Division*, www.deadiversion.usdoj.gov/pubs/docs/dwp_buprenorphine.htm.

[vi] Chen, Kelly Y., et al. "Buprenorphine–Naloxone Therapy in Pain Management." *Anesthesiology*, vol. 120, no. 5, 2014, pp. 1262-1274.

[vii] Rosen, Kristen, et al. "Sublingual Buprenorphine for Chronic Pain." *The Clinical Journal of Pain*, vol. 30, no. 4, 2014, pp. 295-300.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	**May 22, 2018**
To:	**Members of the Joint Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management (DSaRM) Advisory Committee**
From:	**Division of Risk Management (DRISK)** **Office of Medication Error Prevention and Risk Management (OMEPRM)** **Office of Surveillance and Epidemiology (OSE)**
Drug Name:	**Buvaya (buprenorphine sublingual spray 0.125 mg, 0.25 mg, 0.5 mg)**
Application Number:	**NDA 209588**
Subject:	**Risk Evaluation and Mitigation Strategy (REMS)**

The Agency continues to monitor use, misuse, and abuse of prescription opioid analgesics. Of the approximately 196 million prescriptions for opioid analgesics dispensed from U.S. outpatient retail pharmacies in 2017, approximately 91% were for immediate-release (IR) formulations.[1] Consistent with this wide availability, recent data indicate that IR opioid analgesics continue to be associated with large numbers of intentional abuse exposure calls to poison control centers and reports of recent abuse among individuals entering treatment for substance use disorders.[2]

In accordance with section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), the FDA has determined that a REMS is necessary for opioid analgesics that are expected to be used in the outpatient setting to ensure the benefits of the drugs outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing,

[1] IQVIA National Prescription Audit (NPA). Year 2017. Extracted February 2018.

[2] Iwanicki JL, Severtson SG, McDaniel H, et al. Abuse and Diversion of Immediate Release Opioid Analgesics as Compared to Extended Release Formulations in the United States. PLoS One. 2016;11(12):e0167499.

abuse, and misuse. On September 28, 2017, FDA notified all application holders of immediate-release (IR) opioid analgesics that are expected to be used in the outpatient setting that are not already covered by another REMS program informing them of this requirement. The letter further informed the application holders that in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs for drugs with similar serious risks, FDA determined that all application holders should work together, using the existing infrastructure of the Extended-Release/Long-Acting (ER/LA) Opioid Analgesics REMS, to develop a shared system Opioid Analgesics REMS.

The Opioid Analgesic REMS is intended to reduce risks and improve safe use of opioid analgesics while continuing to provide access to these medications for patients in pain. The proposed Opioid Analgesic REMS must include the following:

Medication Guide: FDA has determined that opioid analgesics used in in the outpatient setting poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Buvaya. FDA has determined that Buvaya is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Buvaya. FDA has also determined that Buvaya is a product for which patient labeling could help prevent serious adverse events. The Medication Guide should have both common content applicable to all opioid analgesics, as well as product specific information that is necessary for safe and effective use of the drug.

Elements to Assure Safe Use: Elements to assure safe use are necessary to mitigate the serious risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse, listed in the labeling of the drug. The REMS must include elements to mitigate these risks, including at least the following:

1. The applicant must ensure that training is provided to prescribers who prescribe Buvaya and other healthcare providers involved in the treatment and monitoring of patients with pain. See draft FDA Blueprint Appendix A. The training must include successful completion of a knowledge assessment and proof of successful program completion. To minimize the burden on the healthcare delivery system, FDA expects applicant holders to meet this requirement by providing educational grants to accredited independent continuing education (CE) providers who offer training to prescribers at no or nominal cost.

2. The applicant must provide to health care providers involved in the treatment and monitoring of patients with pain information that those health care providers can use to educate patients in the safe use, storage, and disposal of opioids.

3. The applicant must inform prescribers and other health care providers involved in the treatment and monitoring of patients with pain (e.g., pharmacists, nurses) of the existence of the REMS and the need to successfully complete the necessary training.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be at 6 months and 1 year and then annually from the date of the approval of this REMS.

Because Buvaya is an immediate-release opioid analgesic expected to be used in the outpatient setting, FDA has determined that this product will need a REMS to ensure that the benefits outweigh the risks and should be part of the shared system Opioid Analgesic REMS.

Attachments: Appendix A

Appendix A

Introduction
FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain (January 2018)

Background

In July 2012, FDA approved the Extended-Release and Long-Acting (ER/LA) Opioid Analgesic Risk Evaluation and Mitigation Strategy (ER/LA REMS) to ensure that the benefits of ER and LA opioid analgesics used in the outpatient setting outweigh the risks. That REMS is undergoing modification and, once approved, the new *Opioid Analgesic REMS* will include, in addition to ER/LA opioid analgesics, all immediate-release (IR) opioids used in the outpatient setting that are not already covered by another REMS program. The *Opioid Analgesic REMS* is intended to support other national efforts underway to address the misuse and abuse of prescription opioid analgesics.

As part of the Opioid Analgesic REMS, all opioid analgesic companies must provide the following:

- Education for healthcare providers (HCPs) who participate in the treatment and monitoring of pain. For the purpose of the Opioid Analgesic REMS, HCPs will include not only prescribers, but also HCPs who participate in the treatment and monitoring of patients who receive opioid analgesics, including pharmacists and nurses.
    - Education will be offered through accredited continuing education (CE) activities. These activities will be supported by unrestricted educational grants from opioid analgesic companies.
- Information for HCPs to use when counseling patients about the risks of ER, LA, and IR opioid analgesic use.

To facilitate the development of CE educational materials and activities as part of the Opioid Analgesic REMS, FDA has also revised the education blueprint — originally designed to facilitate development of CE educational materials under the ER/LA REMS. FDA has completed the revisions to the *FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* (FDA Blueprint), following publication of a draft version and consideration of received public comments, and is making it available in advance of the approval of the Opioid Analgesic REMS.

The revised FDA Blueprint contains a high-level outline of the core educational messages that will be included in the educational programs developed under the Opioid Analgesic REMS. The FDA Blueprint focuses on the fundamentals of acute and chronic pain management and provides

a contextual framework for the safe prescribing of opioid analgesics. The core messages are directed to prescribers, pharmacists, and nurses, but are also relevant for other HCPs who participate in the management of pain. The course work is not intended to be exhaustive nor a substitute for a more comprehensive pain management course.

Accrediting bodies and CE providers will ensure that the CE activities developed comply with the standards for CE of the Accreditation Council for Continuing Medical Education, [3,4] or another CE accrediting body, depending on the target audience's medical specialty or health care profession.

FDA is making the FDA Blueprint, which will be approved as part of the Opioid Analgesic REMS, available on the REMS@FDA Website (www.fda.gov/REMS), where it will remain posted for use by CE providers as they develop the CE materials and activities. A list of the REMS-compliant CE activities supported by unrestricted educational grants from the opioid analgesic companies to accredited CE providers will be made available when the Opioid Analgesics REMS is approved.

Reasons Why HCP Education Is So Important

Adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse of opioids have emerged as major public health problems. It is critical that HCPs are knowledgeable about the risks associated with opioid analgesics as they pertain to their patients as well as from a public health perspective. The data continue to show problems associated with prescription opioid analgesics.

- In 2015, over 52,404 Americans died from drug poisonings, and of these, 24% or approximately 12,570 deaths involved opioid analgesics.[5]

- Based on the 2016 National Survey on Drug Use and Health (NSDUH), an estimated 11.5 million Americans aged 12 or older misused a prescription pain reliever in the past year — with hydrocodone, oxycodone, and codeine products being the most commonly reported.[6]

[3] Accreditation Council for Continuing Medical Education. 2016. Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria. Accessed on February 20, 2017.

[4] Accreditation Council for Continuing Medical Education. 2016. Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support. Accessed on February 20, 2017.

[5] See https://www.cdc.gov/nchs/data/factsheets/factsheet_drug_poisoning.pdf. Accessed October 2017.

[6] Substance Abuse and Mental Health Services Administration. (2017). *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from (https://www. samhsa.gov/data/).

- The most common source of pain relievers in the 2016 NSDUH was "a friend or relative" (53%). "A physician's prescription" was the second most common source, reported by approximately 35% of respondents.[7]

The nation is facing competing public health problems: the need to adequately treat a large number of Americans with acute and chronic pain and an epidemic of prescription opioid abuse. Described in the 2011 report by the National Academies of Science, Engineering, and Medicine (NASEM), *Relieving PAIN in America, A Blueprint for Transforming Prevention, Care, Education, and Research*,[8] 100 million Americans suffer from common chronic pain conditions; fewer than half of Americans undergoing surgery report adequate pain relief; and 60% of Americans visiting the emergency department with acute painful conditions receive analgesics.

The increasing availability of prescription opioids since the 1990's has been accompanied by an epidemic of opioid addiction. The Substance Abuse and Mental Health Services Administration's *National Survey of Drug Use and Health* has shown that most people who use prescription analgesics "nonmedically" obtain them from friends or family, who it is believed obtained the drugs from a doctor's prescription.[9]

Some of the immediate consequences of untreated or undertreated pain include reduced quality of life, impaired physical function, and high economic costs. Chronic pain is associated with physical disability, fear, anger, depression, anxiety, and reduced ability to carry out the roles of family member, friend, and employee. It is critically important that HCPs have all the information they need to properly treat their patients and safely manage their pain. It is also critical for HCPs to understand when opioid analgesics are the appropriate treatment and how to implement best practices to ensure their patients' safety. A 2017 report by NASEM, *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*, describes the challenges of providing adequate pain management and calls for the establishment of "comprehensive pain education materials and curricula" for HCPs.[10]

Having broad knowledge about how to manage patients with pain can create the opportunity for HCPs to consider ***all*** options for pain management, including nonpharmacologic and non-opioid pharmacologic options, and to reserve opioids for when non-opioid options are inadequate and when the benefits of the opioids are expected to outweigh the risks. This information can also aid HCPs in identifying and intervening when encountering obstacles that may reduce access to nonpharmacological and non-opioid medication options. Fully informed HCPs can help contribute to national efforts to address opioid addiction and reduce opioid misuse and abuse.

[7] Ibid.

[8] http://www.nationalacademies.org/hmd/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx. Accessed October 2017.

[9] https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf, Table 6.53A. Accessed October 2017.

[10] http://nationalacademies.org/hmd/Reports/2017/pain-management-and-the-opioid-epidemic.aspx. Accessed October 2017.

FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain

Purpose of the Opioid Analgesic REMS HCP Educational Effort

Following completion of educational activities under the Opioid Analgesic REMS, HCPs should be knowledgeable about the following.

- The fundamental concepts of pain management, including definitions and mechanisms of pain
- How to assess patients in pain, identifying risk factors for abuse and addiction
- The range of therapeutic options for managing pain, including nonpharmacologic approaches and pharmacologic (non-opioid and opioid analgesics) therapies
- How to integrate opioid analgesics into a pain treatment plan individualized to the needs of the patient
- How to safely and effectively manage patients on opioid analgesics in the acute and chronic pain settings, including initiating therapy, titrating, and discontinuing use of opioid analgesics
- How to counsel patients and caregivers about the safe use of opioid analgesics, including proper storage and disposal
- How to counsel patients and caregivers about the use of naloxone for opioid overdose
- When referral to a pain specialist is appropriate
- The fundamental elements of addiction medicine
- How to identify and manage patients with opioid use disorder

In addition, HCPs will gain an understanding of current information about safe opioid practices and about current Federal[11] and State regulations, national guidelines,[12] and professional organization[13] and medical specialty guidelines on treating pain and prescribing opioids. HCPs will also become familiar with the use of naloxone and with the importance of its availability for use by patients and caregivers both in the community and in the home.

Section 1: The Basics of Pain Management

I. THE NEED FOR COMPREHENSIVE PAIN EDUCATION

[11] For example, see https://www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt htm and https://www.deadiversion.usdoj.gov/21cfr/21usc/829.htm. Accessed October 2017.

[12] For example, see Dowell D, Haegerich TM, Chou R. 2016. CDC Guideline for Prescribing Opioids for Chronic Pain –United States, 2016. MMWR Recomm Rep 2016; 65 (No.RR-1): 1-49. Accessed February 22, 2017.

[13] For example, see 2013 Federation of State Medical Boards Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain. Accessed February 22, 2017.

The FDA Blueprint was developed with two, competing, U.S. public health concerns in mind, (1) the large number of Americans with acute and chronic pain and (2) the epidemic of prescription opioid abuse.

1. Providing health care providers (HCPs) with a thorough understanding of the risks associated with opioids can give HCPs the opportunity to consider all pain management options, including nonpharmacologic and pharmacologic options, prescribing opioids only when non-opioid options are inadequate and when the benefits of using an opioid are expected to outweigh the risks.

2. When HCPs have information about the risks of opioid misuse and abuse, they will be better able to create opportunities for patient counseling and other strategies to reduce these risks.

II. DEFINITIONS AND MECHANISMS OF PAIN

Pain can be categorized according to its duration, underlying pathophysiology of the original insult, and whether a central sensitization component has developed. An understanding of these different categorizations can help direct therapeutic decisions.

When defining, and classifying pain, the following should be taken into consideration:

1. Biological significance of pain (survival value)
2. Relationship between acute and chronic pain
3. Distinction between nociceptive and neuropathic pain

III. ASSESSING PATIENTS IN PAIN

HCPs should be knowledgeable about how to assess each patient when initiating a pain management program. When appropriate, evidence-based, standardized scales and tools can be used to document pain characteristics and guide management decisions throughout treatment, noting the strengths and weaknesses regarding specificity and sensitivity of these scales.

Important elements of an initial assessment should include the following:

1. Patient history

2. Screening tools to evaluate the known risk factors for development of chronic pain after an acute injury or disease

3. Screening tools to evaluate the known risk factors for opioid use disorder (OUD) or abuse

4. Queries of state prescription drug monitoring programs (PDMPs)

5. Pain assessment scales/tools

6. Functional assessment scales

7. Physical examination

8. Family planning, including information about use of contraceptives, pregnancy intent/status and plans to breastfeed

9. Psychological and social evaluation

10. Diagnostic studies when indicated

Section 2: Creating the Pain Treatment Plan

A comprehensive pain treatment plan should be developed and customized to the needs of the individual patient. The treatment plan should include the types of therapies planned, the goals of treatment, and an explanation of the patient and prescriber roles and responsibilities. The goals of treatment should be based on (1) expected outcomes of pain reduction; (2) improvement in functional outcomes impaired by pain (e.g., activities of daily living); and (3) quality of life.

If HCPs encounter potential barriers to managing patients with pharmacologic and/or nonpharmacologic treatment options, such as lack of insurance coverage or inadequate availability of certain HCPs who treat patients with pain, attempts should be made to address these barriers. The overall treatment approach and plan should be well documented in the patient record, including written agreements and informed consent/patient provider agreements (PPAs) that reinforce patient-provider responsibilities and avoid punitive tones.

I. COMPONENTS OF AN EFFECTIVE TREATMENT PLAN

1. The goals of treatment, including the degree of improvement in pain and function when function has been impaired by pain

2. Possible constituents of the treatment plan, including nonpharmacologic approaches and pharmacologic therapies

3. Patient/prescriber/health care team interactions, including
   - Patient responsibilities/compliance with the plan
   - Responsibilities of the prescriber and health care team, including patient monitoring
   - Plans for reviewing functional goals
   - Use of supplemental medication for intermittent increases in pain
   - Use of PPAs

II. GENERAL PRINCIPLES OF NONPHARMACOLOGIC APPROACHES

Pain can arise from a wide variety of causes. There are a number of nonpharmacologic and self-management treatment options that have been found to be effective alone or as part of a comprehensive pain management plan, particularly for musculoskeletal pain and chronic pain. Examples include, but are not limited to, psychological, physical rehabilitative, and surgical approaches, complementary therapies, and use of approved/cleared medical devices for pain management. HCPs should be knowledgeable about the range of treatment options available, the types of pain that may be responsive to those options, and when they should be used as part of a multidisciplinary approach to pain management. HCPs should also be aware that not all nonpharmacologic options have the same strength of evidence to support their utility in the management of pain, and some may be more applicable for some conditions than others.

III. GENERAL PRINCIPLES OF PHARMACOLOGIC ANALGESIC THERAPY

A variety of analgesics, including non-opioid and opioid medications, are available for use to manage pain symptoms. HCPs should be well informed about the range of analgesics available and the types of pain that may be responsive to those analgesics.

A. Non-opioid medications

When using non-opioid medications in pain management, HCPs should be knowledgeable about the following:

1. Mechanism of action of analgesic effect
2. Indications and uses for pain management
3. Routes of administration and formulations used in pain management
4. Initial dosing, dose titration, dose tapering (when appropriate) for analgesia
5. Contraindications
6. Adverse events, with emphasis on labeled warnings
7. Drug interactions — both pharmacodynamic and pharmacokinetic

B. Opioid analgesic medications

Opioid analgesic medications can be used successfully as a component of pain management. However, opioids carry risks not present with most non-opioid analgesics, specifically the risks of addiction, abuse and misuse, which can lead to respiratory depression, overdose and death. Therefore, it is the responsibility of HCPs to be knowledgeable, not just about the presence of such risks, but about how to weigh these risks before prescribing an opioid and about how to properly manage patients who are prescribed opioids, both for short-term and long-term use. When using opioid analgesics as part of pain management, HCPs should be knowledgeable about the following:

1. General precautions
    a. Even at prescribed doses, opioid analgesics carry the risk of misuse, abuse, opioid use disorder, overdose, and death

b. Importance of the appropriate use of PDMPs[14] and their use as a clinical decision support tool
c. DSM-5 (R) criteria (or the most recent version) for OUD and the concepts of abuse (taking an opioid to get high) vs. misuse (taking more than prescribed for pain or giving to someone else in pain)[15]
d. The concepts of tolerance and physiological dependence and how they differ from OUD (addiction)
e. Recognition that some opioid analgesics (e.g., Transmucosal Immediate Release Fentanyl products, some ER/LA products) are safe only for opioid-tolerant patients

2. Mechanism of action and analgesic effect

3. Types of opioids (full agonists, partial agonists)

4. Indications and uses for pain management

5. Range of opioid analgesic products available for pain management and their related safety concerns
   a. Routes of administration including oral, transmucosal, transdermal
   b. Release characteristics of immediate release (IR), extended-release (ER), long-acting (LA)
   c. Abuse-deterrent formulations (ADFs)
      - Definition of ADF based on the FDA guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling*[16]
      - Recognition that all ADFs have the same potential for addiction and overdose death as non-abuse-deterrent opioids
      - How to understand FDA-approved ADF product labeling

6. Initial dosing, dose titration, dose tapering (when appropriate) for analgesia
   a. Concepts and limitations of the conversion charts in labeling and the limitations of relative potency or equianalgesic dosing tables in literature
   b. Interindividual variability of response
   c. Special populations
      - Pregnant, postpartum, breastfeeding, and neonatal opioid withdrawal syndrome
      - Renal and hepatic impairment
      - Children and adolescents
      - Genetic and phenotypic variations
      - Older adults
      - Sleep disorders
      - Common and uncommon psychiatric disorders

[14] SAMHSA Prescription Drug Monitoring Programs: A Guide for Healthcare Providers accessed April 12, 2017.

[15] American Psychiatric Association DSM-5-Opioid Use Disorder Diagnostic Criteria accessed April 12, 2017.

[16] See FDA guidance for industry *Abuse-Deterrent Opioids —Evaluation and Labeling*. accessed April 12, 2017.

7. Contraindications

8. Adverse Events
    a. Medication errors
    b. Periods of greater risk for significant respiratory depression, including at treatment initiation and with dose increases
    c. Serious adverse drug reactions (including overdose and death)
    d. Labeled warnings
    e. Common adverse drug reactions

9. Drug interactions
    a. Pharmacokinetic interactions based on metabolic pathway
    b. Pharmacokinetic and pharmacodynamic interactions with alcohol
    c. Concerns with particular drug–drug interactions, including, but not limited to:
        - Benzodiazepines and other central nervous system depressants, including alcohol
        - Monoamine oxidase inhibitors
        - Antidiuretic hormone drugs

10. Key safety strategies for use with opioid medications
    a. Dosing instructions including daily maximum
    b. Safe storage to reduce risk of accidental exposure/ingestion by household contacts, especially children/teens and to reduce risk of theft
    c. Naloxone products for use in the home to reduce risk of overdose deaths in patients and household contacts
    d. Proper disposal of used (e.g., transdermal systems) and unused opioids
    e. Pain management after an opioid overdose
    f. Driving and work safety

IV. MANAGING PATIENTS ON OPIOID ANALGESICS

HCPs should be knowledgeable about the appropriate use of opioids in patients with acute and chronic pain, including the importance of balancing potential benefits with the risks of serious adverse outcomes such as overdose and death.

