

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209819Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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<b>Application Type</b>	NDA
<b>Application Number</b>	209819
<b>PDUFA Goal Date</b>	November 30, 2017
<b>OSE RCM #</b>	2017-1054
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<b>Review Completion Date</b>	November 30, 2017
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Buprenorphine Extended-Release
<b>Trade Name</b>	Sublocade
<b>Name of Applicant</b>	Indivior Incorporated
<b>Therapeutic Class</b>	Opioid Agonist
<b>Formulation(s)</b>	Long Acting Depot Injection for subcutaneous injection
<b>Dosing Regimen</b>	300 mg/month x 2 doses followed by 100 mg/month, with option to increase to 300 mg/month

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## EXECUTIVE SUMMARY

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is necessary for Sublocade, a single entity drug-device combination product with buprenorphine base in the ATRIGEL Delivery System, to ensure the benefits outweigh its risks. Indivior Incorporated (Indivior) submitted a New Drug Application (NDA) 209819 for Sublocade with the proposed indication for the treatment of moderate-to-severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. Sublocade is a prefilled syringe and will be packaged with a needle designed for subcutaneous injection once monthly to be administered by a healthcare provider. The risks associated with Sublocade are consistent with other opioids, such as respiratory depression and Neonatal Opioid Withdrawal Syndrome (NOWS). The Agency is, however, particularly concerned that intravenous injection presents a risk of serious harm or death as Sublocade forms a solid mass upon contact with body fluids. The Applicant's proposed REMS consists of Medication Guide, elements to assure safe use (ETASU) that Sublocade would be dispensed only in certain settings, an implementation system, and a timetable for submission of assessments.

DRISK has determined that a REMS with ETASU is needed to ensure the benefits of Sublocade outweigh its risks of serious harm or death with intravenous self-administration. The Sublocade REMS will ensure that healthcare settings and pharmacies are certified and only dispense Sublocade directly to a healthcare provider for administration by a healthcare provider. This differs from the Applicant's proposal of certifying certain healthcare settings only as DRISK has determined that all settings that dispense Sublocade should be certified.

The Applicant's amended REMS submission received November 30, 2017 has included all the necessary changes communicated on November 16, 22, and 29, 2017. DRISK is recommending approval of the Sublocade REMS.

## 1 Introduction

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure the benefits outweigh its risks for Sublocade, a prefilled syringe single entity drug-device combination product with buprenorphine base in the ATRIGEL Delivery System. Indivior submitted a New Drug Application (NDA 209819) for Sublocade proposed for the treatment of moderate-to-severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. This application is under review in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). The Applicant's proposed REMS consists of Medication Guide and elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Sublocade is a single entity drug-device combination product with *buprenorphine* base in the ATRIGEL

Delivery System in a prefilled syringe. Buprenorphine, the active ingredient in Sublocade, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981. The ATRIGEL Delivery System has been used in other FDA approved products such as ELIGARD, which is indicated for the palliative treatment of advanced cancer. Sublocade provides sustained plasma levels of buprenorphine over a minimum of 28 days and is intended for the treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. Sublocade is designed to be subcutaneously injected in the abdominal area once monthly.

The product is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Individual proposed dosing regimens include 300 mg monthly for the first two months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient. If approved, Sublocade would be the first once-monthly injectable buprenorphine product indicated for the treatment of OUD.

NDA 209819 is a 505 (b)(2) application with a designated priority review. The referenced product is Subutex sublingual tablet, NDA 20732. The active ingredient in Sublocade is buprenorphine and is available currently as sublingual tablets, buccal film and an implant for indicated for medication-assisted treatment (MAT). Currently, all buprenorphine products indicated for MAT of OUD are approved with a REMS. This includes the Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS and the Probuphine REMS.

Currently buprenorphine products for MAT are approved under three separate REMS. The Suboxone/Subutex REMS, and BTOD REMS and the Probuphine REMS. The Suboxone/Subutex REMS, and BTOD REMS consists of a Medication Guide and ETASU (i.e., safe use conditions and monitoring) which are not linked to distribution. The REMS for these products were required to address an increase in accidental exposures to children, increased misuse and abuse, as well as to improve prescribing practices of these products. Probuphine is an implantable formulation of buprenorphine.

The goal of the Probuphine REMS is to mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associated with insertion and removal of Probuphine and the risks of accidental overdose, misuse and abuse. The Probuphine REMS consists of a Medication Guide and ETASU which includes healthcare provider (HCP) certification (e.g., HCP that prescribes and/or inserts Probuphine must be certified) and patient monitoring for removal of Probuphine. There are corresponding REMS materials for HCP education, enrollment, logging of insertion and removal procedures and patient education. The training with this REMS is linked to the ability to prescriber, insert and remove Probuphine.

As an injectable depot device, Sublocade differs significantly from the sublingual and oral formulations of buprenorphine. Those products are self-administered by patients in their homes and the REMS are designed to mitigate risks associated with accidental overdose, particularly in children as well as misuse,

and abuse. This is in contrast to Sublocade which was designed to be administered by a HCP. Probuphine was similarly designed to be administered by HCP, but carries different risks as it is an implant device.

### 1.1 DRISK REVIEWS CONTRIBUTING TO THIS ORIGINAL APPLICATION

Dunn, S. Division of Risk Management Review of the Sublocade REMS materials and Supporting Document, submitted to DARRTS November 16, 2017.

Dunn, S. Division of Risk Management Review of the Sublocade REMS materials and Supporting Document, submitted to DARRTS November 22, 2017.

Dunn, S. Division of Risk Management Review of the Sublocade REMS materials and Supporting Document, submitted to DARRTS November 29, 2017.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209819 relevant to this review:

- 9/28/2016: At this Type C Guidance meeting, the Applicant inquired about the need for a REMS and the need for restricted distribution. They were advised to justify the need for a REMS and that they would need ensure proposed distribution plans are not in violation of applicable laws.
- 12/14/2016: Pre-NDA meeting was held.
- 5/30/2017: NDA 209819 was submitted and the application included a REMS proposal. (b) (4)
- [REDACTED]
- 8/23/2017: The Agency sent an IR to inquire about details of the proposed REMS distribution and operations.
- [REDACTED] (b) (4)
- 9/22/2017: The Agency inquired how the Applicant would ensure that pharmacies within large integrated healthcare settings would ensure that Sublocade would not be dispensed directly to patients.
- 9/28/2017: The Applicant submitted a response to the IR proposing that pharmacies within large integrated healthcare settings would be certified.
- 10/31/2017: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss NDA 209819. The committee voted on evidence of effectiveness in the clinical program and voted in favor of the evidence 17:2. They also voted that the data provided supported the use of the Sublocade 300 mg/300 mg dosing regimen 13:6. They discussed the role of this regimen in potential treatment. For the REMS, they discussed the pros and cons of restricted distribution as proposed by the Applicant and the Agency. They were overwhelmingly in favor of restricted distribution and not allowing Sublocade to be dispensed directly to patients. Some committee members did express concern about access to the product in rural areas. The committee voted 18:1 to approve Sublocade.
- November 9, 2017: The Agency held a teleconference with the Applicant discussing the REMS requirements and detailed plan on how to develop the REMS Document and materials prior to the action date. The Agency provided drafts via email of a templated Fact Sheet and a proposed

- draft REMS Document to the Applicant to assist with the development of the materials.
- 11/14/2017: The Agency provided a draft templated Healthcare Setting and Pharmacy Enrollment Form for the Applicant to assist with development.
  - 11/14/2017: The Applicant amended their submission and submitted materials in response to the 11/9/2017 teleconference via email and to the EDR on 11/15/17 (Seq 0034).
  - 11/16/2017: The Agency provided comments on the Applicant REMS materials 0034 (above).
  - 11/20/2017: The Applicant amended their REMS submission via email in response to the FDA's 11/16/2017 comments and submitted to the EDR on 11/21/17 (Seq 0036).
  - 11/22/2017: The Agency held a teleconference with the Applicant discussing the main points that need to be addressed in the REMS Document, REMS Supporting Document and other REMS materials.
  - 11/22/2017: The Agency provided comments on the Applicant REMS materials (Seq 0036) (above).
  - 11/27/2017: The Agency held a teleconference with the Applicant discussing some of their questions about the Agency's comments and edits on the REMS materials communicated on 11/22/2017. The materials discussed were those initially proposed by the Applicant on 11/21/2017 (Seq 0036).
  - 11/28/2017: The Applicant amended their submission and submitted materials in response to the 11/27/2017 teleconference and 11/22/2017 comments and edits via email and to the EDR (Seq 0039).
  - 11/29/2017: The Agency provided comments on the Applicant REMS materials (Seq 0039) (above).
  - 11/30/2017: The Applicant amended their submission and submitted final materials in response to the 11/29/2017 Agency comments and edits (Seq 0040).

### **3 Therapeutic Context and Treatment Options**

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#### **3.1 DESCRIPTION OF THE MEDICAL CONDITION**

Opioid use disorder or OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences. Rates of overdose and related deaths continue to have a serious impact on public health; in 2015, more than 15,000 people died from overdoses involving prescription opioid analgesics.<sup>a</sup> In addition, opioid analgesic misuse and abuse remains a significant public health crisis contributing to destruction of individuals and families. Overall, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) report that nonmedical use of prescription opioids by adults more than doubled in the U.S. from 2001-2002 to 2012-2013. They also report that the number of people who meet the criteria for prescription opioid addiction has substantially increased during this timeframe as well, with 2.1 million adults reporting symptoms of

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<sup>a</sup> Prescription Opioid Overdose Data Centers for Disease Control, downloaded from <https://www.cdc.gov/drugoverdose/data/overdose.html>

“nonmedical prescription opioid use disorder.”<sup>b</sup> In the face of this public health crisis, new therapies for treatment are necessary.

### **3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS**

Treatment of addiction with methadone is limited to federally regulated Opioid Treatment Programs (OTP). In terms of buprenorphine treatment, the Substance Abuse and Mental Health Services Administration (SAMHSA) manages the Drug Addiction Treatment Act of 2000 (DATA 2000) in which physicians that apply and hold waivers can prescribe and/or dispense buprenorphine products for MAT. SAMHSA sets eligibility and certification requirements as well as an interagency notification review processes for physicians who apply. Buprenorphine treatment may be prescribed by physicians with a DATA 2000 waiver in office practice settings.

Addiction treatment is multifactorial and should address an individual’s medical, psychological, social, vocational, and legal problems. It is a long-term process and should include behavioral therapies that can include counseling which may involve group settings or other family members. MAT is an important part of addiction treatment with OUD.<sup>c</sup>

Table 1 describes medications available for treatment of OUD.

