

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209128Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	209128
Applicant Name	AcelRx Pharmaceuticals, Inc.
Date of Submission	May 3, 2018
PDUFA Goal Date	November 2, 2018
Proprietary Name / Established (USAN) Name	DSUVIA (sufentanil)
Dosage Forms / Strength	Sublingual tablet / 30 mcg
Proposed Indication(s)	Management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting
Recommended Indication(s)/Population(s)	DSUVIA is indicated for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
Applicant Proposed Dosing Regimen(s)	A single sufentanil sublingual tablet 30 micrograms (SST 30 mcg), on an as needed basis, per patient request, with a minimum of 1 hour between doses. Dosing not to exceed 12 tablets in 24 hours.
Action NME:	Approval

Signatory Authority Review Template

1. Introduction

This memo will discuss the rationale for approval of this application.

This is the second review cycle for a 505(b)(2) new drug application (NDA) for Dsuvia, a drug-device combination product containing 30 mcg of the potent opioid agonist, sufentanil, for use as an analgesic in a medically-supervised setting. The Applicant is AcelRx Pharmaceuticals, Inc. The product is intended to be administered by a healthcare provider on an as-needed basis with a minimum interval of one hour between doses. The application received a complete response action based on the following deficiencies excerpted from the action letter:

1. The safety database, while suitable in number of patients, did not contain a sufficient number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of Dsuvia. This is particularly important as there is a nearly 4-fold increase in the exposure and a more than 2-fold increase in the maximum concentration when Dsuvia is dosed at steady state.

To address this deficiency:

Collect additional data in at least 50 patients with postoperative pain sufficient to evaluate the safety of Dsuvia for a period following the maximum dosing proposed.

2. We have determined that the human factors (HF) validation study data did not demonstrate that the user interface supports safe and effective use of the product by intended users for intended uses and environments. Failures that result in dropped sufentanil tablets pose a risk for accidental exposure, improper dosing, and diversion. Overall, we do not find the risk acceptable and note that you did not propose any additional measures to further mitigate the risk.

To address this deficiency:

Develop mitigation strategies to address the risk of dropped sufentanil tablets. Conduct another HF validation study to demonstrate the effectiveness of the recommended mitigation strategies in addressing the use-related errors that were observed in your validation study and to ensure that the changes do not introduce new risks.

Additional recommendations for the instructions for use and graphics on the product pouch were also provided.

2. Background

The applicant has adequately responded to the complete response. There were additional stability data, no new nonclinical data, and no new clinical pharmacology data. They were modifications made to the proposed REMS which is intended to keep Dsuvia out of the home and restrict its use to supervised medical settings with adequate monitoring ability.

The additional material was reviewed, and is summarized in the combined Clinical/CDTL review:

The application is supported by reference to the Agency's previous findings of efficacy and safety for Sufenta (sufentanil citrate for injection; NDA 19050), cross reference to safety data for sufentanil sublingual tablets 15 mcg (proposed tradename Zalviso; NDA (b) (4)), another drug-device combination product that contains 15 mcg of sufentanil and was intended to be administered by a patient using a different device, a Phase 3 placebo-controlled sufentanil sublingual tablet 30 mcg trial (SAP301), and two Phase 3 open-label sufentanil sublingual tablets 30 mcg studies. Of note, the sufentanil sublingual tablets 15 mcg application received a complete response on July 25, 2014, primarily due to issues surrounding the device and inadvertent loss of dispensed tablets.

The efficacy of sufentanil sublingual tablets 30 mcg was evaluated in one placebo-controlled Phase 3 trial in post-surgical adult patients following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery with acute pain. This trial was adequate and well-controlled and provided evidence of the efficacy of sufentanil sublingual tablets 30 mcg in treating acute pain, based on the time-weighted summed pain intensity difference from baseline over 12 hours (SPID12).

The safety profile of sufentanil sublingual tablets 30 mcg in acute pain was consistent with the typical safety profile of an opioid agonist, however there were two area of safety concern that required further evaluation: the safety of sufentanil sublingual tablets 30 mcg in patients requiring the maximum dosing proposed for labeling and the risk of misplaced tablets. Given these safety concerns, the application received a complete response and was not approved on October 11, 2017. The focus of this review is the Applicant's resubmission to address these concerns. To address the safety of sufentanil sublingual tablets 30 mcg in patients requiring the maximum dosing proposed for labeling, the Applicant reduced the maximum daily dose from 24 to 12 sufentanil sublingual 30 mcg tablets per day and provided new pooled safety analyses. The Applicant's analyses support the proposed maximum daily dose. To address the concern of misplaced tablets, the Applicant modified the directions for use and performed another human factors validation study. The Agency has determined that the human factors validation study support the safe and effective use of the product.

The application was discussed at an Anesthetic and Analgesic Advisory Committee meeting on October 12, 2018, and the majority of committee members recommended. Sufentanil sublingual tablets 30 mcg offer a benefit for the treatment of acute pain and the risks are consistent with other opioids or can be managed with a REMS with ETASU.