A. Initiating treatment with opioids — acute pain

1. Patient selection — consider when an opioid is an appropriate option and consult the PDMP
2. Dosing — as needed vs. around-the clock dosing, prescribing an appropriate quantity based on the expected duration of pain, i.e., the least amount of medication necessary to treat pain and for the shortest amount of time

3. Naloxone for home use — prescribe and discuss the use of naloxone products and the various means of administration

4. Screening tools for risk of abuse

B. Initiating treatment with opioids — chronic pain

1. Patient selection
   a. Differences in benefit and risk and expected outcomes for patients with chronic pain, palliative care, or end-of-life care
   b. Differences in initiating treatment in opioid nontolerant vs. opioid-tolerant patients

2. Dosing
   a. As needed vs. around-the-clock
   b. How to determine a safe initial dose
   c. Safe conversion from other opioids

3. Considerations in opioid selection
   a. IR or ER/LA
   b. Special precautions with methadone
   c. Products restricted to opioid-tolerant patients

4. When and how to use an opioid or non-opioid analgesic to supplement pain management

C. Ongoing management of patients on opioid analgesics

1. Periodic review of pain and functional goals

2. Review adverse events at each visit
   - Eliciting signs or symptoms of opioid abuse
   - Screening for endocrine function may be recommended
   - Importance of adverse event reporting and mechanisms to report

3. Review refill history/review PDMP

4. How to determine when an opioid analgesic is no longer necessary/beneficial

D. Long-term management

1. Evaluation of the patient with worsening pain for changes in underlying condition and for signs of OUD before increasing opioid dosage
2. Changing opioid medications
   - Concept of incomplete cross-tolerance when converting patients from one opioid to another
   - Concepts and limitations of the conversion charts in labeling and the limitations of relative potency or equianalgesic dosing tables in literature

3. Monitoring of patient adherence to the treatment plan, especially regarding misuse and abuse:
    - Perform medication reconciliation — recognize, document, and address aberrant drug-related behavior
    - Determine if nonadherence is due to inadequate pain management
    - Understand the utility and interpretation of urine drug testing (e.g., screening and confirmatory tests) and use as indicated
    - Screen and refer for substance use disorder treatment when concerns arise

E. How to recognize and intervene upon suspicion or identification of an OUD

HCPs should understand how to monitor patients taking opioid analgesics and identify the signs and symptoms of opioid misuse, abuse, and OUD and be knowledgeable about how to begin the process of intervention upon suspicion of an OUD.

F. When to consult with a pain specialist

HCPs should be knowledgeable about when referral to a pain management specialist is indicated, including identifying patients at high risk for OUD and patients unable to achieve adequate pain management.

G. Medically directed opioid tapering

HCPs should be knowledgeable about how to safely taper opioid analgesics, including how to recognize and manage signs and symptoms of opioid withdrawal. HCPs should be knowledgeable about the particular risks associated with tapering during pregnancy.

H. Importance of patient education

HCPs should recognize their role in reducing the risks associated with opioid analgesics through patient education at initiation of an opioid and throughout long-term management.

1. Inform patients about pain management expectations and managing pain through different pharmacologic and nonpharmacologic modalities.

2. Use the *Patient Counseling Document* and *Medication Guide* as part of discussion with patients and caregivers when prescribing opioid analgesics.

3. Counsel the patient about the following:
    a. Importance of adherence to prescribed dosing regimen
    b. Patients should use the least amount of medication necessary to treat pain and for the shortest amount of time
    c. The risk of serious adverse events that can lead to death
    d. The risk of addiction that can occur even when product is used as recommended

e. Known risk factors for serious adverse events, including signs and symptoms of overdose and opioid-induced respiratory depression, GI obstruction, and allergic reactions, among others
f. The most common side effects, along with the risk of falls, working with heavy machinery, and driving
g. When to call the prescriber (e.g., managing adverse events, ongoing pain)
h. How to handle missed doses
i. The importance of full disclosure of all medications and supplements to all HCPs and the risks associated with the use of alcohol and other opioids/benzodiazepines
j. Product-specific concerns, such as not to crush or chew ER products; transdermal systems and buccal films should not be cut, torn, or damaged before use, etc.
k. How to safely taper dose to avoid withdrawal symptoms
l. Safe storage and disposal, risks of theft by family members and household visitors
m. Never share any opioid analgesic with another person
n. How and when to use naloxone products and their various means of administration
o. Seeking emergency medical treatment if an opioid overdose occurs
p. How to report adverse events and medication errors to FDA (1-800-fda-1088 or via http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf)

V. ADDICTION MEDICINE PRIMER

HCPs should be knowledgeable about the basic elements of addiction medicine and be familiar with the definition, neurobiology, and pharmacotherapy of OUDs. In particular, stigmatizing or blaming language should be replaced with language that acknowledges that addiction, reclassified as *substance use disorder*[17] in the revised Diagnostic Statistical Manual–V, is a disease. The term *opioid use disorder* [18] should be used when referring to the use of opioids, rather than other substances.

It should also be noted that there may be a different approach with a patient who misuses an opioid analgesic by taking the product differently than prescribed for the purpose of managing pain, in contrast to the patient who abuses an opioid analgesic with the intent of getting high. HCPs should be familiar with the following:

1. The neurobiology of OUD (addictive cycle)

2. Use of screening tools to identify patients at risk, based on known risk factors, and to identify patients developing signs of opioid dependence or addiction as early as possible.

3. Management of OUD, including the types of pharmacologic and nonpharmacologic treatments available and when to refer to an addiction medicine specialist.

[17] Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association

[18] Id.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology Review

Date:	April 11, 2018
Reviewer:	Cynthia Kornegay, Ph.D. Division of Epidemiology II, (DEPI II) Office of Pharmacoepidemiology and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE)
Secondary Reviewer:	Jana McAninch, MD, MPH, MS DEPI II, OPE, OSE
Associate Director for Public Health Initiatives:	Judy Staffa, PhD, RPh Associate Director for Public Health Initiatives OSE
Subject:	Assessment of abuse-related issues associated with buprenorphine sublingual spray
Drug Name:	Buvaya
Application Type/Number:	NDA 209588
Applicant/sponsor:	Insys Corporation
OSE RCM #:	2018-454

CONTENTS

1. EXECUTIVE SUMMARY

Buprenorphine Sublingual Spray (NDA 209588), a novel dosage form of buprenorphine intended to treat moderate-to-severe acute pain, was submitted to FDA for approval on September 27, 2017 by Insys Corporation (sponsor). There will be an Advisory Committee Meeting to discuss this NDA on May 22, 2018. To support the committee, the Division of Anesthesia, Analgesia, and Addiction Products asked that the Office of Surveillance and Epidemiology (OSE) address some questions related to the formulation and indication.

In July 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) issued the report *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use* (NASEM 2017). The report suggests that a comprehensive approach to reviewing and approving opioids might involve assessing evidence of a product's potential for diversion and misuse, predicted risks to family members and society, and the likelihood of promoting transition to illicit drugs. Considering the novel combination of drug, dosage form, and indication, the Office of Surveillance and Epidemiology (OSE) has reviewed the epidemiologic data to help inform the committee's consideration of the risk-benefit balance of this buprenorphine product. Specifically, OSE reviewed the available literature and other data on the following:

- **Abuse of opioid sublingual spray dose forms:**
  The literature on these products was very limited. The single study found was a small, French study (N=160) of patients prescribed intranasal fentanyl. While the authors found that misuse was common in the study population, the non-U.S. setting and other significant limitations limit the level of evidence that it contributes to address the question.
- **Relative abuse risk of single-ingredient versus buprenorphine-naloxone (BNX) combination products:**
  The literature did not suggest a clear abuse preference for single ingredient buprenorphine products compared to BNX combination products. A complication in interpreting this literature is that populations using buprenorphine analgesic products and those using buprenorphine and BNX products for medication assisted therapy (MAT) for opioid use disorder (OUD) may have very different baseline risks and patterns of abuse.
- **The risk of abuse and overdose associated with the currently marketed buprenorphine analgesic products, Butrans (buprenorphine transdermal system, BTDS) and Belbuca:**
  In two studies that compared BTDS abuse to other buprenorphine and opioid analgesic formulations, BTDS had either the lowest rate or was among the lowest rates of abuse, even after estimates were adjusted for BTDS's relatively low prescription volume. Very few cases of abuse of Belbuca were identified, but it has been on the market for a relatively short period of time.
- **Abuse of buprenorphine analgesic products via injection**
  In studies that examined the different buprenorphine dose forms, the data were limited and inconsistent regarding whether injection was more or less common in abuse of BTDS relative to buprenorphine MAT products or other opioid analgesics.

- **Off-label use of buprenorphine and BNX products, and patient characteristics that may lead prescribers to preferentially prescribe higher dose buprenorphine MAT products for analgesia:**

  Studies of off-label buprenorphine use were generally in patients with complicated pain regimens, depression or other psychiatric issues, suspected of confirmed substance abuse issues, or some combination of these factors. These studies included exclusively opioid-experienced individuals. In addition, studies that focused on pain patients had populations with known or a high risk of OUD. Since these studies focused primarily on buprenorphine MAT products, it is not certain how these results might apply to buprenorphine analgesic products.

While there is a sizeable literature on abuse of buprenorphine products indicated for treatment of OUD, there is far less information on the abuse of buprenorphine analgesic products. These studies were mainly of BTDS, and indicate that while it is abused, the abuse rates are generally lower compared to other buprenorphine products and other opioid analgesics. However, the base study populations were difficult to define and/or at high risk of abuse, and may not reflect the abuse patterns in the broader population. Overall, the epidemiologic data provide very limited insight on the risks of misuse, abuse, or overdose associated with buprenorphine sublingual spray compared to other buprenorphine products or other opioid analgesics.