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<sup>b</sup> NIAAA Press Release on June 22, 2016. Rates of nonmedical prescription opioid use and opioid use disorder double in 10 years. Downloaded from <https://www.niaaa.nih.gov/news-events/news-releases/rates-nonmedical-prescription-opioid-use-and-opioid-use-disorder-double-10>

<sup>c</sup> NIDA Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition). Principles of Effective Treatment reviewed at <https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/principles-effective-treatment>

**Table 1: Currently available treatments for opioid use disorder or opioid dependence**

<i>Daily Products</i>			
<b>Generic/Chemical Name</b>	<b>Trade Name</b>	<b>Sponsor</b>	<b>Dosage form(s)</b>
Buprenorphine/naloxone	Suboxone tablet (generics only)	Indivior	Sublingual tablet
	Suboxone film (also generics)	Indivior	Sublingual film
	Bunavail (also generics)	Biodelivery Sci Intl	Buccal film
	Zubsolv (also generics)	Orexo AB	Sublingual tablet
Buprenorphine	Subutex (generics only)	Indivior	Sublingual tablet
Methadone HCl	Methadose (also generics)	Mallinckrodt	Oral solution Bulk powder Tablet Dispersible tab
Methadone HCl	Dolophine (also generics)	Roxane	Tablet Oral concentrate Oral solution
Naltrexone HCl	ReVia (also generics)	Duramed	Tablet
<i>Modified release Products</i>			
Naltrexone HCl	Vivitrol	Alkermes	Injectable suspension
Buprenorphine	Probuphine	Braeburn (Previously Titan)	Implant

Source: Emily Deng, MD FDA Sublocade Clinical Review Table 2, November 10, 2017.

#### **4 Benefit Assessment<sup>d</sup>**

Efficacy data to support the NDA approval came from an opioid blockade study (13-002) and Phase 3 pivotal, double-blind, placebo-controlled study (13-0001). The opioid blockade study (13-0002) determined that 300 mg dose was the dose to block exogenous opioids using hydromorphone challenge tests and then the 300 mg dose of was subsequently used for the pivotal efficacy study (13-0001).

Study 13-0001 included a randomized total of 504 subjects with moderate to severe OUD as defined by DSM-5 diagnosis, age 18-65, males and females. The primary efficacy endpoint was cumulative distribution function of the percentage abstinence (weekly urine drug screen (UDS) negative for opioids and self-reports negative for illicit opioid use) from week 5 through 24. The study compared the

<sup>d</sup> Dr. Emily Deng's FDA (DAAAP) Clinical Review of Sublocade darrted November 10, 2017 contains detailed evaluation and analysis on both safety and efficacy.

Sublocade 300/300 mg (6 doses of 300 mg) and the 300/100 mg regimen (two initial dose of 300 mg followed by four doses of 100 mg). Primary endpoint analysis indicated that the cumulative distribution function of the percentage abstinence from week 5 through 24 was statistically significantly superior in both the RBP-6000 300/300 mg group and the RBP-6000 300/100 mg groups. The difference from placebo in the distribution function was statistically significant with p-value<0.0001. Both the Sublocade 300/300 mg and the Sublocade 300/100 mg groups showed a significant increase in responder rate or treatment success rate by approximately 20% compared with the placebo group. The efficacy of Sublocade was further supported by a Phase 2, inpatient, opioid blockade study (13-0002). The opioid blockade study (13-0002) identified that 300 mg of Sublocade achieved a target plasma concentration greater than 2 ng/ml after the first subcutaneous injection and provided effective blockade of opioid effects, using hydromorphone challenge tests.

## 5 Risk Assessment & Safe-Use Conditions

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The safety profile of Sublocade was based on data collected from 848 subjects who received Sublocade 300/300 mg regimen, the 300/100 mg regimen, or 300/flexible dose subcutaneous injection in the phase 3 double-blind, efficacy and safety study and the phase 3 open-label, long-term safety study. There were 68 patients that received placebo. Based on the known profile for buprenorphine, the major toxicities of concern with Sublocade were liver toxicity, central nervous system effects and gastrointestinal effects. The safety profile seen in the Sublocade clinical program was consistent with the safety profile of transmucosal buprenorphine products. There were no Hy's law cases identified and the rates of treatment emergent adverse events (TAEs) did not reveal any unexpected concerns.

In terms of adverse event (AE) profile for injectable products, Sublocade did not raise any particular safety concerns. Due to the depot formulation, injection site reactions were considered an adverse event AE of special interest. In her review, Dr. Deng notes that most of the injection site AEs, most commonly documented as pain, pruritis or erythema at the injection site, were mild to moderate except with one subject reported severe injection site pruritus in the RBP-6000 300/300 mg group. Overall, local injection tolerability is consistent with other approved products using the ATRIGEL Delivery System.

There was one fatal serious adverse event (SAE) report (Study 13-0001, gunshot wound) in the clinical development program as of the NDA data cut-off date. In addition, a total of 75 non-fatal SAEs occurred among 65 subjects across the studies in the clinical program. No SAEs related to injection site reactions were reported and there were no particular SAEs that emerged as a new concern for this particular formulation of buprenorphine or as unexpected in this treatment population. The review team's causality assessments revealed that the majority of SAEs were not drug related and most were due to pre-existing diseases. One patient developed severe hepatic injury 14 days after the exposure to a single dose of Sublocade 300 mg and required hospitalization and surgical depot removal at day 15; however, hepatitis C and past intravenous (IV) drug abuse were confounding factors for this case. The subject recovered after Sublocade depot removal. It is worth noting that this is the only case that required surgical removal of Sublocade in the clinical development program. Data for surgical removal of the product in case of medical emergency is limited for the clinical development program. On October 31, 2017, the PDAC DSaRM AC panel brought up the concern of need to remove Sublocade that has already

been administered to patients in cases where they are in some sort of medical emergency. The Agency has asked the Applicant to address this in their label.

The Applicant proposed labeling includes a “Warning and Precautions” section addresses respiratory depression, NOWS and hepatic events. The “Use in Specific Populations” section also addresses use of Sublocade in patients with hepatic impairment. [REDACTED] (b) (4)

### 5.1 POTENTIAL SERIOUS RISK OF SUBLOCADE

The Applicant provided in vitro assay data showing that when Sublocade was injected in a tube containing dog blood, immediate clogging occurred. Based on the in vitro tube assay results, Dr. Deng, the clinical reviewer in DAAAP, noted that it is likely that an occlusion would form due to rapid solidification of the formulation when placed in aqueous fluid. The Agency has determined that IV injection presents a risk of serious harm or death since Sublocade forms a solid mass upon contact with body fluids. As a result, potential consequences of IV administration include occlusion, local tissue damage, and thrombo-embolic events, including life-threatening pulmonary emboli. Dr. Deng notes in her review that in the clinical development program, the product was administered by healthcare providers in clinical settings and as such, the chance of improper injection as a medication error was very low. However, once marketed, there is concern that there is a potential for intravenous administration if provided the refilled syringe is provided directly to a patient.<sup>e</sup>

If injected IV, the dose ranges from 8 mg to 300 mg and the formulation does not contain naloxone. There is a potential for abuse and misuse with this product since, given the proposed indication, many patients prescribed this medication will have a history of IV drug abuse. More than 40% subjects in the clinical studies reported history of injection drug use. Importantly, as it is not the proposed route of administration, results of IV injection of Sublocade were not studied in the clinical program. The Agency is concerned that potential AEs that may result from IV injection (i.e. tissue damage, embolus, rapid dissolution resulting in high levels of opioid and respiratory depression). Overall, the risks associated with IV administration were not well characterized in the clinical program. However, this product will be available in a prefilled syringe with a needle attached and many patients will likely have history of IV drug abuse, therefore the Agency has particular concerns with potential consequences of IV injection. The Applicant has proposed “Dosage and Administration” labeling language that states that this product is for subcutaneous injection only and that it “should only be prepared and administered by a healthcare provider.” They also have a “Warning and Precaution” [REDACTED] (b) (4) stating that a solid depot is formed following subcutaneous administration; the product should not be administered subcutaneously or intramuscularly.

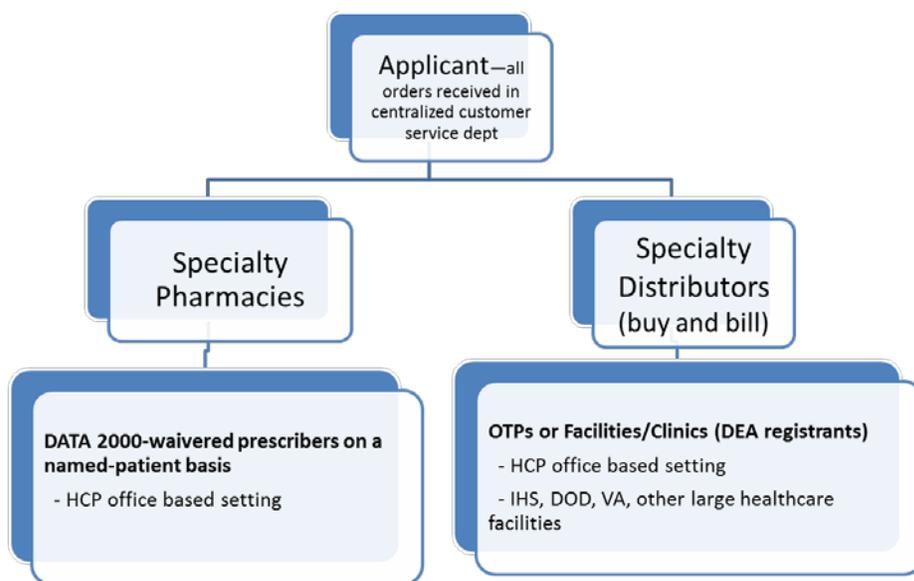
## 6 Expected Postmarket Use

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<sup>e</sup> Dr. Emily Deng’s FDA (DAAAP) Clinical Review of Sublocade darrted November 10, 2017.