This product will have an evaluation and risk mitigation strategy, (REMS) with elements to assure safe use, (ETASU). As summarized in the Clinical/CDTL review:

Because of the small tablet size of sufentanil sublingual tablet 30 mcg there is a risk of dropping or misplacing the tablet during administration which increases the risk of accidental exposure,

overdose, and death, particularly in children. We determined that the benefit may outweigh the risk of accidental exposure if sufentanil sublingual tablet 30 mcg is administered by a healthcare provider only in certified medically supervised settings. Sufentanil sublingual tablet 30mcg is not intended for outpatient use (e.g., dispensed by a retail pharmacy or in a patient's home). If restricted to medically supervised settings in which sufentanil sublingual tablet 30 mcg was studied, such as hospitals, emergency departments, and surgery centers, it would reduce the risk of accidental exposure and ensure that sufentanil sublingual tablet 30 mcg is administered by a HCP who is able to manage acute respiratory depression in a setting equipped for opioid overdose. This REMS will not specifically address the risks of abuse, misuse, and addiction because this product will be used exclusively in inpatient settings and other opioids intended for inpatient use have not required a REMS to mitigate these risks.

The Agency's proposed REMS is intended to support the safe use of sufentanil sublingual tablet 30 mcg while imposing the minimal burden for prescribers, dispensers, and the targeted patient population.

3. Discussion

The United States is struggling with an opioid crisis. Prescription opioid abuse has been a major part of this crisis. Every decision about whether to approve a new opioid analgesic must be based on the considerations of benefit and risk for the patient, and for negative (or positive) impact on the public health.

The first question for this application is whether there is a favorable benefit – risk balance. Sufentanil is listed under schedule II of the Controlled Substances Act; it does have a high risk for abuse. It is common for patients to require an opioid analgesic following surgical procedures when they are still in the hospital, and in many other supervised settings such as the emergency department, and these are generally schedule II opioids. There was evidence of efficacy for sufentanil in the form of Dsuvia from an adequate and well-controlled clinical trial. The safety profile was consistent with the adverse events expected with an opioid, and the product was generally well tolerated by study subjects. The review team found the balance acceptable for the intended population, in a medically supervised setting.

An advisory committee meeting was convened, and although not a joint meeting with the Drug Safety and Risk Management (DSaRM) Advisory Committee, the Anesthetic and Analgesic Drug Product Advisory Committee (AADPAC) was supplemented with five individuals invited because of their safety backgrounds, including medication safety experts, safety pharmacists, and a critical care nurse, and their input was quite valuable. The four current AADPAC members included two anesthesiologists, a pain specialist, and a biostatistician. The nine temporary members included two anesthesiologists, a pharmacist serving as the director of medication safety for a large integrated health system, a professor of a college of pharmacy and a consumer representative (all five of whom had participated in many prior AADPAC meetings), a pharmacoepidemiologist, a critical care nurse, and a pharmacy coordinator for clinical research and education at an academic medical center. There was also a patient representative with a long history of personal and professional experience with painful conditions.

During the advisory committee meeting, it was noted by some committee members that the efficacy was not as great as they would have expected. There were no major concerns about the safety of the product in general, nor was there concern due to the small tablet size as long as it was restricted to supervised medical settings, as planned, and described in the REMS. There was some agreement that a new alternative to intravenous opioid analgesics could be useful and that there might be a niche for the product. It was also noted that there was only limited experience with elderly patients. The vote of the committee was 10 in favor and three against approval. The members who voted no described the reasons for their vote as: too onerous for med/surg nurses, may be useful in emergency department or battlefield; the efficacy is poor, but the safety is not a concern; the efficacy is too slow, may lead to dose stacking, should be narrowed to emergency department and battlefield, too inflexible for dose titration, and not enough experience in the elderly. Comments from the members who voted yes generally included may be useful in a narrow population, safety not a major concern as long as it remains restricted to supervised medical settings.

The next question is whether the risk for accidental exposure due to misplaced pills could be adequately mitigated by the REMS. The agreed upon REMS will require certification of supervised medical settings in order for Dsuvia to be distributed to those settings and it will not be available through outpatient pharmacies. The REMS also calls for training of the medical staff who will be prescribing and administering Dsuvia.

A more general question is whether new approvals correlates with increased use. A recent study¹ examined the number of approvals of new opioid analgesic drug products and the number of prescriptions for opioid analgesics from 1997 through 2015. During this period, there were 263 new opioid analgesic applications approved, including 222 abbreviated new drug applications and 41 new drug applications with a greater number of approvals was greater in the second half of the study period. The nationally estimated number of prescriptions dispensed for opioid analgesics initially increased 80% from 145 million prescriptions in 1997 to a peak of 260 million prescriptions in 2012 and then decreased by 12% to 228 million prescriptions in 2015. So there was no correlation with the number of new opioid analgesic approvals and the number of prescriptions.

¹ Chai G, Xu J, Osterhout J, Liberatore MA, Miller KL, Wolff C, Cruz M, Lurie P, Dal Pan G. New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015. *Anesthesiology* 2018; 128:953-66.

4. Decision/Action

- Regulatory Action – Approval

Taking all of the data in the application, the reviews from the entire review team, and vote and comments from the advisory committee meeting, DSUVIA has a favorable benefit risk balance for the proposed indication and with the proposed REMS.

- Recommendation for Postmarketing Risk Management Activities

Dsuvia will have a product specific REMS as described, to restrict use to supervised medical settings.

- Recommendation for other Postmarketing Study Commitments

There will be a Post Marketing Requirement for deferred pediatric studies in patients 6 to ^(b)₍₄₎ years of age. The studies will be deferred until 2 years after approval to allow for review of postmarketing safety data from experience with adult patients, from the REMS assessments. If there are concerns with the safety of Dsuvia in adults, and if there are data that the REMS is not achieving its goals, the pediatric study requirement may be reconsidered.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOSHUA M LLOYD on behalf of SHARON H HERTZ
11/02/2018