ABBREVIATIONS

AAPCC: American Association of Poison Control Centers

DAAAP: Division of Anesthesia, Analgesia, and Addiction Products

DEPI: Division of Epidemiology

ER: Extended Release

FDA: U.S. Food and Drug Administration

MAT: Medically Assisted Therapy

mcg/hr: micrograms/hour

NASEM: National Academy of Sciences, Engineering, and Medicine

NDA: New Drug Application

NPDS: National Poison Data System

OSE: Office of Surveillance and Epidemiology

OTP: Opioid Treatment Program

OUD: Opioid Use Disorder

PCP: Poison Control Program

RADARS: Researched Abuse, Diversion, and Addiction-Related Surveillance

SKIP: Survey of Key Informants' Patients

TCP: RADARS Combined Treatment Center Programs, (i.e., OTP and SKIP)

URDD: Unique Recipients of Drug Dispensed

U.S.: United States

2. INTRODUCTION

Buprenorphine Sublingual Spray (NDA 209588) was submitted to FDA for approval on September 27, 2017 by Insys Corporation. It is a novel dosage form of buprenorphine with the intended indication of treatment for moderate to severe acute pain. Insys proposes strengths of 0.125, 0.25, and 0.5 milligrams of buprenorphine hydrochloride per spray.

In July 2017, the National Academies of Sciences, Engineering, and Medicine (NASEM) issued the report *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*. (NASEM 2017) One of the aims of this report was to advise FDA regarding actions it could undertake to balance the needs of pain patients and the need to address opioid misuse. Specifically, the NASEM committee's charge was to help FDA develop a framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of opioid misuse. The report suggests that such a comprehensive approach might involve assessing evidence of a product's potential for diversion and misuse, predicted risks to family members and society, and the likelihood of promoting transition to illicit drugs such as heroin and illicitly manufactured fentanyl. The authors emphasize that use of this broader perspective is both legally permissible under the current statutes and rules and consistent with the public health mission of FDA. (Bonnie, 2017)

The Anesthetic and Analgesic Drug Products Committee and the Drug Safety and Risk Management Committee will be participating in a joint Advisory Committee Meeting on May 22, 2018 to discuss the approval of this NDA. To assist the committee in considering how this product may be misused or abused in the postapproval setting, particularly given the novel dosage form and lack of mechanisms intended to deter abuse, DAAAP requested that the Division of Epidemiology in the Office of Safety and Epidemiology (DEPI, OSE) review the relevant epidemiologic data.

Table 1 lists the approved formulations of buprenorphine, including dose and indication information.

Table 1. List of approved buprenorphine and buprenorphine-naloxone (BNX) products:

Buprenorphine Single-Ingredient Products				
Brand Name	**Dosage Form/Route**	**Indications**	**Strengths**	**Initial U.S Approval**
Belbuca	Film/Buccal	Chronic Pain	▪ 0.075mg ▪ 0.15mg ▪ 0.30mg ▪ 0.45mg ▪ 0.60mg ▪ 0.75mg ▪ 0.90mg	October 23, 2015
Buprenex	Injectable/Injection	Moderate to Severe Pain	▪ 0.3mg/mL	December 29, 1981
Butrans (BTDS)	Extended-Release Film/Transdermal	Chronic Pain	▪ 0.005mg/hr ▪ 0.0075mg/hr ▪ 0.01mg/hr ▪ 0.015mg/hr ▪ 0.02mg/hr	June 30, 2010
Probuphine	Implant/Implantation	OUD*	▪ 80mg/implant	May 26, 2016
Sublocade	Solution, Extended-Release/Subcutaneous	OUD	▪ 100mg/0.5mL ▪ 200mg/1mL	November 30, 2017
Subutex	Tablet/ Sublingual	OUD	▪ 2mg ▪ 8mg	October 8, 2002
Buprenorphine generics	Tablet/ Sublingual	OUD	Multiple	Multiple
	Injectable/Injection	Moderate to Severe Pain	Multiple	
BNX Combination Products				
Brand Name	**Dosage Form/Route**	**Indications**	**Strengths**	**Initial U.S Approval**
Bunavail	Film/Buccal	OUD	▪ 2.1mg/0.3mg ▪ 4.2mg/0.7mg ▪ 6.3mg/1mg	June 6, 2014
Suboxone	Film/Buccal, Tablet/Sublingual**	OUD	▪ 2mg/0.5mg ▪ 4mg/1mg ▪ 8mg/2mg ▪ 12mg/3mg	August 30, 2010
Zubsolv	Tablet/Sublingual	OUD	▪ 0.7mg/0.18mg ▪ 1.4mg/0.36mg ▪ 2.9mg/0.71mg ▪ 5.7mg/1.4mg ▪ 8.6mg/2.1mg ▪ 11.4mg/2.9mg	July 3, 2013
BNX generics	Tablet/Sublingual	OUD	Multiple	Multiple

*OUD: opioid use disorder

**Suboxone (BNX) sublingual tablets were withdrawn from the market March 2013.

Although most of the products are indicated for the treatment of opioid use disorder (OUD), three, Butrans (buprenorphine transdermal delivery system, BTDS), Belbuca, and Buprenex (and other generic injectable products) are indicated for pain. Among these three, BTDS and Belbuca are indicated specifically for treatment of long-term pain. Buprenex not often used in the

outpatient setting, and will not be discussed in this review (Wong 2018). Insys intends for buprenorphine sublingual spray to be a more easily administered dosage form of buprenorphine for pain, suitable for the outpatient setting.

A notable difference between buprenorphine analgesic products and those indicated for OUD is the available dosage strengths. Analgesic product strengths are below 1 mg or 1 mg/hour, depending on dosage form. For products to treat OUD, 1 mg is the lower end of the dose range of dose strengths, which can be as high as 12 mg (Suboxone), and higher for extended-release injectable and implant products.

The literature contains many studies on the abuse of buprenorphine products used in medication assisted therapy (MAT) for OUD; however, these were not the focus of this review, since the product under consideration is indicated for analgesia. This is important because abuse patterns in a high-risk population of individuals with OUD may be quite different from the patterns in a population receiving buprenorphine for analgesia.

The novel combination of drug, dosage form, and indication led to a series of questions that OSE attempted to address:

- What is known about the abuse of opioid sublingual spray formulations?
- What is known about the abuse of single-ingredient buprenorphine products compared to BNX combination products?
- What is known specifically about the abuse and overdose of the currently marketed buprenorphine analgesic products, BTDS and Belbuca?
- What is known about abuse of buprenorphine analgesic products via the injection route?
- What is known about the off-label use of buprenorphine and BNX products and what patient characteristics may lead health care providers to consider specifically prescribing buprenorphine products for analgesia?

The purpose of this review is to address these questions in support of the upcoming buprenorphine sublingual spray Advisory Committee meeting.

3. METHODS

Pubmed was searched using the following terms: “buprenorphine”, “buprenorphine-naloxone”, “Suboxone”, “Subutex”, “sublingual buprenorphine”, “transdermal buprenorphine”, “sublingual fentanyl”, “fentanyl spray”, “pain”, “misuse”, “overdose”, and “abuse” to obtain epidemiologic articles related to the questions of interest. Fentanyl search terms were included because it has spray dosage forms similar to buprenorphine sublingual spray. To accommodate the evolving nature of opioid abuse research, the dates were limited to between 2012 and 2018. Epidemiologic studies, case series, and review articles were included. Clinical trials and studies of buprenorphine for MAT were excluded.

Additional information on BTDS and Belbuca abuse was obtained from the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS). A description of this data resource can be found in Appendix A. The AAPCC NPDS database was searched for all intentional misuse and abuse exposure calls involving Butrans (BTDS) or

Belbuca from January 1, 2015 through March 27, 2018, stratified by route of exposure (ingestion, inhalation, parenteral, ocular, dermal). The search was limited to human exposures and closed cases. Since the route of abuse of a drug product cannot reliably be determined when multiple products are recorded for a call, only single-substance cases were included in the route of exposure analyses. An independent quality assurance (QA)/quality control (QC) was performed by a separate FDA analyst using the same criteria.

4. RESULTS

4.1 ABUSE OF SUBLINGUAL SPRAY OPIOID DOSAGE FORMS

To provide context when considering the public health impact of the novel dosage form, information on the abuse of other opioid sprays was sought. The only other opioid currently available in the same dosage form in the U.S. is fentanyl. While the active moiety is different, it could provide insights on the frequency, route, and method of abuse for buprenorphine sublingual spray.

The epidemiologic literature was very limited concerning the abuse of spray opioid products. The most relevant article was an abstract concerning misuse and abuse of intranasal fentanyl spray in a French patient population (Blin 2014). Intranasal fentanyl (Instanyl) was approved in France in 2009 for breakthrough pain associated with chronic cancer pain. The authors collected information from patients using an anonymous questionnaire between July 2011 and November 2012. They found that out of 272 eligible questionnaires returned, only 160 respondents reported a cancer diagnosis. Over 90% of respondents admitted to misusing the product, primarily by dose-related misuse (86%), or taking it for a non-indicated condition or in the presence of a contraindication (76%). Twenty-one patients reported using Instanyl for emotional reasons, relaxation, or sleep, and two respondents admitted to passing the product to another person. The authors concluded that increased education was needed for both prescribers and patients in how to safely and properly use the product.

4.2 ABUSE OF SINGLE-INGREDIENT BUPRENORPHINE PRODUCTS COMPARED TO BNX COMBINATION PRODUCTS

The buprenorphine sublingual spray product under review does not contain naloxone or other mechanisms intended to deter abuse via specific routes. The real-world ability of any opioid-containing formulation to deter abuse using various mechanisms is still a subject of investigation. To help determine the impact that naloxone may have on abuse risk, articles that compared abuse rates between single-ingredient buprenorphine and BNX products were sought. Although this may inform the question of whether naloxone deters some types of abuse, abuse patterns for buprenorphine or BNX MAT products may be quite different from buprenorphine analgesic products, since individuals with existing OUD may be more likely to divert and abuse the drugs, compared to patients being treated for pain.

4.2.1 Literature

A 2013 review of this subject by DEPI found that the evidence was inconclusive as to whether overall abuse risk was lower for BNX combination products compared to single-ingredient

buprenorphine products. (McAninch 2013). Two additional papers examined the abuse of various dosage forms of buprenorphine and BNX combinations. Lavonas et al. (2014) examined the abuse rates of various buprenorphine sublingual formulations, while Cicero et al. (2014) looked at rates and reasons for various buprenorphine and BNX products. Of note, the Lavonas (2014) study was restricted to buprenorphine products used in MAT, while the Cicero (2014) investigation included BTDS.

Lavonas (2014) examined the abuse rates for buprenorphine tablets, BNX tablets, and BNX film using data gathered from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) Poison Center (PCP), Drug Diversion, Opioid Treatment Program (OTP), Survey of Key Informants (SKIP), and College Survey Programs between 2010 and 2012 (see Appendix A for data source descriptions). Abuse rates from each of these data resources were calculated for each quarter of the study period using Unique Recipients Dispensed Drug (URDD) as the denominator (Table 2). Across all the data resources, abuse and diversion rates were statistically significantly higher for buprenorphine and BNX tablets compared to BNX film. Using the BNX film abuse rates as a reference, the abuse and diversion rate ratios ranged from 1.6 to 11.1 for buprenorphine tablets, and 2.2-10.9 for BNX tablets.