During the clinical development period, Sublocade was administered by a HCP and the Applicant has included this in their labeling. Sublocade was not studied or evaluated for take-home use or self-administration by patients. In their proposed REMS (further discussed in Sections 7 and 8 below), to minimize abuse, misuse and diversion, the Applicant states that office settings with HCP who have a DATA 2000 waiver would be a potential setting for administration of this product. In addition, they propose that settings that are DEA registrants such as hospitals, integrated health systems, outpatient clinics, long-term care facilities, Department of Defense (DOD) and Veteran Administration (VA) facilities, prisons, inpatient psychiatric units and federally approved OTPs would all be potential sites for administration. The Applicant proposed that Sublocade would not be distributed to patients by retail pharmacies. (b) (4)

As an injectable depot formulation, Sublocade could be a potential treatment for patients that have compliance issues or having difficulty taking their daily medications. Based on the clinical program, proposed indication, and proposed locations of administration, Sublocade would be likely be prescribed by providers in inpatient settings, OTPs, or by providers in outpatient settings with a DATA 2000 waiver. In summary, the Applicant proposed the following distribution scheme:



**Figure 1 Applicant Proposed Distribution Plan of Sublocade**

Source: FDA AC Slides 10/31/2017

The proposed distribution scheme could ensure that Sublocade is dispensed to clinical settings and administered by a healthcare provider. As a result, the potential for IV administration by the patient is minimized. In general, the Agency agrees with the Applicant’s distribution scheme, however their REMS does not ensure that their products would remain within the proposed distribution scheme. The REMS

requirements that the Agency has determined are necessary to ensure the benefits outweigh the risks are described in Section 8.

## **7 Discussion of Need for a REMS**

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The Clinical Reviewer, Dr. Deng, recommends approval of Sublocade with a REMS based on the efficacy and safety information currently available. The product formulation for Sublocade differs from the other buprenorphine products indicated for MAT and as discussed in Section 2.1 and contributes to a different risk profile. Probuphine has risks associated with migration of the implant. Transmucosal buprenorphine MAT products are intended for the patient to take at home and risks are similar to that seen with other opioids such as misuse, overdose and respiratory depression. Sublocade was not developed as a take-home formulation; if a HCP administers the depot injection as proposed, studied and indicated, misuse and overdose by the patient are not likely to occur. In addition, the risk of accidental exposure to children is reduced because the product is not stored in the home. The injection site reactions were not concerning as discussed in Section 5, however, the Agency is particularly concerned with this injectable formulation because Sublocade forms a solid mass upon contact with body fluids. Other concerns that would be addressed by having a HCP administer Sublocade included that this is an opioid agonist in a prefilled injectable syringes with needles attached, it is ready to inject. As noted by the Applicant, there is a potential risk for abuse and misuse with this product since, given the proposed indication, many patients prescribed this medication will have a history of IV drug abuse and the product doses are very high and the formulation does not include naloxone. More than 40% subjects in the clinical studies reported history of injection drug use. Importantly, as it is not the proposed route of administration, results of IV injection of Sublocade was not studied in the clinical program. The Agency is concerned about the potential AEs that may result from IV injection (i.e. embolus, rapid dissolution resulting in high levels of opioid).

Sublocade route of administration is similar to other injectable depot and subcutaneous products dispensed for outpatient use. The Agency is very concerned that since dispensing subcutaneous and injectable depot medication to patients occurs in practice, Sublocade may be dispensed to patients. Due to the aforementioned risks, a REMS is necessary to ensure the benefits outweigh the risks of Sublocade and ensure that it is administered by a HCP.

## **8 Risk Management Activities Proposed by the Applicant**

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The Applicant proposed a REMS with ETASU to be sure that Sublocade is administered by a healthcare provider and not dispensed directly to patients. Their rationale for the REMS included that the product contains high doses of medication (100 mg or 300 mg of buprenorphine) and the long-acting formulation increases the risk for CNS depression if used concomitantly with other CNS depressants. In addition, they share the Agency's concerns that the high doses, lack of naloxone and readily injectable formulation may appeal to those who abuse opioids by injecting them. They also studied the

extractability of Sublocade and found that if the product was diverted and extraction was attempted, the buprenorphine could be easily extracted with common household solvents. To limit the ability for Sublocade to be diverted, misused and abused, they proposed a REMS with a Medication Guide and ETASU.

## **8.1 REVIEW OF APPLICANT'S PROPOSED REMS**

In their initial NDA submission, the Applicant proposed a REMS with a Medication Guide, ETASU, implementation plan and a timetable for submission of assessments. They proposed ETASU that included safe use and monitoring, like the elements in the Suboxone/Subutex and BTOD REMS. In addition, they proposed ETASU of certain healthcare settings. The proposed settings would use the existing federal requirements to limit the dispensing of the medication to settings that have a DATA 2000 waived prescriber or are DEA registrants. Their original proposed REMS proposed that distribution would exclude dispensing in retail pharmacy settings, which they believed would prevent dispensing directly to the patient for self-administration. The REMS proposal was complete and included a REMS Document, REMS Supporting Document and materials.

### **8.1.1 REMS Goals**

The proposed REMS goal is to:

- Mitigate the risks of accidental overdose, misuse and abuse
- Inform prescribers, pharmacists and patients of the serious risks of Sublocade
- Inform prescribers, pharmacists and patients about the long-acting nature of Sublocade

***Reviewer's Comments:** DRISK does not recommend mitigating accidental overdose as a goal of the REMS because requiring administration by a HCP will prevent the risk of accidental overdose of Sublocade. The Agency is particularly concerned about the potential risks of Sublocade that could result from intravenous self-administration by the patient. As labeling will indicate, this product should be administered by a HCP and not be provided to the patient to administer at home. The REMS goals for sublingual and oral buprenorphine products indicated for MAT were to mitigate risks that were more likely to occur if product was taken and stored within the patient's home.*

*To address the Agency's and the October 31, 2017 Advisory Committee most serious concern with this product, the Agency proposes the following goal:*

*The goal of the SUBLOCADE REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by:*

- *Ensuring healthcare settings and pharmacies are certified and only dispense SUBLOCADE directly to a healthcare provider for administration by a healthcare provider*

### **8.1.2 REMS Requirements-Medication Guide**

The Applicant proposed that the Medication Guide (MG) be included as part of the REMS.

**Reviewer's Comments:** *The Agency agrees that a MG would be a useful resource for patients to understand their treatment and the risks associated with buprenorphine. However, DRISK has determined it is not necessary to include the MG as an element of the REMS, but should be included as part of the product labeling. As such, the REMS ETASU and materials (described below) need only to include what is minimally necessary to support the goal.*

### **8.1.3 REMS Requirements-ETASU**

The Applicant asserted that once injected into the subcutaneous space Sublocade is not readily abused and diverted. They proposed to minimize misuse, abuse and diversion of Sublocade by requiring that it dispensed only in certain healthcare settings and administered by an HCP. Prescribers, pharmacies and distributors need to follow all applicable federal and state laws with regard to DEA registration and DATA 2000 waivers. Therefore, the Applicant proposed to use already existing databases such as the DEA Registration Validation website or the SAMHSA Buprenorphine Practitioner Verification websites to verify the status of the facility and/or prescriber of their ability to prescribe, receive and store the product. However, for DATA 2000 waived prescribers, the product could be dispensed by a pharmacy in the specific name of the patient to be administered in that office or clinic. The dispensation occurs prior to a patient appointment, see Figure 1.

The Applicant also proposed to include ETASU on safe use and monitoring which are similar to Suboxone/Subutex and BTOD REMS. In the Suboxone/Subutex and BTOD REMS, the REMS materials focus on the induction of treatment, provide guidance on monitoring the patient during treatment and counseling the patient on storing their medications safely. The Sponsor's proposed materials for Sublocade focus on general risks associated with all opioids, such as increased risk of CNS depression when taken concurrently with other depressants, as well as what the patient should expect when they have taken Sublocade, such as lump at the injection site.

**Reviewer's Comments:** *The Agency agrees that Sublocade should be administered by a HCP. The drug was administered by the HCP in the clinical trials and no additional data has been provided to support alternative options for administration. Based on the available data and the potential risks, the Agency has determined that a REMS is necessary to mitigate the risk of serious harm or death that could result from intravenous self-administration by patient, by ensuring healthcare settings and pharmacies are certified and only dispense Sublocade directly to a healthcare provider. These healthcare settings and pharmacies will need to ensure that appropriate safety measures are in place so the product is administered by a HCP. The REMS as designed, is helping to ensure that Sublocade is used and administered by a HCP; however, HCP compliance with the REMS requirements are key to ensuring that the product is administered by a HCP and not dispensed directly to patient.*

*DRISK held several teleconferences with healthcare providers and administrators from American Society of Health-System Pharmacists (ASHP) including representation from the Cleveland Clinic, Indian Health Service (IHS) and Veteran's Administration (VA) to gain a better understanding how this type of product would move through their medication-use system. We were particularly interested in what policies and processes are currently in place for procurement, storage and distribution within these healthcare systems. These took place on the following dates:*

- 10/16/2017: DRISK held a teleconference with ASHP and a representative from the Cleveland Clinic.
- 10/18/2017: DRISK held a teleconference with IHS healthcare representatives.
- 10/20/2017: DRISK held a teleconference with VA healthcare representatives.

*The Agency was interested in identifying possible gaps that where a healthcare system or site may dispense this type of product directly to patients. The teleconferences were instrumental in recognizing the differences between these hospitals and healthcare settings and their clinics and pharmacies. DRISK notes that in some healthcare settings there is a centralized pharmacy for inpatient and outpatient and other systems may have use a separate pathway for procurement of drugs for out pharmacies. DRISK also inquired via an IR how the Applicant proposed to ensure that all dispensing sites, including those in large settings would ensure that Sublocade was not dispensed to patients. In their response, the Applicant proposed certifying and enrolling sites in large healthcare settings. The Agency has determined that all sites receiving product from the wholesaler/distributor should be certified and enrolled. This will ensure that in each case, under the various healthcare settings, there will be processes and procedures in place to ensure that dispensing staff are aware Sublocade should be administered by a HCP and cannot be given directly to patients. To assist healthcare providers with understanding the requirements of the REMS, the Agency is requiring a Fact Sheet that explains how obtain Sublocade for patients in various settings. The Agency is also requiring an enrollment form for pharmacies and healthcare settings to enable certification in the REMS.*

*As Sublocade is a novel treatment as a first depot injection of buprenorphine, because it is administered as a monthly injection it removes the need for daily doses of MAT and therefore could be a useful addition to helping patients with OUD. The PDAC and DSaRM AC voted in favor of Sublocade for approval. The Committee supported a REMS for Sublocade, but expressed concern about limiting access in rural settings if the product is not available in retail pharmacies. Since Sublocade is intended to be administered by HCP and the unadministered product should not be given to patients, the Agency is requiring certification of all pharmacies and healthcare settings that dispense Sublocade. However, individual practitioners that have a DATA 2000 wavier do not need to certify, if they are ordering Sublocade for a named patient through a certified pharmacy.*

