Testimony Before the FDA's Anesthetic and Analgesic Drug Products Advisory Committee Regarding Sublingual Sufentanil

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We have no financial conflicts of interest.

Introduction: Sufentanil Sublingual Tablet 30 mcg

- Intravenous sufentanil was approved in 1984
- **It is 5-10 times more potent than its analogue, fentanyl, making it the most potent opioid in this dosage form**
- This drug has raised concerns of safety and efficacy in initial submission

Sufentanil Sublingual Tablet 30 mcg Efficacy

While the applicant (AcelRx Pharmaceuticals) has addressed deficiencies outlined by the FDA regarding the company's initial submission and has demonstrated the efficacy of sufentanil sublingual tablet 30 mcg compared with a placebo, they have failed to demonstrate sufficient evidence that the efficacy of sufentanil sublingual tablet 30 mcg for the management of moderate-to-severe acute pain **cannot be accomplished with** available alternative treatments.

This product does not address any unmet medical need.

"Available opioid products include meperidine, tramadol, codeine, hydrocodone, oxycodone, morphine, oxymorphone, hydromorphone, and fentanyl. The available products can be given via various routes of administration, such as oral, transdermal, intramuscular, subcutaneous, intravenous, transmucosal, and epidural/intrathecal."

"Since sufentanil sublingual tablet 30 mcg was only compared to placebo in the one completed Phase 3 clinical study, there are no data available on the efficacy of sufentanil sublingual tablet 30 mcg compared to other therapies."

FDA Briefing Document, Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), October 12, 2018. PDF pp. 10 and 14

Sufentanil Sublingual Tablet 30 mcg Safety Concerns

"Overall, although sufentanil sublingual tablet 30 mcg appears to have a typical safety profile of an opioid agonist, there were two areas of safety concern with this product that required further evaluation: [1] the safety of sufentanil sublingual tablet 30 mcg in patients requiring the maximum dosing proposed for labeling and [2] the risk of misplaced tablets."

FDA Briefing Document, Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), October 12, 2018. PDF p. 22

Safety Concerns of Sufentanil Sublingual Tablet 30 mcg-Maximum Dose

Initial Review	Resubmission
Safety database deficiency due to inadequate number of patients dosed at the maximum proposed dose	1. Reduced the maximum daily dose from 720 mcg to 360 mcg 2. Pooled safety data from all studies of the sufentanil sublingual tablet (SST) with treatment periods of at least 24 hours (Pool 8)

Safety Concerns of Sufentanil Sublingual Tablet 30 mcg -Proposed Maximum Dose

"It is important to note that there are significant limitations to the safety analyses based on dose received and sufentanil concentration."

Limitations of pooled safety analysis:

1. Administration of sufentanil sublingual tablet 30 mcg as needed, thereby complicating safety analysis
2. Analyses were based on sufentanil dose and concentration in the first 24 hours

FDA Briefing Document, Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), October 12, 2018. pp. 25

Safety Concerns of Sufentanil Sublingual Tablet 30 mcg-Misplaced Tablets & Accidental Exposure

Initial Submission Concerns	Actions to Address Concerns	Ensuing Concerns
Size of tablet-difficult to retrieve if fallen	N/A	Size of tablet
High Potency-can pose a health threat to children or anyone else who may come in contact with it	N/A	High Potency
Improper device use	Modified directions for use (DFU) to include visual confirmation + human factors validation study for dropped tablet evaluation (popPK)	N/A
Inappropriate tablet sublingual placement	Modified DFU + Restriction to healthcare setting that fall into a specific criteria to ensure proper use	It is remains unclear how likely this further restriction will be effective in the real (non-clinical trial) world of clinical practice

Conclusions

While the applicants have addressed the initial safety concerns raised by the FDA, we urge the advisory committees **not** to approve this drug for the following reasons:

1. Sufentanil sublingual tablets 30 mcg **do not** provide any additional unique advantages not achievable with currently available alternative opioids
2. Its high potency, in the context of this new oral dosage form may present unique, serious adverse effects such as respiratory depression to either the intended patient or to someone who has come into contact with it
3. Consistent with the critical public health concept of the *precautionary principle*, the lack of any unique benefit and the unmitigated concern for unique risks mandate non-approval