Table 2. Average rates of abuse and diversion of three sublingual buprenorphine formulations, adjusted for drug availability, in RADARS. (Lavonas 2014)

	Rate (program events per 10,000 URDD)	95% Confidence interval		Rate ratio compared with combination film	95% Confidence interval		Significance
Poison Center Program							
Buprenorphine tablets	1.5	1.2	1.9	1.6	1.1	2.4	$p = 0.009$
Buprenorphine/naloxone tablets	3.7	3.4	4.0	4.1	3.0	5.7	$p < 0.001$
Buprenorphine/naloxone film	0.9	0.8	1.1	Reference			
Drug Diversion Program							
Buprenorphine tablets	8.5	7.4	9.7	6.4	4.2	9.7	$p < 0.001$
Buprenorphine/naloxone tablets	13.1	12.3	14.0	10.9	7.3	16.4	$p < 0.001$
Buprenorphine/naloxone film	1.4	1.2	1.6	Reference			
Combined treatment programs (OTP + SKIP)							
Buprenorphine tablets	62.4	59.4	65.5	6.5	5.3	7.9	$p < 0.001$
Buprenorphine/naloxone tablets	20.8	19.8	21.9	2.2	1.8	2.7	$p < 0.001$
Buprenorphine/naloxone film	9.5	9.0	10.1	Reference			
College Survey Program							
Buprenorphine tablets	2.3	1.8	2.8	11.1	7.4	16.6	$p < 0.001$
Buprenorphine/naloxone tablets	0.4	0.3	0.6	2.2	1.4	3.4	$p < 0.001$
Buprenorphine/naloxone film	0.2	0.1	0.3	Reference			

URDD: unique recipients of a dispensed drug; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients Program.
Analytic period: Poison Center and Drug Diversion Programs, October 2010–December 2012; treatment programs, April 2011–December 2012; College Survey Program, spring term 2011–fall term 2012.
Poison Center Program data are limited to intentional abuse exposures. Abuse reports in the treatment programs refer to use "to get high" in the past month. Abuse reports in the College Survey Program refer to non-medical use in the past semester. Diversion reports in the Drug Diversion Program are law enforcement investigations initiated in the year/quarter.

Cicero (2014) examined abuse rates and reasons for abuse between 2008 and 2013 using the SKIP, Researchers and Participants Interacting Directly (RAPID), and Drug Diversion Programs from RADARS. The RAPID sample consisted of SKIP participants who completed an additional unstructured questionnaire that asked more detailed questions concerning their drug abuse activities. Over 10,000 individuals were included in the sample. One point six percent of SKIP and 0.7% of RAPID respondents abused buprenorphine as a primary substance (Table 3), however approximately 12% of participants overall had abused buprenorphine in the past 30 days. The authors found that abuse rates for buprenorphine as a primary drug quadrupled during the study period. Figure 1 shows the relative rates of abuse for the buprenorphine dosage forms studied examined in this study. Throughout the study, BNX products (tablet and oral film) were the most common products abused. The switch between BNX tablets and film was coincident

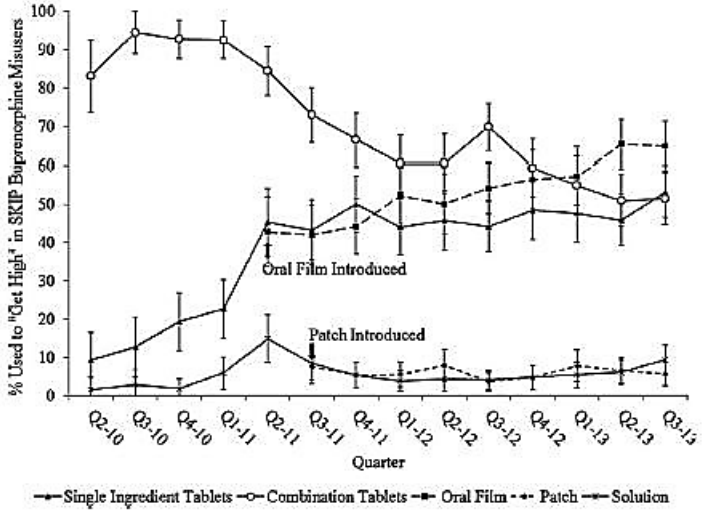
with the withdrawal of BNX tablets from the U.S. market. Abuse of single-ingredient tablets steadily increased during this time. BTDS, first included in July-August 2011, had an abuse rate of between 5% and 10% until the end of the study.

Table 3. Comparison of SKIP and RAPID demographic data and primary drugs of abuse reported. (Cicero 2014)

	SKIP[1] (n=10,568)	RAPID[2] (n=208)
Gender		
Male	50.4	48.4
Average age (±SEM)	34.2 ± 0.11	34.9 ± 0.81
Race/ethnicity		
White	78.4	86.4
African American	9.0	4.3
Latino	4.9	3.7
Other	7.7	5.6
Primary drug		
Buprenorphine	1.6	0.7
Fentanyl	1.0	2.0
Heroin	29.8	36.2
Hydrocodone	19.7	20.4
Hydromorphone	3.8	1.3
Methadone	5.6	2.0
Morphine	4.0	3.3
Oxycodone	32.4	29.6
Oxymorphone	1.1	1.3
Tapentadol	0.0	0.0
Tramadol	1.1	3.3

[1] Data collected from January 1, 2008–September 30, 2013.
[2] Data collected from October 1, 2013–December 31, 2013.

Figure 1. Percent of RADARS SKIP respondents indicating any past month use of buprenorphine to get high who reported abusing specific buprenorphine dosage forms, with 95% CIs, by calendar quarter, Q2 2010 – Q3 2013 (Cicero 2014)



4.3 RISK OF ABUSE AND OVERDOSE ASSOCIATED WITH BTDS AND BELBUCA

Another concern that may arise when considering this product is the rate of abuse and overdose associated with other buprenorphine analgesics. While these types of examinations should be

interpreted cautiously, as the differences in dose and dosage form between products may have important effects on the risks of abuse and overdose, they may nevertheless contribute some insights into how buprenorphine sublingual spray may be abused.

Data on overdose risk associated with buprenorphine analgesic products are limited due to several inherent challenges of studying buprenorphine products in the postmarket setting. The patient population prescribed buprenorphine for MAT is at increased risk of adverse outcomes, including fatal overdose, and it is generally not possible to differentiate MAT from analgesic buprenorphine products in the currently available mortality data. Because of this, it is often difficult to determine when a buprenorphine analgesic product is involved in overdose events, or to compare the risk of overdose associated with buprenorphine to that associated with other prescription opioids.

4.3.1 Literature

Three articles (Lesén 2013, Coplan 2017, Wiegand 2016) were identified that studied abuse of BTDS. No literature was identified that specifically investigated Belbuca abuse, nor was any found that assessed overdose associated with either BTDS or Belbuca.

Lesén et al. (2013) examined dose escalation in a cohort of long-term users of BTDS in Sweden. Although this study primarily measured utilization and did not directly assess abuse, the authors hypothesized that excessive dose increases could lead to an enhanced risk of abuse. The study included 7,099 individuals who were on BTDS therapy for 24 weeks or longer, with a median dose of 11.2 micrograms/hour (mcg/hr). The average age of BTDS users was 77 years, and most patients were female (74%, N=5,245). After one year, 1704 patients (24%) remained on therapy at an average dose of 15.2 mcg/hr. At two and three years, 249 and 44 patients remained on therapy at doses of 18.9 and 23.6 mcg/hr, respectively (Table 4). Although the increases in dose were statistically significant, the authors believed that they were in the range of appropriate treatment, and were not indicative of problematic behaviors. Only 4% of participants remained on BTDS after 2 years, which the investigators noted was consistent with other low-dose BTDS studies.

Table 4. Buprenorphine dose at baseline, dose at last treatment period, and change in dose (N=7,099) (Lesén 2013)

	Dose (µg/h)		
	Mean (SD)	Median (IQR)	*P* Value
Baseline	11.2 (8.7)	9.5 (5.5–13.2)	
Last treatment period	15.2 (12.3)	11.5 (7.2–19.6)	
Change from baseline until last period	4.0 (10.1)	1.7 (–0.6–6.7)	<0.001

The *P* value was calculated with the Wilcoxon signed rank test.
IQR = interquartile range; SD = standard deviation.

Wiegand et al. (2016) examined abuse of BTDS in several RADARS programs, including PCP, Drug Diversion, College Survey, and Treatment Center (TCP) which is a combination of the OTP and SKIP programs. (Appendix A). The databases were analyzed from 2011 and 2013 for BTDS and selected comparators: all other buprenorphine and BNX products (other

buprenorphine), fentanyl patch, ER opioid tablets, and ER tramadol products. Frequency tables were constructed, and abuse rates using population and prescription denominators were calculated using Poisson regression techniques. Both BTDS and extended-release (ER) tramadol had low and stable prescription rates during the study period. During the study period, there were fewer reports indicating abuse of BTDS compared to other drug products across all the data resources included (Table 5). The relative rate of abuse for BTDS was statistically significantly lower than comparators when the population denominator was used (Table 6). However, when the results were adjusted by prescription volume, the relative abuse rates for BTDS were not significantly different from the fentanyl patch abuse rate in the TCP databases, or from other buprenorphine products or the fentanyl patch in the College Survey database (Table 7). Also notable were the wide confidence intervals, particularly in the rates for the College Survey and Drug Diversion databases.