*DRISK has determined that HCP training and patient education are not necessary elements to support the goal. HCPs in an office setting must obtain a DATA 2000 waiver to prescribe buprenorphine for MAT outside of OTPs settings, therefore they are already receiving required training on treating OUD with buprenorphine. Due to the depot, injectable formulation of Sublocade, this formulation of buprenorphine has risks that differ from the other buprenorphine products for MAT. As discussed, most of these products are taken and stored at home and as a result are more susceptible to misuse, abuse and accidental overdose. Respiratory depression and NOWS are risks that increase with opioid medications that handled by patients and stored in their homes for use. Since this product, once administered, is not handled by patients, the Appropriate Use Checklist and HCP Brochure, which provide guidance on counseling patients on these risks, are not needed to support the goal of the Sublocade REMS. The REMS*

*for Probuphine is designed to mitigate risks associated with implant formulation. This risk is also not applicable to Sublocade.*

*The Agency's REMS includes the necessary requirements; thoughtful consideration was given to minimizing additional burden on healthcare providers and patients. For this reason, the Sublocade REMS includes a one-time healthcare setting and pharmacy certification and as part of the certification these entities are required to put policies and procedures in place to ensure that Sublocade is not dispensed to patients and train all relevant staff involved in dispensing that the drug must be dispensed directly to a healthcare provider for administration by a healthcare provider, and the drug must not be dispensed to the patient.*

#### **8.1.4 REMS Materials & Key Risk Messages**

The Sponsor has proposed the following materials relevant to their proposed REMS:

- HCP Brochure—this material summarizes important safety issues and messages needed to manage and counsel patients about safe use of this product for prescribers and pharmacists.
- Appropriate Use Checklist—a tool for prescribers to use with patients at the office visits.
- Patient Alert Card—a card for patients to carry that alerts HCPs that they have are on Sublocade therapy and some of the characteristics of this treatment that HCPs should be aware of.
- Letters to prescribers, pharmacists and professional societies informing them about the REMS
- REMS Website

**Reviewer's Comments:** *The Agency does not believe that the HCP Brochure or the Appropriate Use Checklist are needed to support the Sublocade REMS. The Patient Alert Card, which may be a useful tool for patients or caregivers in healthcare settings, also does not support the goal of the REMS. However, letters to healthcare professionals describing the REMS and how to obtain Sublocade are needed. In addition, the website is also a REMS requirement. As discussed, the Agency also proposed a Sublocade REMS Fact Sheet.*

#### **8.1.5 REMS Assessment Plan**

The Applicant proposed a REMS Assessment Plan for Sublocade to include the following for the reporting period:

- An analysis and summary of surveillance and monitoring activities for overdose and misuse and any intervention taken resulting from signals of overdose and misuse. Surveillance will include, among other sources, reports from street ethnography programs.
- An analysis to evaluate Sublocade utilization patterns including frequency of office visits/patient/prescriber, and other indicators of adherence to practices important for safe use.

- An evaluation of patients' and prescribers' understanding of the REMS goals and objectives, (b) (4)
- An evaluation of implementation of REMS outreach during the assessment period, (b) (4)
- A summary of the audits of the specialty pharmacies and specialty distributors

**Reviewer's Comments:** This plan was revised to align with the final REMS (b) (4) the assessment plan includes but is not limited to the following requirements.

#### REMS Operations and Utilization

- a. Number of certified entities; provide for the current reporting period and cumulatively
  - i. healthcare settings that dispense SUBLOCADE
  - ii. pharmacies that dispense SUBLOCADE
- b. Number of wholesalers/ distributors shipping SUBLOCADE; provide for the reporting period and cumulatively
- c. Call Center Report
  - i. Number of contacts
  - ii. Summary of reason for call (Examples include "enrollment question, location of certified healthcare setting, etc") by reporter (prescriber, authorized representative, healthcare setting, pharmacy, patient/caregiver, other)

#### 2. REMS Compliance

- a. Number of audits of certified healthcare settings, pharmacies and wholesalers/distributors or other audits conducted during the reporting period
  - i. Provide the number of expected audits and the number of actual audits conducted, reasons why expected audits weren't conducted, and plan to audit these entities
  - ii. Number of de-certified pharmacies and healthcare settings resulting from audit findings
  - iii. Number of wholesalers/ distributors deactivated resulting from audit findings
  - iv. Summary of all corrective actions and any resulting preventative actions resulting from audit findings for each non-compliant entity
- b. Number of shipments of SUBLOCADE to non-certified healthcare settings or pharmacies, or other locations (e.g., patient's home), source of report, and corrective actions to prevent shipment to non-certified settings and pharmacies.





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11/30/2017

CYNTHIA L LACIVITA  
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Concur

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: November 29, 2017

Reviewer(s): Somya Dunn, M.D., Risk Management Analyst  
Division of Risk Management (DRISK)  
  
Joan Blair, R.N., M.P.H., Health Communications Analyst,  
DRISK

Team Leader: Selena Ready, Pharm.D, DRISK

Division Director: Cynthia LaCivita, Pharm.D, DRISK

Drug Name(s): Buprenorphine extended-release (Sublocade)

Therapeutic Class: Opioid Partial Agonist

Dosage and Route: 100 mg and 300 mg Subcutaneous Depot Injection

Application Type/Number: NDA 209819

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## **1 INTRODUCTION**

The purpose of this review is to document the Division of Risk Management's (DRISK) comments on REMS materials included in the proposed risk evaluation and mitigation strategy (REMS) for Sublocade, a single entity drug-device combination product with buprenorphine base in the ATRIGEL Delivery System. In May 2017, Indivior Incorporated (Indivior) submitted a New Drug Application (NDA 209819) for Sublocade with the proposed indication for the treatment of moderate-to-severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. This NDA was submitted with a proposed REMS and amended on November 14, 20, and 28, 2017. The REMS proposal amended on November 28, 2017 is the subject of this review.

Sublocade is a prefilled syringe and will be packaged with a needle designed for subcutaneous injection once monthly to be administered by a healthcare provider. The risks associated with Sublocade are consistent with other opioids, such as respiratory depression and Neonatal Opioid Withdrawal Syndrome (NOWS). The Agency is however, particularly concerned about potential adverse consequences resulting from intravenous self-administration the risks of misuse and abuse of Sublocade by intravenous self-administration. The Applicant's proposed REMS consists of Medication Guide and elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

DRISK determined that a REMS with ETASU is needed to ensure the benefits of Sublocade outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense Sublocade to ensure that it is administered by healthcare providers and not dispensed directly to patients.

### **1.1 BACKGROUND**

Sublocade is a single entity drug-device combination product with buprenorphine base in the ATRIGEL Delivery System in a prefilled syringe. Buprenorphine, the active ingredient in Sublocade, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981. The ATRIGEL Delivery System has been used in other FDA approved products such as ELIGARD, which is indicated for the palliative treatment of advanced cancer. Sublocade provides sustained plasma levels of buprenorphine over a minimum of 28 days and is intended for the treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. Sublocade is designed to be subcutaneously injected in the abdominal area once monthly.

The product is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Indivior proposed dosing regimens include 300 mg monthly for the first two months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient. If approved, Sublocade would be the first once-monthly injectable buprenorphine product indicated for the treatment of OUD.

NDA 209819 is a 505 (b)(2) application with a designated priority review. The referenced product is Subutex Sublingual Tablet, NDA 20732. The active ingredient in Sublocade is buprenorphine and is available currently as oral tablets, buccal film and also in implant for indicated for Medication-Assisted Treatment (MAT). Currently, all buprenorphine products indicated for MAT of OUD are approved with a REMS. This includes the Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS and the Probuphine REMS.

As an injectable depot device, the Sublocade formulation differs significantly from the sublingual and oral formulations of buprenorphine. Those products are self-administered by patients in their homes and the REMS are designed to mitigate risks associated with accidental overdose, particularly in children as well as misuse, and abuse. This is in contrast to Sublocade which was designed to be administered by a HCP. Probuphine was similarly designed to be administered by HCP, but carries different risks as it is an implant device.

## 1.2 DRISK REVIEWS CONTRIBUTING TO THIS ORIGINAL APPLICATION

Dunn, S. Division of Risk Management Review of the Sublocade REMS materials and Supporting Document, submitted to DARRTS November 16, 2017.

Dunn, S. Division of Risk Management Review of the Sublocade REMS materials and Supporting Document, submitted to DARRTS November 28, 2017.

## 1.3 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209819 relevant to this review:

- 9/28/2016: At this Type C Guidance meeting, the Applicant inquired about the need for a REMS and the need for restricted distribution. They were advised to justify the need for a REMS and that they would need ensure proposed distribution plans are not in violation of applicable laws.
- 12/14/2016: Pre-NDA meeting was held.
- 5/30/2017: NDA 209819 was submitted and the application included a REMS proposal.
-  (b) (4)
- 8/23/2017: The Agency sent an IR to inquire about details of the proposed REMS distribution and operations.
-  (b) (4)
- 9/22/2017: The Agency inquired how the Applicant would ensure that pharmacies within large integrated healthcare settings would ensure that Sublocade would not be dispensed directly to patients.

- 9/28/2017: The Applicant submitted a response to the IR proposing that pharmacies within large integrated healthcare settings would be certified.
- 10/31/2017: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss NDA 209819. The committee voted on evidence of effectiveness in the clinical program and voted in favor of the evidence 17:2. They also voted that the data provided supported the use of the Sublocade 300 mg/300 mg dosing regimen 13:6. They discussed the role of this regimen in potential treatment. For the REMS, they discussed the pros and cons of restricted distribution as proposed by the Applicant and the Agency. They were overwhelmingly in favor of restricted distribution and not allowing Sublocade to be dispensed directly to patients. Some committee members did express concern about access to the product in rural areas. The committee voted 18:1 to approve Sublocade.
- 11/9/2017: The Agency held a teleconference with the Applicant discussing the REMS requirements and provided detailed plan describing what was the needed to develop the REMS Document and materials prior to the action date. The Agency stated that we would require the following materials to be part of the REMS:
  - REMS Document
  - Supporting Document
  - Healthcare Setting and Pharmacy Enrollment Form
  - Fact Sheet describing how various settings obtain Sublocade
  - Letters to Healthcare Providers
  - Updated Website
  - Communication Material for pharmacies to distribute with all product dispensed for named patients to individual DATA 2000 waived prescribers
- 11/9/17: The Agency provided drafts via email of a templated Fact Sheet and a proposed draft REMS Document to the Applicant to assist with the development.
- 11/14/2017: The Agency provided a draft templated Healthcare Setting and Pharmacy Enrollment Form for the Applicant to use as a base to develop their own form.
- 11/14/2017: The Applicant amended their submission and submitted materials in response to the 11/9/2017 teleconference via email and to the EDR on 11/15/17 (Seq 0034).
- 11/16/2017: The Agency provided comments on the Applicant REMS materials 0034 (above).
- 11/20/2017: The Applicant amended their REMS submission via email in response to the FDA's 11/16/2017 comments and submitted to the EDR on 11/21/17 (Seq 0036).
- 11/22/2017: The Agency held a teleconference with the Applicant discussing some of the main points that need to be addressed in the REMS Document, REMS Supporting Document and other materials.
- 11/22/2017: The Agency provided comments on the Applicant REMS materials 0036 (above).

- 11/27/2017: The Agency held a teleconference with the Applicant discussing some of their questions about the Agency’s comments and edits on the REMS materials communicated on 11/22/2017. The materials discussed were those initially proposed by the Applicant on 11/21/2017 (Seq 0036).
- 11/28/2017: The Applicant amended their submission and submitted materials in response to the 11/27/2017 teleconference and 11/22/2017 comments and edits via email and to the EDR (Seq 0039).

## 2 MATERIALS REVIEWED

- Indivior, Inc. REMS Amendment to NDA 209819 for Sublocade, submitted November 28, 2017 (Seq. No. 0039)

## 3 SUMMARY OF APPLICANT’S REMS SUBMISSION AND DRISK COMMENTS

### 3.1 ELEMENTS TO ASSURE SAFE USE

#### 3.1.1 REMS DOCUMENT

In October of 2017, the Agency posted a draft Format and Content of a REMS Document Guidance for Industry<sup>1</sup> which provides updated recommendations for the format and content of a risk evaluation and mitigation strategy (REMS) document for a prescription drug product, including a biological drug products. Because this is a new guidance, DRISK provided a draft REMS Document populated with the proposed Sublocade REMS. The Applicant has had the opportunity to review and provide edits and comments on the REMS Document. In the most recent submission on 11/28/2017, the Applicant made edits to clarify some timing issues that needed to be addressed, such as when they would notify settings that they are certified. They also proposed language to the healthcare setting audit requirements.

Reviewer Comment:

(b) (4) DRISK had communicated with the Applicant on 11/27/2017 and explained that audit language is standard in REMS Documents. So, this will be communicated again today. The REMS Document has been internally cleared and will be sent to the Applicant today, November 29,2017. The goal has been revised to match the current draft boxed warning. It now reads:

*The goal of the SUBLOCADE REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by:*

- *Ensuring healthcare settings and pharmacies are certified and only dispense SUBLOCADE directly to a healthcare provider for administration by a healthcare provider*

*Other changes to the REMS Document were to keep it consistent with templated language. See the attached redlined REMS Document.*

### **3.1.2 REMS SUPPORTING DOCUMENT**

The Supporting Document (SD) describes the Applicant's proposed distribution plan, proposed operations and the Agency proposed Assessment Plan. The Applicant made minor edits to the SD.

#### Reviewer Comment

*The Applicant will need to continue to align the Supporting Document with current labeling and also with the REMS Document. We had minor clarifying edits to the SD. We are requesting that they submit an attachment or appendices of the entire website screenshot document (including the homepage and portal screenshots) with the SD. See the redlined SD.*

### **3.1.3 SUBLOCADE REMS HEALTHCARE SETTING AND PHARMACY ENROLLMENT FORM**

The Applicant has complied with suggestions provided by the Agency. However, the form they submitted had some redundancy and needs further clarifications.

#### Reviewer Comment

*The Agency made additional edits to this form to make it more user friendly. See redlined version of this form for detailed edits.*

### **3.1.4 SUBLOCADE REMS PROGRAM FACT SHEET**

The Applicant had minor edits to this form.

#### Reviewer Comment

*Minimal edits are needed for clarification and to align with the label, see redlined version of this material for detailed edits.*

### **3.1.5 DEAR HEALTHCARE PROVIDER LETTERS**

The Applicant had minor edits to these letters.

#### Reviewer Comment

*Minimal edits are needed for clarification and to align with the label, see redlined version of this material for detailed edits.*

### **3.1.6 SUBLOCADE PROGRAM WEBSITE**

The Applicant provided updated screenshots (b) (4).

#### Reviewer Comment:

*They will need to revise the website screenshots to align with new tracked changes made on the separate document "Sublocade REMS Website Content." They will need some additional changes to align it with the revised enrollment form. See redlined version of this material for detailed edits.*

 (b) (4)  
See  
the request to the Applicant to include a full website screenshot document as an attachment to the Supporting Document.

#### **4 DISCUSSION AND CONCLUSIONS**

Overall, DRISK does agree with most of the changes made to the materials submitted by the Applicant. They have aligned their materials with the label. Audits will be required and the language for this requirement cannot be amended. In addition, they need to make further edits as seen in the attached redlined materials to clarify their program operations and REMS materials.

#### **5 COMMENTS FOR THE SPONSOR**

##### **General Comments:**

- Note redlined revisions and comments on the attached MS Word versions of the materials and make the same changes to the pdf formatted versions of the materials and the website screenshots.
- Ensure that all content is consistent across all the REMS materials and website.

##### ***Sublocade REMS Document***

As discussed, audit language is standard in REMS Documents. The REMS Document has been edited to reflect this. Note this has a revised goal to match the current draft boxed warning. It now reads:

The goal of the SUBLOCADE REMS is to mitigate the risk of serious harm or death that could result from intravenous self-administration by:

- Ensuring healthcare settings and pharmacies are certified and only dispense SUBLOCADE directly to a healthcare provider for administration by a healthcare provider

All your materials should align with this goal. Other changes to the REMS Document were to keep it consistent with templated language. See the attached redlined REMS Document.

##### ***Sublocade REMS Supporting Document***

You will need to continue to align the Supporting Document with current labeling and also with the REMS Document. We had minor clarifying edits to the SD. With your next

submission, submit an attachment or appendices of the **entire website screenshot document (including the homepage and portal screenshots)** with the SD.

See the redlined SD.

***Sublocade REMS Program Healthcare Setting and Pharmacy Enrollment Form:***

- Note proposed changes to clarify the enrollment process for the user and to align with the revised REMS Document.
- Align online enrollment text, content, and options with changes made to this form. The revised screenshots illustrating online enrollment should be revised to reflect changes to this form.
- Make the title of this form on the final formatted pdf version more prominent, so the user immediately knows the intent and purpose of this form. The entire title should be centered and placed in bold and larger font.

***Sublocade REMS Program Dear Healthcare Provider Letter:***

- Align boxed warning content with what is in the revised PI as needed.

***Sublocade REMS Program Fact Sheet: How to Obtain Sublocade:***

- Note redlined comments and review further to ensure that the fact sheet aligns with the revised label.

***Sublocade REMS Program Website Screenshots:***

- Revise the website screenshots to align with new track changes made on the separate document "Sublocade REMS Website Content." You will note additional changes to align it with the revised enrollment form.
- Note: The "Sublocade REMS Website Content" document does not need to be submitted as part of your final REMS submission. However, its content should be used to update the final home page website screenshot.
- The REMS website screenshots for the final REMS submission (b) (4)

**They should be homepage shots only.** See the request to include a full website screenshot document (for the entire site that you have completed as of the submission) as an attachment to the Supporting Document. Overall there will be two separate website screenshot documents. One is a full version attached to the Supporting Document. The other will be a standalone document without the portal screenshots.

**Resubmission Instructions:**

Submit the FINAL REMS materials to your application by **Noon, Thursday, November 30, 2017.** **Any questions on the materials should be communicated immediately upon opening of the business day.** **All content in the materials must align with the revised REMS Document and Prescribing Information.**

The next submission via email and to the Gateway should include Clean MS Word, and final formatted versions of the following eight documents:

- *Sublocade REMS Document*
- *Sublocade REMS Supporting Document*
- *Sublocade REMS Program Healthcare Setting and Pharmacy Enrollment Form*
- *Sublocade REMS Program Dear Healthcare Provider Letter*
- *Sublocade REMS Program Fact Sheet: How to Obtain Sublocade*
- *Sublocade REMS Program Website Screenshots*
- *A compiled pdf document which includes the REMS Document, all REMS materials, and website screenshots (note these screenshots are homepage shots only). This would not include the REMS Supporting Document or MS Word version of the Website Content.*

#### **ATTACHMENTS**

1. Sublocade REMS Document
2. Sublocade REMS Supporting Document (email only)
3. Sublocade REMS Program Healthcare Setting and Pharmacy Enrollment Form
4. Sublocade REMS Program Dear Healthcare Provider Letter
5. Sublocade REMS Program Fact Sheet: How to Obtain Sublocade
6. Sublocade REMS Website Content

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11/29/2017

SELENA D READY  
11/29/2017

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: November 22, 2017

Reviewer(s): Somya Dunn, M.D., Risk Management Analyst  
Division of Risk Management (DRISK)  
  
Joan Blair, R.N., M.P.H., Health Communications Analyst,  
DRISK

Team Leader: Selena Ready, Pharm.D, DRISK

Division Director: Cynthia LaCivita, Pharm.D, DRISK

Drug Name(s): Buprenorphine extended-release (Sublocade)

Therapeutic Class: Opioid Partial Agonist

Dosage and Route: 100 mg and 300 mg Subcutaneous Depot Injection

Application Type/Number: NDA 209819

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## **1 INTRODUCTION**

The purpose of this review is to document the Division of Risk Management's (DRISK) comments on REMS materials included in the proposed risk evaluation and mitigation strategy (REMS) for Sublocade, a single entity drug-device combination product with buprenorphine base in the ATRIGEL Delivery System. In May 2017, Indivior Incorporated (Indivior) submitted a New Drug Application (NDA 209819) for Sublocade with the proposed indication for the treatment of moderate-to-severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. This NDA was submitted with a proposed REMS and amended on November 14 and 20, 2017 via email. The REMS proposal amended on November 20, 2017 is the subject of this review.

Sublocade is a prefilled syringe and will be packaged with a needle designed for subcutaneous injection once monthly to be administered by a healthcare provider. The risks associated with Sublocade are consistent with other opioids, such as respiratory depression and Neonatal Opioid Withdrawal Syndrome (NOWS). The Agency is however, particularly concerned about potential adverse consequences resulting from intravenous self-administration the risks of misuse and abuse of Sublocade by intravenous self-administration. The Applicant's proposed REMS consists of Medication Guide and elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

DRISK determined that a REMS with ETASU is needed to ensure the benefits of Sublocade outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense Sublocade to ensure that it is administered by healthcare providers and not dispensed directly to patients.