Table 5: Abuse calls, cases, and responses indicating abuse of BTDS and/or comparators, 2011 – 2013*. (adapted from Wiegand 2016)

	Poison Control (Number of abuse calls)	**Treatment Ctr (Number of abuse cases)**	**College Survey (Number of abuse responses)**
BTDS	16	199	14
Other buprenorphine**	1419	3536	215
Fentanyl patch	1137	1438	159
ER opioid analgesics	2141	7940	848
ER tramadol***	53	-	175

*Number of cases not provided for Drug Diversion program
**Includes all other marketed buprenorphine and BNX products
***No information provided for TCP participants

Table 6: Relative abuse rates per 1,000,000 population (95% CI) for BTDS and comparators, 2011-2013. (adapted from Wiegand 2016)

	Poison Control (Number of abuse calls)	**Treatment Ctr (Number of abuse cases)**	**College Survey (Number of abuse responses)**	**Drug Diversion (Number of diversion cases)**
BTDS	ref	Ref	ref	Ref
Other buprenorphine**	88.7 (57.5, 136.7)	17.8 (15.2, 20.8)	15.4 (6.9, 34.1)	126.8 (69, 233)
Fentanyl patch	71.1 (46.2, 109.3)	7.2 (5.9, 8.8)	11.4 (4.9, 26.3)	45.5 (23.7, 80.1)
ER opioid analgesics	133.8 (84.7, 211.3)	39.9 (33.3, 47.8)	60.6 (27.4, 133.7)	361.1 (196.5, 663.6)
ER tramadol***	3.31 (2.0, 5.3)	-	12.5 (5.5, 28.4)	7.1 (3.3, 15.2)

**No information provided for TCP participants
***Includes all other marketed buprenorphine and BNX products

Table 7: Relative abuse rates per 1000 prescriptions dispensed (95% CI) for BTDS and comparators, 2011-2013. (adapted from Wiegand 2016)

	Poison Control (Number of abuse calls)	**Treatment Ctr (Number of abuse cases)**	**College Survey (Number of abuse responses)**	**Drug Diversion (Number of diversion cases)**
BTDS	ref	ref	ref	ref
Other buprenorphine**	3.6 (2.2, 5.7)	1.4 (1.2, 1.6)	1.1 (0.6, 2.1)	5.0 (2.8, 9.4)
Fentanyl patch	5.5 (3.4, 8.7)	0.9 (0.7, 1.1)	1.3 (0.6, 2.6)	3.3 (1.8, 6.1)
ER opioid analgesics	3.2 (2.0, 5.2)	2.0 (1.7, 2.4)	2.1 (1.1, 4.2)	8.2 (4.5, 15.2)
ER tramadol***	1.9 (1.1, 3.3)	-	7.4 (3.7, 14.8)	3.9 (1.9, 8.1)

**No information provided for TCP participants
***Includes all other marketed buprenorphine and BNX products

Coplan et al. (2017) assessed exposure calls to U.S. poison control centers that involved abuse, suicidal intent, and fatalities associated with BTDS and selected comparators between 2012 and 2014 using NPDS data (Appendix A). Intentional abuse call rates adjusted for prescriptions dispensed were calculated for BTDS, ER oxymorphone, fentanyl patch, ER morphine, ER oxycodone, and methadone products (Table 8). For each call category examined, BTDS had the lowest number of calls, and the lowest call rate per million prescriptions dispensed.

Table 8. Absolute counts and prescription-adjusted rates of abuse, cases of suspected suicidal intent, and fatalities by opioid type (NPDS, 3Q2012-2Q2014) (Coplan 2017)

	Rate (program events per 10,000 URDD)	95% Confidence interval		Rate ratio compared with combination film	95% Confidence interval		Significance
Poison Center Program							
Buprenorphine tablets	1.5	1.2	1.9	1.6	1.1	2.4	$p = 0.009$
Buprenorphine/naloxone tablets	3.7	3.4	4.0	4.1	3.0	5.7	$p < 0.001$
Buprenorphine/naloxone film	0.9	0.8	1.1	Reference			
Drug Diversion Program							
Buprenorphine tablets	8.5	7.4	9.7	6.4	4.2	9.7	$p < 0.001$
Buprenorphine/naloxone tablets	13.1	12.3	14.0	10.9	7.3	16.4	$p < 0.001$
Buprenorphine/naloxone film	1.4	1.2	1.6	Reference			
Combined treatment programs (OTP + SKIP)							
Buprenorphine tablets	62.4	59.4	65.5	6.5	5.3	7.9	$p < 0.001$
Buprenorphine/naloxone tablets	20.8	19.8	21.9	2.2	1.8	2.7	$p < 0.001$
Buprenorphine/naloxone film	9.5	9.0	10.1	Reference			
College Survey Program							
Buprenorphine tablets	2.3	1.8	2.8	11.1	7.4	16.6	$p < 0.001$
Buprenorphine/naloxone tablets	0.4	0.3	0.6	2.2	1.4	3.4	$p < 0.001$
Buprenorphine/naloxone film	0.2	0.1	0.3	Reference			

URDD: unique recipients of a dispensed drug; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients Program.
Analytic period: Poison Center and Drug Diversion Programs, October 2010–December 2012; treatment programs, April 2011–December 2012; College Survey Program, spring term 2011–fall term 2012.
Poison Center Program data are limited to intentional abuse exposures. Abuse reports in the treatment programs refer to use "to get high" in the past month. Abuse reports in the College Survey Program refer to non-medical use in the past semester. Diversion reports in the Drug Diversion Program are law enforcement investigations initiated in the year/quarter.

4.3.2 AAPCC/NPDS

A total of 25 BTDS and 6 Belbuca misuse and abuse calls were identified in the AAPCC/NPDS database between January 1st, 2015 and March 27th, 2018. Of those, 60% of BTDS (N=15) and 50% of Belbuca (N=3) only involved a single substance (Table 9).

Table 9. Intentional misuse and abuse exposure calls from Jan 1, 2015 through March 27, 2018, NPDS.

	Total misuse and abuse calls	**Total single-substance misuse and abuse calls**	**Single-substance misuse and abuse calls, by route**				
			Ingestion	**Inhalation**	**Parenteral**	**Ocular**	**Dermal**
BTDS	25	15	7	0	0	1	7
Belbuca	6	3	3	0	0	0	0

4.4 INJECTION BTDS ABUSE

Buprenorphine abuse by injection has been recognized as a public health issue in several countries outside the U.S. for some time (Lofwall 2014). In the U.S., although buprenorphine injection is not commonly identified as a primary drug and method of abuse (Lofwall 2014), injection abuse is more common among individuals entering substance abuse treatment (Lofwall 2014, Cicero 2014).

The 2013 review of this subject by DEPI also found that the observational data available at that time suggested the possibility of lower rates of IV abuse of BNX combination products as compared to single-ingredient buprenorphine products among opioid-dependent individuals who are not primarily dependent on buprenorphine. However, the studies had major limitations precluding definitive conclusions. (McAninch 2013).

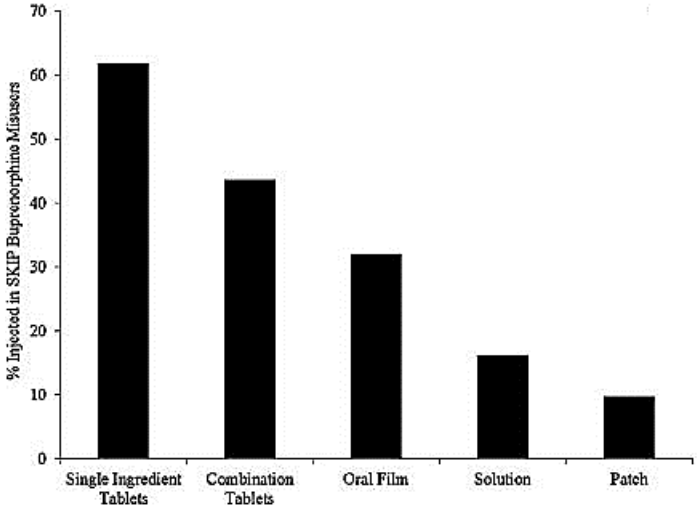
Considering these findings, it is reasonable to think about the risks of injection abuse associated with buprenorphine analgesic products. Akin to the other questions considered, the factors that may affect these risks are likely quite different between buprenorphine MAT and analgesic populations.

4.4.1 Literature

The Lavonas study (2014), described in Section 4.2.1, also examined the rates of abuse by alternate routes in the comparison of the abuse rates in sublingual buprenorphine products. Although buprenorphine analgesic products were not included in the study, it can provide some understanding of the relative abuse rates for alternate routes of single-ingredient buprenorphine and BNX. In both the PCP and TCP samples, BNX film had a statistically significantly lower rate of abuse per unique recipient of drug dispensed (URDD) when compared to either buprenorphine or BNX tablets.

The Cicero (2014) study, also described in section 4.2.1, found that in the five-year study period, among the respondents who had used buprenorphine to get high in the past 30 days (N=1320), approximately 34% (N=461) had injected the drug. Figure 2 shows the relative frequency of buprenorphine products injected among those who reported injecting any buprenorphine in the month prior to entering treatment. These respondents most often reported injecting single ingredient buprenorphine tablets (61.8%, N=285), while BTDS was the least commonly injected buprenorphine product (approximately 10%, N=46). These estimates are not adjusted for the relative availability of the different products.

Figure 2. The total percentage of buprenorphine product formulations injected by SKIP respondents indicating any past month injection of buprenorphine to get high.



Wiegand's 2016 examination of buprenorphine abuse in multiple RADARS databases had mixed results regarding injection abuse of buprenorphine. In the PCP and College Survey samples, BTDS was rarely abused via injection; however, it was abused via injection (55% of BTDS abuse cases) more commonly than comparators in the combined OTP and SKIP (TCP) sample of people entering treatment for opioid use disorders (Table 12).

Table 12: Abuse calls, cases, and responses (%) indicating injection abuse of BTDS and/or comparators, 2011 – 2013*. (adapted from Wiegand 2016)

	Poison Control (Number of abuse calls)	**Treatment Ctr (Number of abuse cases)**	**College Survey (Number of abuse responses)**
BTDS total cases	16	199	14
N (%) injection cases	1 (6.3)	110 (55)	1 (7.1)
Other buprenorphine total cases**	1419	3536	215
N (%) injection cases	238 (16.8)	718 (20.3)	8 (3.8)
Fentanyl patch total cases	1137	1438	159
N (%) injection cases	96 (8.4)	296 (20.6)	10 (6.3)
ER opioid analgesics total cases	2141	7940	848
N (%) injection cases	239 (11.2)	1411 (17.8)	41 (4.8)
ER tramadol total cases***	53	-	175
N (%) injection cases	1 (1.9)	-	11 (6.3)

*Number of cases not provided for Drug Diversion program
**Includes all other marketed buprenorphine and BNX products
***No information provided for TCP participants

4.4.2 AAPCC/NPDS

When AAPCC/NPDS data between September 1, 2015 and March 27, 2018 were examined, there were no calls that mentioned injection abuse of either BTDS or Belbuca (Table 9).