### **1.1 BACKGROUND**

Sublocade is a single entity drug-device combination product with buprenorphine base in the ATRIGEL Delivery System in a prefilled syringe. Buprenorphine, the active ingredient in Sublocade, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981. The ATRIGEL Delivery System has been used in other FDA approved products such as ELIGARD, which is indicated for the palliative treatment of advanced cancer. Sublocade provides sustained plasma levels of buprenorphine over a minimum of 28 days and is intended for the treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. Sublocade is designed to be subcutaneously injected in the abdominal area once monthly.

The product is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Indivior proposed dosing regimens include 300 mg monthly for the first two months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient. If approved, Sublocade would be the first once-monthly injectable buprenorphine product indicated for the treatment of OUD.

NDA 209819 is a 505 (b)(2) application with a designated priority review. The referenced product is Subutex Sublingual Tablet, NDA 20732. The active ingredient in Sublocade is buprenorphine and is available currently as oral tablets, buccal film and also in implant for indicated for Medication-Assisted Treatment (MAT). Currently, all buprenorphine products indicated for MAT of OUD are approved with a REMS. This includes the Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS and the Probuphine REMS.

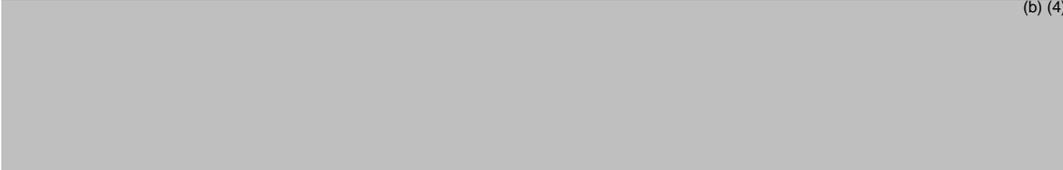
As an injectable depot device, the Sublocade formulation differs significantly from the sublingual and oral formulations of buprenorphine. Those products are self-administered by patients in their homes and the REMS are designed to mitigate risks associated with accidental overdose, particularly in children as well as misuse, and abuse. This is in contrast to Sublocade which was designed to be administered by a HCP. Probuphine was similarly designed to be administered by HCP, but carries different risks as it is an implant device.

## 1.2 DRISK REVIEWS CONTRIBUTING TO THIS ORIGINAL APPLICATION

Dunn, S. Division of Risk Management Review of the Sublocade REMS materials and Supporting Document, submitted to DARRTS November 16, 2017.

## 1.3 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209819 relevant to this review:

- 9/28/2016: At this Type C Guidance meeting, the Applicant inquired about the need for a REMS and the need for restricted distribution. They were advised to justify the need for a REMS and that they would need ensure proposed distribution plans are not in violation of applicable laws.
- 12/14/2016: Pre-NDA meeting was held.
- 5/30/2017: NDA 209819 was submitted and the application included a REMS proposal.
-  (b) (4)
- 8/23/2017: The Agency sent an IR to inquire about details of the proposed REMS distribution and operations.
-  (b) (4)
- 9/22/2017: The Agency inquired how the Applicant would ensure that pharmacies within large integrated healthcare settings would ensure that Sublocade would not be dispensed directly to patients.
- 9/28/2017: The Applicant submitted a response to the IR proposing that pharmacies within large integrated healthcare settings would be certified.

- 10/31/2017: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss NDA 209819. The committee voted on evidence of effectiveness in the clinical program and voted in favor of the evidence 17:2. They also voted that the data provided supported the use of the Sublocade 300 mg/300 mg dosing regimen 13:6. They discussed the role of this regimen in potential treatment. For the REMS, they discussed the pros and cons of restricted distribution as proposed by the Applicant and the Agency. They were overwhelmingly in favor of restricted distribution and not allowing Sublocade to be dispensed directly to patients. Some committee members did express concern about access to the product in rural areas. The committee voted 18:1 to approve Sublocade.
- 11/9/2017: The Agency held a teleconference with the Applicant discussing the REMS requirements and provided detailed plan describing what was the needed to develop the REMS Document and materials prior to the action date. The Agency stated that we would require the following materials to be part of the REMS:
  - REMS Document
  - Supporting Document
  - Healthcare Setting and Pharmacy Enrollment Form
  - Fact Sheet describing how various settings obtain Sublocade
  - Letters to Healthcare Providers
  - Updated Website
  - Communication Material for pharmacies to distribute with all product dispensed for named patients to individual DATA 2000 waived prescribers
- 11/9/17: The Agency provided drafts via email of a templated Fact Sheet and a proposed draft REMS Document to the Applicant to assist with the development.
- 11/14/2017: The Agency provided a draft templated Healthcare Setting and Pharmacy Enrollment Form for the Applicant to use as a base to develop their own form.
- 11/14/2017: The Applicant amended their submission and submitted materials in response to the 11/9/2017 teleconference via email and to the EDR on 11/15/17 (Seq 0034)
- 11/16/2017: The Agency provided comments on the Applicant REMS materials 0034 (above).
- 11/20/2017: The Applicant amended their REMS submission via email in response to the FDA's 11/16/2017 comments and submitted to the EDR on 11/21/17 (Seq 0036). These are reviewed here.
- 11/22/2017: The Agency held a teleconference with the Applicant discussing some of the main points that need to be addressed in the REMS Document, REMS Supporting Document and other materials. These are discussed below.

## **2 MATERIALS REVIEWED**

- Indivior, Inc. REMS Amendment to NDA 209819 for Sublocade, submitted November 21, 2017 (Seq. No. 0036)

- Lee, K. FDA Office of Prescription Drug Promotion Review of Sublocade REMS materials, submitted to DARRTS November 16, 2017.

### **3 OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP) CONSULT**

DRISK consulted OPDP on November 8, 2017 for the Sublocade REMS materials. They received the REMS materials from DRISK on November 15, 2017. Koung Lee, the OPDP reviewer entered his review into DARRTS on November 16, 2017.

The logo for Sublocade was forwarded to OPDP for their review on November 21, 2017. Koung Lee, OPDP reviewer noted via email that they had no concerns with the Applicant's proposed logo for Sublocade.

DRISK considered OPDP's comments and noted OPDP's concerns. DRISK agreed with all OPDP's comments and made changes to the REMS materials accordingly, these comments are incorporated into discussion below.

### **4 SUMMARY OF APPLICANT'S REMS SUBMISSION AND DRISK COMMENTS**

#### **4.1 ELEMENTS TO ASSURE SAFE USE**

##### **4.1.1 REMS DOCUMENT**

In October of 2017, the Agency posted a draft Format and Content of a REMS Document Guidance for Industry<sup>1</sup> which provides updated recommendations for the format and content of a risk evaluation and mitigation strategy (REMS) document for a prescription drug product, including a biological drug products. Because this is a new guidance, DRISK provided a draft REMS Document populated with the proposed Sublocade REMS for their review on 11/9/2017. The Applicant reviewed the REMS Document and made several edits. These included (b) (4)

(b) (4) They also changed the word "train" to (b) (4), throughout the document. They added that healthcare settings would have to (b) (4)

(b) (4).  
They also added details about timing of mailings, audits and approval. For example, they state that audits of pharmacies and distributors would occur within one year of commercial product availability. They proposed that they will have online enrollment.

In the communication sent to the Applicant regarding their edits on 11/16/17, the Agency clarified that all the healthcare settings and pharmacies that dispense Sublocade will need to be certified and asked the Applicant to align all their materials with this requirement.

In the teleconference with the Applicant on 11/22/17, the Agency explained the rationale for maintaining the Agency's draft language in the REMS Document as it follows the recently released *draft Format and Content of a REMS Document*

*Guidance for Industry* and in general promotes standardization with REMS.

Reviewer Comment:

*The pre-cleared REMS Document will be sent to the Applicant today, November 21, 2017. The goal has been revised to match the current draft boxed warning. It now reads:*

*The goal of the REMS is to mitigate the risk of serious harm or death with intravenous self-administration by:*

- *Ensuring healthcare settings and pharmacies are certified and only dispense Sublocade directly to a healthcare provider for administration by a healthcare provider*

*Other changes to REMS Document includes when possible retention of templated language from the guidance and additional clarification regarding auditing requirements. See the attached REMS Document.*

#### **4.1.2 REMS SUPPORTING DOCUMENT**

The Supporting Document (SD) describes the Applicant's proposed distribution plan and proposed operations and as requested the Applicant updated it to align with the Agency's requirement to certify all sites that dispense Sublocade. It also incorporates language from the label and from the proposed REMS Document. The Agency has provided details on what specific types of adverse event reporting should be included and specific compliance metrics, including shipment data and details on the program outreach. These were incorporated into a proposed Assessment Plan and then incorporated into the SD.

Reviewer Comment

*The Applicant will need to align the Supporting Document with current labeling and also with the REMS Document. As discussed on the teleconference, we have provided additional metrics to their REMS Assessment Plan. In addition, the Applicant needs to include how distributors will ensure that there are DATA 2000 waived HCPs at the shipment sites.*

#### **4.1.3 SUBLOCADE REMS HEALTHCARE SETTING AND PHARMACY ENROLLMENT FORM**

The Applicant updated the form to include an additional page to capture the sub-settings that may exist under a larger healthcare setting or within a healthcare system. There were other changes as well, including the mention of a "(b) (4)" at sub-setting sites. They also edited the attestations (b) (4)

Reviewer Comment

*The Agency made additional edits to this form to make it more user friendly and clarify that sub-setting sites under one authorized representative can either be classified as pharmacies or healthcare settings. We also informed the Applicant at the teleconference on 11/22/17 that all certified sites would need to abide by the alert attestation and that*

*attestation would need to remain with no exemption. See redlined version of this form for detailed edits.*

#### **4.1.4 SUBLOCADE REMS PROGRAM FACT SHEET**

The Applicant aligned this material with the Agency's request to have this material focus on how various stakeholders would obtain Sublocade.

Reviewer Comment

*Minimal edits were needed, see redlined version of this material for detailed edits.*

#### **4.1.5 DEAR HEALTHCARE PROVIDER LETTERS**

The Applicant submitted letters consistent with the Agency edits and suggestions on 11/16/17. They updated the boxed warning statement from the label and Indivior's Medical Information phone number. They also proposed attaching a list of certified pharmacies to this letter.

Reviewer Comment

*The Agency would like the letter reformatted so that it does not exceed two pages (front and back). See redlined version of this material for detailed edits.*

#### **4.1.6 SUBLOCADE PROGRAM WEBSITE**

(b) (4). They also revised content on the homepage of the website regarding getting started in the enrollment process and how to enroll online, via fax, email, and mail. They expressed understanding of the Agency's previous communication (11/16/17) that online enrollment must be fully operational by the date Sublocade is first commercially distributed.

Reviewer Comment:

*See redlined version of this material for detailed edits.*

### **5 DISCUSSION AND CONCLUSIONS**

Overall, DRISK does agree with most of the changes made to the materials submitted by the Applicant. They have aligned their materials with the requirement that all the healthcare settings and pharmacies that dispense Sublocade will need to be certified and have amended the Sublocade REMS Program Healthcare Setting and Pharmacy Enrollment Form to capture data from and clarify all the sites that may be under one authorized representative. Audits will be required and this was communicated in the teleconference as well as on the material edits being provided today. In addition, they need to make further edits as seen in the attached redlined materials to clarify their program operations and REMS materials.

### **6 COMMENTS FOR THE SPONSOR**

**General Comments:**

- Note redlined revisions and comments on the attached MS Word versions of the materials and make the same changes to the pdf formatted versions of the materials and the website screenshots.
- Put page numbers at the bottom of each page of the REMS materials as follows: "Page 1 of 3, 2 of 3, 3 of 3," etc.
- **Use darker font throughout all the REMS materials for easier reading and copying.**
- Spell out "HCP" in all the materials as "healthcare provider."
- Ensure that all content is consistent across all REMS materials and website.
- Add a period to the end of all complete sentences, including "Where Can I Find More Information..." sections in the REMS materials.
- The term "authorized representative" should **not** be capitalized in the REMS materials, except when noted as an option in the enrollment form.
- Align the list of possible healthcare settings throughout the REMS materials with the revised list noted on the "Healthcare Setting Information" page of the enrollment form.

### **Resubmission Instructions:**

Submit the following revised **FINAL** REMS materials to your application by **noon, eastern standard time Tuesday, November 28, 2017.** **All content in the materials must align with the revised REMS Document and Prescribing Information.**

This will be the final materials submission. You will need to include a compiled pdf document which includes the REMS Document, all REMS materials, and website screenshots. This compiled pdf. would not include the REMS Supporting Document or MS Word version of the Website Content.

### **REMS Document**

The goal has been revised to match the current draft boxed warning. It now reads:

The goal of the REMS is to mitigate the risk of serious harm or death with intravenous self-administration by:

- Ensuring healthcare settings and pharmacies are certified and only dispense Sublocade directly to a healthcare provider for administration by a healthcare provider

Other changes to REMS Document include retention of templated language and detailed audit requirements. See the attached REMS Document.

### **REMS Supporting Document**

The Agency has determined what specific types of adverse event reporting we would will require, specific compliance requirements, and what information we will need to assess the REMS. These were incorporated into a proposed Assessment Plan and incorporated

into the SD. At the teleconference today, we asked you to explain if and how distributors will ensure that there are DATA 2000 waived HCPs at the shipment sites. You have indicated that this is part of the process. Questions to clarify this operation are included with the redlined SD.

### **Sublocade REMS Program Healthcare Setting and Pharmacy Enrollment Form**

- Ensure that all language aligns with the revised REMS Document, particularly the attestations and use of the word "train" vs. "(b) (4)." ."
- Reformat this form so the text fits on 2-3 pages. Use of a smaller font size is acceptable.
- Add data fields/lines on the last page of the form "Healthcare Setting Information" for the authorized representative name and some basic contact information, so the REMS program will know that this particular healthcare setting is associated with a specific authorized representative.
- Note proposed changes to options for setting type on "Healthcare Setting Information" page.
- Align online enrollment text, content, and options with changes made to this form. The revised screenshots illustrating online enrollment should be revised to reflect changes to this form.

### **Sublocade REMS Program Fact Sheet: How to Obtain Sublocade**

Note redlined comments and review further to ensure that the fact sheet aligns with the revised label.

### **Sublocade REMS Program Dear Healthcare Provider Letter**

- Align boxed warning content with what is in the revised PI.
- Reformat the text and layout so the letter is no longer than two pages.

### **Sublocade REMS Program Website Screenshots**

- Remove (b) (4)
- Spell out "HCP" on the homepage of the website.
- Use complete names of REMS materials in the list of "Materials for Sublocade REMS."
- Align all website content with changes made in the other REMS materials (particularly the enrollment form), REMS Document, the label, and the text from the separate document "Sublocade REMS Website Content."

Note: The "Sublocade REMS Website Content" document does not need to be submitted as part of your final REMS submission. However, its content should be used to update the final homepage website screenshot.

## **ATTACHMENTS**

1. Sublocade REMS Document
2. Sublocade REMS Supporting Document (email only)
3. Sublocade REMS Program Healthcare Setting and Pharmacy Enrollment Form
4. Sublocade REMS Program Dear Healthcare Provider Letter
5. Sublocade REMS Program Fact Sheet: How to Obtain Sublocade
6. Sublocade REMS Website Content

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOMYA V DUNN  
11/22/2017

CYNTHIA L LACIVITA  
11/22/2017

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW**

Date: November 16, 2017

Reviewer(s): Somya Dunn, M.D., Risk Management Analyst  
Division of Risk Management (DRISK)  
  
Joan Blair, R.N., M.P.H., Health Communications Analyst,  
DRISK

Team Leader: Selena Ready, Pharm.D, DRISK

Division Director: Cynthia LaCivita, Pharm.D, DRISK

Drug Name(s): Buprenorphine extended-release (Sublocade)

Therapeutic Class: Opioid Partial Agonist

Dosage and Route: 100 mg and 300 mg Subcutaneous Depot Injection

Application Type/Number: NDA 209819

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## 1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) comments on REMS materials included in the proposed risk evaluation and mitigation strategy (REMS) for Sublocade, a single entity drug-device combination product with buprenorphine base in the ATRIGEL Delivery System. In May 2017, Indivior Incorporated (Indivior) submitted a New Drug Application (NDA 209819) for Sublocade with the proposed indication for the treatment of moderate-to-severe opioid use disorder in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. Sublocade is a prefilled syringe and will be packaged with a needle designed for subcutaneous injection once monthly to be administered by a healthcare provider. The risks associated with Sublocade are consistent with other opioids, such as respiratory depression and Neonatal Opioid Withdrawal Syndrome (NOWS). The Agency is however, particularly concerned about potential adverse consequences resulting from intravenous self-administration the risks of misuse and abuse of Sublocade by intravenous self-administration. The Applicant's proposed REMS consists of Medication Guide and elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

DRISK determined that a REMS with ETASU is needed to ensure the benefits of Sublocade outweigh its risks. The ETASU will consist of a one-time certification of healthcare settings and pharmacies that order and dispense Sublocade to ensure that it is administered by healthcare providers and not dispensed directly to patients.

### 1.1 BACKGROUND

Sublocade is a single entity drug-device combination product with buprenorphine base in the ATRIGEL Delivery System in a prefilled syringe. Buprenorphine, the active ingredient in Sublocade, is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Buprenorphine was approved for medical use in the United States in 1981. The ATRIGEL Delivery System has been used in other FDA approved products such as ELIGARD, which is indicated for the palliative treatment of advanced cancer. Sublocade provides sustained plasma levels of buprenorphine over a minimum of 28 days and is intended for the treatment of moderate to severe opioid use disorder (OUD) in patients who have undergone induction to suppress opioid withdrawal signs and symptoms with a transmucosal buprenorphine-containing product. Sublocade is designed to be subcutaneously injected in the abdominal area once monthly.

The product is proposed to be used as part of a complete treatment plan to include counseling and psychosocial support. Indivior proposed dosing regimens include 300 mg monthly for the first two months followed by maintenance treatment of 100 mg or 300 mg monthly based on the clinical condition of the patient. If approved, Sublocade would be the first once-monthly injectable buprenorphine product indicated for the treatment of OUD.

NDA 209819 is a 505 (b)(2) application with a designated priority review. The referenced product is Subutex Sublingual Tablet, NDA 20732. The active ingredient in Sublocade is buprenorphine and is available currently as oral tablets, buccal film and also

in implant for indicated for Medication-Assisted Treatment (MAT). Currently, all buprenorphine products indicated for MAT of OUD are approved with a REMS. This includes the Suboxone/Subutex REMS, the shared system Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS and the Probuphine REMS.

As an injectable depot device, the Sublocade formulation differs significantly from the sublingual and oral formulations of buprenorphine. Those products are self-administered by patients in their homes and the REMS are designed to mitigate risks associated with accidental overdose, particularly in children as well as misuse, and abuse. This is in contrast to Sublocade which was designed to be administered by a HCP. Probuphine was similarly designed to be administered by HCP, but carries different risks as it is an implant device.

## 1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209819 relevant to this review:

- 9/28/2016: At this Type C Guidance meeting, the Applicant inquired about the need for a REMS and the need for restricted distribution. They were advised to justify the need for a REMS and that they would need ensure proposed distribution plans are not in violation of applicable laws.
- 12/14/2016: Pre-NDA meeting was held.
- 5/30/2017: NDA 209819 was submitted and the application included a REMS proposal.
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- 8/23/2017: The Agency sent an IR to inquire about details of the proposed REMS distribution and operations.
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- 9/22/2017: The Agency inquired how the Applicant would ensure that pharmacies within large integrated healthcare settings would ensure that Sublocade would not be dispensed directly to patients.
- 9/28/2017: The Applicant submitted a response to the IR proposing that pharmacies within large integrated healthcare settings would be certified.
- 10/31/2017: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held to discuss NDA 209819. The committee voted on evidence of effectiveness in the clinical program and voted in favor of the evidence 17:2. They also voted that the data provided supported the use of the Sublocade 300 mg/300 mg dosing regimen 13:6. They discussed the role of this regimen in potential treatment. For the REMS, they discussed the pros and cons of restricted distribution as proposed by the Applicant and the Agency. They were overwhelmingly in favor of restricted distribution and not allowing Sublocade to

be dispensed directly to patients. Some committee members did express concern about access to the product in rural areas. The committee voted 18:1 to approve Sublocade.