4.4 OFF-LABEL USE OF BUPRENORPHINE AND BNX PRODUCTS, AND PATIENT CHARACTERISTICS ASSOCIATED WITH PRESCRIBING THESE PRODUCTS FOR ANALGESIA

Availability of a drug product for abuse in the community can be affected by the extent to which it is prescribed for conditions other than those for which the drug is labeled. While the dosage form of the buprenorphine product under review may be novel, buprenorphine has a well-established history in the U.S. For this reason, part of our literature search focused on studies of off-label buprenorphine use involving either single-entity or BNX combination products labeled for use in the treatment of OUD but being prescribed to treat pain or other conditions. While there is no way to predict exactly how buprenorphine sublingual spray might be prescribed, these studies may provide some insight into how higher dose buprenorphine products are currently being used in the community, beyond their use in treatment of OUD.

We also tried to determine if there were any specific patient characteristics that may lead healthcare practitioners to prescribe buprenorphine for analgesia instead of another opioid analgesic. While it would be reasonable to assume that patients with a history of opioid use disorder might be preferentially prescribed buprenorphine, there was a question of what additional characteristics prescribers might consider. With regard to the potential public health impact of buprenorphine sublingual spray, an accurate profile of patients who might be more likely to receive buprenorphine for analgesia compared to other opioid analgesics could also help determine its potential clinical use in the postmarket arena.

4.5.1 Literature

There were several small cohort studies and reviews evaluating the effectiveness of BNX for treatment of chronic pain and depression (Chen et al. 2014, Kornfeld et al. 2015, Cote et al. 2014). The two studies described below (Pade et al, 2012 and Kamajian et al., 2016) describe off-label BNX use in a real-world, community-based setting. No literature was identified that described off-label studies of BTDS or Belbuca.

Pade et al. (2012) described a program in the Co-occurring Disorders Clinic within the New Mexico Veteran's Administration Hospital, which treated high-risk patients (high-dose chronic pain with complex pain regimens, opioid dependence, or substance use disorders) with BNX. One hundred forty-three patients were selected over the course of two years to participate in the program. Once in the program, patients were transitioned from their regimens at entry in the program to BNX. Of note, chart reviews showed that 71% of patients (N=101) also had a psychiatric diagnosis when they started the program. Sixty-five percent (N=93) of patients remained on BNX for at least six months after starting the program. Of the 50 patients who discontinued BNX therapy, 42% (N=21) returned to taking other opioid analgesics, but could use lower doses, and seven patients (14%) stopped taking BNX and opioid analgesics completely.

Although the pain scores did not decrease during the time the patients were on BNX therapy, the authors believe the program was a successful model. However, as patients could have received supplemental counseling and non-pharmacologic therapy for pain while they attended the clinic, the authors could not attribute the results solely to the BNX therapy received.

Kamajian et al. (2016) described a small, retrospective, study of Suboxone for treatment of resistant depression in 25 patients who had been registered with their practice between 2008 and 2012. The practice serves the un- and under-insured, and approximately 30% of the patients attend the practice to receive MAT for OUD. Eighty percent of the patients (N=20) in the study were opioid-experienced at the time they started BNX therapy. After a one-year data collection period, 90% (N=23) of patients remained on BNX for their depression. The authors were encouraged by these results, and suggested that the use of BNX for depression receive further study.

All the studies of buprenorphine use for chronic pain were conducted in patients who were either already on high-dose opioid analgesic therapy regimens or with suspected or confirmed opioid use disorder. Although the Kamajian (2016) study included opioid naïve and experienced patients, the opioid status of the patients in the other depression studies was not evaluated. The Swedish BTDS patients in Lesén's (2013) dose escalation study were older (average age 77 years) and had a higher percentage of women (74%) compared to the other studies outlined above.

5. STUDY ADVANTAGES AND LIMITATIONS

5.1 GENERAL ADVANTAGES AND LIMITATIONS

Many of the studies were done in small, selected populations. This allowed for in-depth patient assessments that may not be feasible to collect in larger investigations. However, the highly selected populations in some of the U.S.-based studies (e.g., RADARS TCP) impede generalizing to the larger, general population. In addition, it is not clear if or how the prescribing practices or patient behaviors in the non-U.S. studies (Blin 2014, Lesén 2013) translate to U.S. populations.

5.2 ADVANTAGES AND LIMITATIONS SPECIFIC TO RADARS, AND NPDS DATA RESOURCES

Since many of the U.S. studies were conducted using RADARS databases, the strengths and limitations of these resources will be addressed together. The NPDS data resource is the source of the RADARS PCP data, so the two databases share many characteristics.

Strengths of NPDS and RADARS PCP data include their meaningful and clinically relevant abuse-related outcome measures, product specificity, and wide geographic coverage. In addition, they can capture information from individuals who might not participate in surveys or interact with the health care delivery system. However, these data have limitations that must be taken into consideration. First, an unknown, and likely small, fraction of abuse and overdose events result in a call to an NPDS Poison Center. It is unclear what factors might influence whether an opioid abuse-related event generates a call, or how these factors might vary over time or across drugs. The ability of these data to reliably distinguish specific product dosage forms and generic products is also unclear. Finally, overdoses resulting in rapid, unattended death are

unlikely to generate a call, with the result that these data may disproportionately fail to capture cases involving drugs with the highest risk of sudden, fatal overdoses.

An important limitation that all self-reported data share is the potential for various types of misclassification, including the specific product(s) being abused. If respondents are not able to reliably distinguish between original or reformulated products, extended- or immediate-release products, and branded or generic products—or if survey instruments change over time in such a way as to change the degree of product misclassification—comparisons over time can be biased. FDA review of analyses of these data suggest that such misclassification may be substantial and may also be differential, influenced by factors such as the order in which products are presented to the respondent and the similarity in appearance between different opioid products.

Another important limitation of OTP, SKIP, College Survey, and Drug Diversion data are that they are convenience samples, and are not nationally representative. The data from these sources are not based on a probability sample from a well-defined sampling frame or population, but are only captured when individuals interact with these surveillance systems. It is therefore difficult to characterize the underlying population about which statements regarding abuse and abuse-related outcomes are to be made, and then generalize those findings to a larger group of individuals.

6. DISCUSSION

The purpose of this review was to address a series of questions relating to the potential public health impact of buprenorphine sublingual spray. DEPI examined the literature, NPDS, and a large database of individuals being assessed for substance abuse treatment to provide an overview of the abuse of buprenorphine analgesic products, primarily BTDS, and high-level assessments of injection abuse, off-label use, and prescribing practices related to analgesic buprenorphine use. While there is extensive literature related to buprenorphine for MAT, fewer studies included assessments of buprenorphine analgesic products.

6.1 WHAT IS KNOWN ABOUT THE ABUSE OF OPIOID SUBLINGUAL SPRAY DOSAGE FORMS?

No literature was identified that specifically addressed this question. The single study located that discussed opioid analgesic spray abuse was a small, population-based survey in a French population of patients prescribed fentanyl nasal spray. The study found that even though the product is indicated for cancer patients, over 50% of respondents did not report having cancer. There was also a high rate of misuse (over 90%), defined as dose-related misuse, taking it for other indicated conditions, or in the presence of a contraindication. Twenty patients of the 160 surveyed used it for emotional reasons or as a sleep aid, and two gave it to friends. There were several limitations that hindered interpretation of this study. The product contained a different molecule, and buprenorphine may be a more (or less) desirable target of abuse compared to fentanyl. The study was in a non-U.S. population, and there could be important differences in how the product is used in the community compared to the U.S. Finally, the authors had unique definitions of misuse and abuse, as well as insufficient detail on prescribing conditions, making it difficult to draw any conclusions regarding specific abuse risks associated with transmucosal spray delivery systems for opioids.

6.2 WHAT IS KNOWN ABOUT THE ABUSE OF SINGLE-INGREDIENT BUPRENORPHINE PRODUCTS COMPARED TO BNX COMBINATION PRODUCTS?

There was not a clear preference for abuse of single-ingredient buprenorphine compared to BNX products, but in general, tablet dose forms were abused at higher rates compared to film dosage forms in the data sources examined. Of note, the Cicero (2014) study, which included BTDS, was in a highly selected population of individuals entering substance abuse treatment, so generalizing beyond the study population is difficult. In addition, individuals in these populations may be quite different from those receiving buprenorphine analgesic therapy, so extrapolations should be made with care.

6.3 WHAT IS KNOWN ABOUT ABUSE AND OVERDOSE ASSOCIATED WITH BTDS AND BELBUCA SPECIFICALLLY

There was very limited information on Belbuca abuse. The lack of literature on Belbuca abuse, and the low number of events seen in the AAPCC/NPDS data, are likely due to the product's relatively short time on the U.S. market compared to the other buprenorphine analgesic products. No information on overdose for either BTDS or Belbuca was identified in the literature, and mortality databases generally do not contain information on specific drug products and dosage forms involved in overdose deaths.

6.4 WHAT IS KNOWN ABOUT INJECTION BTDS ABUSE?

Intravenous buprenorphine abuse is an important public health issue, both abroad and in the U.S., but most of the investigations were focused on buprenorphine MAT products, which are generally used in high-risk populations more likely to use opioid through non-oral routes. When buprenorphine analgesic dosage forms were included in these studies, the data were inconsistent on whether BTDS had a lower (or higher) rate of injection abuse compared to other buprenorphine dosage forms or other opioid analgesic products.

6.5 WHAT IS KNOWN ABOUT THE OFF-LABEL USE OF BUPRENORPHINE AND BNX PRODUCTS IN THE COMMUNITY, AND WHAT PATIENT POPULATION CHARACTERISTICS ARE ASSOCIATED WITH PRESCRIBING BUPRENORPHINE PRODUCTS FOR ANALGESIA?

Studies describing off-label use of buprenorphine and BNX were generally in patients with complicated chronic pain issues, depression or other psychiatric issues, suspected or confirmed substance abuse issues, or some combination of those factors. The studies and reviews that focused on use of buprenorphine and BNX in pain populations consisted exclusively of opioid-experienced individuals. In addition to known or a high risk of OUD, several of the study populations had a high prevalence of depression or other psychiatric issues, even if these were not explicit inclusion criteria for the investigation. Since these studies focused primarily on buprenorphine MAT products, it is not certain how these results might apply to buprenorphine analgesic products.

7. CONCLUSION

While there is a sizeable literature on abuse of buprenorphine products indicated for treatment of OUD, there is far less information on the abuse of buprenorphine analgesic products. These studies were mainly of BTDS, and indicate that while it is abused, the abuse rates are generally lower compared to other buprenorphine products and other opioid analgesics. However, the base

study populations were difficult to define and/or at high risk of abuse, and may not reflect the abuse patterns in the broader population. Overall, the epidemiologic data provide very limited insight on the risks of misuse, abuse, or overdose associated with buprenorphine sublingual spray compared to other buprenorphine products or other opioid analgesics.

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9. APPENDIX A: DATA RESOURCE DESCRIPTIONS

AAPCC/NPDS

The AAPCC maintains the NPDS, which captures data on calls to U.S. poison control centers (PCCs) on a near real-time basis. Currently, AAPCC's 55 PCCs serve the entire U.S. population, including all 50 states and U.S. territories. PCCs receive calls for exposures to a variety of substances through the Poison Help Line 24 hours per day, offer medical advice, and document reported events in the database. Case records in the database reflect information provided when the public or healthcare professionals call and report an actual or potential exposure to a substance or request information or educational materials. Exposures do not necessarily represent a poisoning or overdose, and the AAPCC does not completely verify the accuracy of every report made to member centers. (Mowry et al 2016)

NPDS Definitions for Intentional Exposure Reason Categories	
Intentional Exposure Reasons	**NPDS Definition[1]**
Suspected Suicides	"An exposure resulting in the inappropriate use of a substance for self-harm or self-destruction or manipulative reasons."
Abuse	"An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect", including recreational use of a substance for any effect.
Misuse	"An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect."
Unknown	Exposures that are deemed to be intentional although the specific motive is undetermined.

RADARS Drug Diversion

The RADARS® Drug Diversion Program gathers surveillance data on prescription drug diversion. Approximately 300 drug diversion investigators across 49 states and Puerto Rico submit data quarterly on the number of documented drug diversion cases within their jurisdiction for specific prescription drugs of interest. Drug diversion investigators represent municipal police departments, multi-jurisdictional drug task forces, county sheriffs' departments, regulatory agencies such as state medical and pharmacy boards, state police agencies, prosecutors' offices, and departments of health. In addition to the number of diversion cases, the DDP provides information on the cost of diverted products on the street, based on reports by diversion investigators.

RADARS College Survey

The RADARS College Survey Program assesses the nonmedical use of specific prescription opioids and stimulants in undergraduates. It began data collection in 2008, and individuals who are enrolled as undergraduates in 2- or 4-year college, online, or technical schools at least part time are eligible. It is administered online, three times annually. Data include drugs used,

[1] American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2016.07.11. July 11, 2016

reasons for use, sources and routes, chronic pain assessment, and the Drug Abuse Screening Test. Data are self-reported, and the population is self-selected. The underlying population for this type of volunteer *opt-in* internet survey sample remains unclear, and response rates are unknown (Dart et al., 2015).

RADARS OTP

The RADARS System Opioid Treatment Program samples persons entering federally approved medication-assisted treatment programs nationally. In 2016, 65 treatment centers from 31 states provided information. Patients enrolling in these medication-assisted treatment programs are voluntarily recruited for the study and complete a standardized, self-administered questionnaire. The treatment programs include both methadone- and buprenorphine-based programs. This questionnaire solicits information on specific prescription drugs used by the patient in the past month to get high.

RADARS PCP

RADARS® PCP obtains AAPCC/NPDS data on calls that mention exposure to prescription opioids and stimulants. Information from the majority of poison control centers included in NPDS are represented in the RADARS PCP system. Personnel at each participating poison center collect information using nationally standardized electronic data collection software. The objectives of the PCP are to detect product-specific prescription drug abuse and misuse in near real-time, and to identify geographic areas with disproportionately high rates of abuse and misuse.

RADARS SKIP

The RADARS System Survey of Key Informants' Patients Program samples persons seeking treatment for substance dependence or addiction who report abusing prescription opioids or heroin in the past month. In 2016, 129 treatment centers from 45 states provided information. The Survey of Key Informants' Patients Program collects data from patients entering substance abuse treatment programs (excluding opioid agonist treatment programs). Each newly admitted patient to these programs is offered the opportunity to complete a standardized self-administered questionnaire that solicits information on specific prescription drugs used in the past month to get high.

RADARS TCP

The RADARS® TCP consists of the Opioid Treatment (OTP) and the Survey of Key Informants' Patients (SKIP) Programs.

10. APPENDIX B: STUDY SUMMARIES

Study	Population/setting	Design/Methods	Key Results	Comments/limitations
Blin 2014	272 French patients dispensed fentanyl nasal spray between July 2011 and November 2012	cross-sectional survey	160/272 had a cancer diagnosis Among the 160, • 76% (N=122) used a non-indicated condition or had a contraindication • 86% (N=138) did not take as directed 21 patients took drug for emotional reasons, relaxation, or sleep, and two patients gave to another person	Catchment area was entire country Although indicated specifically for cancer pain, nearly half of patients did not report having cancer
Chen 2014	Qualitative assessment of BNX for chronic pain therapy	review	Several articles indicated BNX was effective in opioid dependent patients; no articles found that studied BNX in opioid-naïve individuals Also looked at buprenorphine single ingredient studies; mixed results for pain reduction in opioid-naïve patients, positive pain reduction results in opioid-experienced patients	Study heterogeneity prevented quantitative analysis

Cicero 2014	10,776 individuals entering substance abuse treatment between Jan 2008 and Sept 2013 30 investigators participating in RADARS Drug Diversion program in 2Q2013	Self-administered survey (N=10,568) and qualitative interview (N=208) for substance abuse treatment respondents Telephone interview for Drug Diversion investigators	1.6% of participants indicated the primary drug of abuse was buprenorphine, but 12% of participants had abused it in the 30 days prior to the survey; 34% of them had injected Percent of individuals who used buprenorphine to get high increased steadily between 2009 and 2013 Buprenorphine was 4th most common drug diverted	Most individuals used buprenorphine to self-treat withdrawal or as a second choice Abuse patterns in patients entering treatment may not be representative of all abusers Anonymous survey/unable to verify key information Drug diversion responses may not be nationally representative
Coplan 2017	13,989 ER/long-acting opioid exposure calls to NPDS between July 2012 and June 2014	Retrospective cohort study Comparators: ER oxymorphone, fentanyl patch, ER morphine, ER oxycodone, methadone	117 total exposure calls were for BTDS (lowest of all drugs included) Of 2687 intentional abuse calls, 5 were for BTDS No fatality cases for BTDS	Did not examine other buprenorphine products BTDS newest formulation on market (of those studied) Unable to control for demographics, medical history, amount abused

Cote 2014	Qualitative assessment of sublingual buprenorphine for chronic pain	review	10 studies were included (of 55 unique articles found), including 1,190 patients Sublingual buprenorphine was effective in reducing pain in all studies, although the extent of the reduction varied In the single RCT included, sublingual buprenorphine and BTDS were equivalent	Substantial heterogeneity prevented quantitative assessment According to the GRADE criteria, most studies were of low quality Optimal daily dose and dosing regimens could not be assessed
Kamajian 2016	25 patients with treatment resistant depression between 2008 and 2012	1-year open label trial of low-dose BNX/descriptive statistics	Patients evaluated at 1,2, and 4 years All patient had significant improvement in depression measures; none stopped treatment for side effects	Very small study No comparators described Unclear if additional medication or other therapies initiated for patients
Kornfeld 2015	3 chronic pain patients/ literature review	Case series	Three chronic pain patients (post lumbar reconstruction/disc replacement, foraminal/canal stenosis, post staphylococcal abscess) titrated off multiple opioid and analgesic therapy to sublingual buprenorphine by using BTDS as a bridge Pain and depression/mood improved, no withdrawal symptoms experiences	Very small case series No objective measure of symptoms during transition Limited number of conditions examined Close monitoring and significant assistance from family members required during transition

Lavonas 2014	1068 RADARS PCP, 1374 Drug Diversion Cases, 2669 TCP respondents, and 183 College Survey responses between October 2010 and December 2012	Cross-sectional survey of sublingual buprenorphine abuse in RADARS data resources Buprenorphine tablet, BNX tablet, BNX film Drug availability adjusted rates with BNX film as the reference	PCP and Drug Diversion: BNX tablets had higher risk of abuse TCP and College Survey: Buprenorphine tablets had higher risk of abuse CTP: higher risk of injection abuse with buprenorphine tablet compared to BNX tablet	Did not discuss other opioids that also may have been used No information on intent Abuse patterns in patients entering treatment may not be representative of all abusers
Lesén 2013	7,099 Swedish patients dispensed BTDS > 24 weeks between July 2005 and February 2011	BTDS dose patterns, assessed every eight weeks/descriptive statistics	64,264 total doses purchased; 34% (N=21742) only used once 74% female, average age 77; 69% of cohort => 75 years old 1704 patients on treatment at 1 year; 249 patients at 2 years Mean change in dose after one year = 3.4 µg/h, and 6.3 µg/h after 2 years	National catchment area and follow-up Among those who remained on treatment, relatively low dose increases over time. Indication, reason for discontinuation or dose changes not known; however high dropout rate similar to other studies in same population
Lofwall 2014	Review buprenorphine misuse, diversion, and public health consequences	Worldwide review; focus on implications for U.S.	Countries where buprenorphine diversion and misuse are particularly pressing can usually trace the problem back to lack of education and/or restrictions on distribution	Methodology and time period for selecting papers to review not described

Pade 2012	143 chronic pain patients a NM VA hospital between July 2009 and December 2011	Retrospective chart review of patients with chronic non-cancer pain and opioid dependence treated with buprenorphine/descriptive statistics	71% of patients also had a current psychiatric diagnosis, most commonly major depression or PTSD 65% (N=93) were treated with BNX for at least 6 months without relapsing Of those that were no longer on BNX, all are on lower opioid doses, and 7 discontinued opioid therapy altogether	Pain scores were not significantly decreased Non-pharmacological therapy was also provided, but not evaluated in this study, so results may not be solely attributable to BNX therapy No comparators or control group
Wiegand 2016	4,766 PCP; 13,113 TCP; 1,411 College Survey respondents; 2,009 Drug Diversion cases captured by RADARS between July 2011 and December 2013	Evaluation of abuse and diversion of BTDS compared to other buprenorphine, fentanyl patch, ER opioid tables, and ER tramadol in RADARS data resources	BTDS was abused and diverted at lower rates vs. comparators across all data resources using either population or prescription adjusted rates	Low prescribing levels did not allow for in-depth analysis Abuse rates may increase as prescribers become more familiar with BTDS Possible misidentification of BTDS may have artificially lowered abuse prevalence rates.