- 11/9/2017: The Agency held a teleconference with the Applicant discussing the REMS requirements and provided detailed plan describing what was the needed to develop the REMS Document and materials prior to the action date. The Agency stated that we would require the following materials to be part of the REMS:
  - REMS Document
  - Supporting Document
  - Healthcare Setting and Pharmacy Enrollment Form
  - Fact Sheet describing how various settings obtain Sublocade
  - Letters to Healthcare Providers
  - Updated Website
  - Communication Material for pharmacies to distribute with all product dispensed for named patients to individual DATA 2000 waived prescribers
- After the meeting, the Agency provided drafts via email of a templated Fact Sheet and a proposed draft REMS Document to the Applicant to assist with the development.
- 11/14/2017: The Agency provided a draft templated Healthcare Setting and Pharmacy Enrollment Form for the Applicant to use as a base to develop their own form.
- 11/14/2017: The Applicant submitted materials in response to the 11/9/2017 teleconference via email. These were submitted to the EDR, see below, and are reviewed here.

## **2 MATERIALS REVIEWED**

Indivior, Inc. REMS Amendment to NDA 209819 for Sublocade, submitted November 15, 2017 (Seq. No. 0034)

## **3 SUMMARY OF APPLICANT’S REMS SUBMISSION AND DRISK COMMENTS**

### **3.1 ELEMENTS TO ASSURE SAFE USE**

#### **3.1.1 REMS DOCUMENT**

In October of 2017, the Agency posted a draft Format and Content of a REMS Document Guidance for Industry<sup>1</sup> which provides updated recommendations for the format and content of a risk evaluation and mitigation strategy (REMS) document for a prescription drug product, including a biological drug products. Because this is a new guidance, DRISK provided a draft REMS Document populated with the proposed Sublocade

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<sup>1</sup><https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>

REMS for their review on 11/9/2017. The Applicant reviewed the REMS Document and made several edits. These included specific examples of healthcare settings that would need to be certified and they (b) (4)

. They also changed the word “train” to (b) (4)” throughout the document. They added that healthcare settings would have to (b) (4)

.” They also added details about timing of mailings, audits and approval. For example, they state that audits of pharmacies and distributors would occur within one year of commercial product availability. They propose that they will have online enrollment.

#### Reviewer Comment

*The Applicant described the healthcare settings that need certification as “certain healthcare settings” and provided examples. In addition, in other materials, described and reviewed below, they indicate that only “certain” settings will need certification. All the healthcare settings and pharmacies that dispense Sublocade will need to be certified. This change will need to be made in the REMS Document as well to the other materials. DRISK does not agree with all the proposed changes, including the examples of healthcare settings and use of the word “(b) (4)” We also do not agree with the timings of audits. Since the REMS Document is still under review and in clearance, DRISK will not provide comments to the Applicant at this time.*

### **3.1.2 REMS SUPPORTING DOCUMENT**

The Supporting Document describes the Applicant’s proposed distribution and plan and proposed operations. It also incorporates language from the label and from the proposed REMS Document. The Applicant does not describe certification of all healthcare settings and pharmacies.

#### Reviewer Comment

*The Applicant will need align the Supporting Document with current labeling and also with the REMS Document. They will need to clarify that ALL healthcare settings and pharmacies that dispense Sublocade are certified. Their description of operations must be consistent with this.*

### **3.1.3 SUBLOCADE REMS HEALTHCARE SETTING AND PHARMACY ENROLLMENT FORM**

The Applicant received a templated Healthcare Setting and Pharmacy Enrollment Form on 11/14/2017. They made minimal changes to this form. However, they were asked to further populate the form to include the information that would be needed in order for settings to certify.

#### Reviewer Comment

*The Applicant will need to adjust this form to gather appropriate information for all healthcare settings and pharmacies to certify. They must consider settings where there is one authorized representative gathering data and certifying for multiple dispensing sites under their authority and include appropriate spaces for this information as well as*

*appropriate attestations for this purpose or propose an alternative method. The Agency has provided some comments and edits for their review.*

### **3.1.4 SUBLOCADE REMS PROGRAM FACT SHEET**

At the 11/9/2017 teleconference, DRISK informed the Applicant that the Fact Sheet should describe how various stakeholders, DATA 2000 waived providers in particular, should obtain Sublocade. The Applicant submitted the Sublocade REMS Program Fact Sheet back to the Agency with significant edits. They described the REMS program in more detail and reorganized the information to include those details at the beginning of the form. They placed the information relevant to DATA 2000 waived providers towards the end of the form.

#### Reviewer Comment

*The purpose of this Fact Sheet is to provide information on how to obtain Sublocade, particularly since DATA 2000 waived providers that want to receive Sublocade for a specific patient for a set appointment do not need to certify in this program. Certification is limited to settings that are dispensing Sublocade. In order to minimize burden on these DATA 2000 waived providers and to enable better access for patients, the Agency believes that this Fact Sheet should be clear and focus on this information. As a result, we reorganized the form to reflect this and minimized details that are available in the Sublocade REMS Healthcare Setting and Pharmacy Enrollment Form, website and Dear Healthcare Provider letters.*

### **3.1.5 DEAR HEALTHCARE PROVIDER LETTERS**

The Applicant submitted letters consistent with their revised Fact Sheet.

#### Reviewer Comment

*The Agency was not in agreement with the revisions to the letters, as a result, the letters required significant changes. The Agency made changes to create shorten the letters to encourage stakeholders to read it. The Applicant should include the Fact Sheet with these letters when mailing to stakeholders so that they know how to obtain Sublocade. They can also refer stakeholders to the enrollment form and REMS website to learn about program requirements and certification.*

### **3.1.6 SUBLOCADE PROGRAM WEBSITE**

The Applicant submitted a word document for this piece of the REMS. Their proposal included a list of REMS materials, indication statement, adverse event reporting, and where to obtain additional information about the REMS program.

#### Reviewer Comment

*The Applicant will need to replace website content with content outlined in a separate Word document entitled, “Sublocade REMS Website Content.” They will need to include the Sublocade product logo for our review. The website screenshots must show all content and functionality of the website, including the healthcare setting enrollment and pharmacy enrollment process. Per the Sublocade REMS Document,*

*online enrollment must be fully operational by the date Sublocade is first commercially distributed.*

(b) (4)

#### **4 DISCUSSION AND CONCLUSIONS**

Overall, DRISK does not agree with many of the changes made to several of the materials submitted by the Applicant. Their program will need certify all the healthcare settings and pharmacies that dispense Sublocade, not “certain healthcare settings” as proposed. They will need to make changes accordingly to the Supporting Document, Sublocade REMS Program Healthcare Setting and Pharmacy Enrollment Form, Sublocade REMS Program Fact Sheet, Sublocade REMS Program Dear Healthcare Provider Letter and Sublocade REMS Website. In addition, they need to make further edits as seen in the attached redlined materials to clarify their program and REMS materials.

#### **5 COMMENTS FOR THE SPONSOR**

##### **General Comments:**

- Do not capitalize all of the letters in Sublocade throughout the REMS materials.
- Use bold and italicized font for all titles of REMS materials through all of the REMS materials.
- Indicate throughout the REMS materials how prescribers will know which pharmacies are certified (other than the REMS website.)
- Ensure that all content that is consistent across all of the REMS materials and website.

##### **Resubmission Instructions:**

Submit the following revised REMS materials to your application by **COB, November 20, 2017**. **All content in the materials must align with the revised REMS Document and Prescribing Information.**

Accept the track changes with which you agree in the MS Word newly redlined documents and only indicate any new ones you propose as redlined changes in your next submission. The next submission via email and to the Gateway should include Clean MS Word, Tracked MS Word, and final formatted versions of each document you submit.

##### **REMS Document**

We note that your REMS Document contained several changes. Since the REMS Document still is undergoing review and clearance, we will not provide comments at this time. However, we will send an updated version for your review in the next week.

Your REMS Document and many of your materials indicate that “certain healthcare settings” will be certified. Note that the Agency is requiring that ALL settings that dispense Sublocade will need to certify. This would include the pharmacies in your proposed distribution plan that dispense to DATA 2000 waived prescribers for named patients. All your materials must be updated to reflect this requirement.

### **REMS Supporting Document**

You will need align the Supporting Document with current labeling and also with the REMS Document. Clarify that ALL healthcare settings and pharmacies that dispense Sublocade are certified. Your description of your operations must be consistent with this requirement.

### **Sublocade REMS Program Healthcare Setting and Pharmacy Enrollment Form**

You will need to adjust this form to gather appropriate information for all healthcare settings and pharmacies to certify. You must consider settings where there is one authorized representative gathering data and certifying for multiple dispensing sites under their authority and include appropriate spaces for this information as well as appropriate attestations for this purpose or propose an alternative method. Note redlined revisions and comments on the attached MS Word document. Online enrollment must be operational before Sublocade is first commercially distributed. The pharmacist should be listed as the first category of authorized representative, as they are most likely to serve in this role.

### **Sublocade REMS Program Fact Sheet: How to Obtain Sublocade**

The purpose of this Fact Sheet is to provide information on how to obtain Sublocade, particularly since DATA 2000 waived providers that want to receive Sublocade for a specific patient for a set appointment do not need to certify in this program. Certification is limited to settings that are dispensing Sublocade. In order to minimize burden on these DATA 2000 waived providers and to enable better access for patients, the Agency believes that this Fact Sheet should be clear and focus on this information. As a result, we reorganized the form to reflect this and minimized details that are available in the Sublocade REMS Healthcare Setting and Pharmacy Enrollment Form, website and Dear Healthcare Provider letters. Note the new title and revisions to create a shorter version of this fact sheet that focuses primarily on how stakeholders can obtain Sublocade. Stakeholders should be directed to the Sublocade REMS Website or enrollment form to learn more about the REMS program requirements and certification process.

### **Sublocade REMS Program Dear Healthcare Provider Letter**

Note revisions to create a shorter version of this letter and to encourage stakeholders to read it. You should include the Fact Sheet when mailing this letter so stakeholders know how to obtain Sublocade. Refer stakeholders to the enrollment form and REMS website to learn about program requirements and certification.

(b) (4)

### **Sublocade REMS Program Website Screenshots**

Replace website content with content outlined in a separate MS Word document entitled, *Sublocade REMS Website Content*. Include the Sublocade product logo for the Agency's review in your next submission. In your next submission, the website screenshots must show all content and functionality of the website, including the healthcare setting enrollment process. Per the Sublocade REMS Document, online enrollment must be fully operational by the date Sublocade is first commercially distributed.

### **ATTACHMENTS**

1. Sublocade REMS Supporting Document (email only)
2. Sublocade REMS Program Healthcare Setting and Pharmacy Enrollment Form
3. Sublocade REMS Program Dear Healthcare Provider Letter
4. Sublocade REMS Program Website Screenshots
5. Sublocade REMS Program Fact Sheet: How to Obtain Sublocade
6. Sublocade REMS Website Content

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOMYA V DUNN  
11/16/2017

SELENA D READY  
11/16/2017