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FDA Drug Safety and Risk Management & Anesthetic and Analgesic Drug Advisory Committees
Buprenorphine sublingual spray: Buvaya

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(I have no financial conflict of interest)

FDA Discussion question 1: Discuss whether the efficacy findings support the indication "management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate."…include any concerns regarding the time to onset of analgesia for Buvaya in the context of an acute pain indication.

- **"Even for the high dose group…it is important to note that more than one third of patients did not experience onset of analgesia. The Applicant's Time to Meaningful Pain Relief analysis also indicates a long latency to clinically meaningful benefit. The median time to pain relief was 92, 122, and 166 minutes in the high, mid, and low-dose groups, respectively (Table 8)."**
- **" [F]or analgesics intended to treat acute pain, there is an expectation that meaningful pain relief will be experienced soon after taking the first dose of drug (generally within one hour). More than half of the patients treated with 0.125 and 0.25 mg BSS [buprenorphine sublingual spray] never experienced meaningful analgesia."**

From FDA briefing document, pages 15-16

FDA Discussion question 1, continued

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

FDA Discussion question 1: Based on the available safety data, discuss whether the safety profile of Buvaya is acceptable for the proposed indication.

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

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

"Thirty-seven percent of patients receiving the 0.5 mg dose of BSS experienced moderate-to-severe vomiting. … A total of 4 (5%) patients treated with placebo required at least one dose of antiemetic drug compared to 17/82 (21%) of patients treated with 0.125 mg BSS, 32 (40%) patients treated with 0.25 mg BSS, and 55 (68%) patients treated with 0.5 mg BSS."

From FDA briefing document, pages 18-19

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

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

Source: CSR, Study 111, Table 13

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

From FDA briefing document, page 21

VOTE: Overall, do the benefits of Buvaya outweigh the risks [harms] for the indication, "the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate," supporting approval of Buvaya?

As shown in the only trial described by FDA as the "one adequate and well-controlled study...Study 062…to assess efficacy and provide safety data," it seems evident that the risks of Buvaya actually outweigh the benefits, instead of the required opposite. The FDA has stated that the acute pain relief was so deficient that "the use of rescue medication and the time to onset of action cast doubt on the appropriateness of BSS for the treatment of acute pain."

Just as the inadequate pain relief required rescue with pain meds for a large proportion of trial participants, the extremely high rate of nausea and vomiting required an analogous rescue with anti-emetic medications. A total of 4 (5%) patients treated with placebo required at least one dose of antiemetic drug compared to 17/82 (21%) of patients treated with 0.125 mg BSS, 32 (40%) patients treated with 0.25 mg BSS, and 55 (68%) patients treated with 0.5 mg BSS.

The quite unfavorable ratio of harms to benefits of Buvaya argues strongly for rejecting Insys' application for approval. FDA's summary of this, on page 25 of the briefing document, sums this up quite well:

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

Insys Statement in its Briefing Package for today's meeting (page 8)

"It is understandable in consideration of media coverage about the company's legacy legal issues related to **allegations of inappropriate sales and marketing practices** to have some concerns about approving a new opioid for the company. To allay those concerns, we are a **markedly different company** today than the one portrayed in many media reports." (Emphases added)

The following is from a brief filed April 13, 2018 in a California District Court by the U.S. Department of Justice in an ongoing case vs Insys, involving its previous illegal criminal activity by the "markedly different company," but which Insys misleadingly trivializes as merely "**allegations of inappropriate sales and marketing practices**"

“Natalie Perhacs was an Insys Sales Representative who worked with Drs. Couch and Ruan. In February 2016, Ms. Perhacs pleaded guilty to criminal charges that included the payment of illegal kickbacks to Drs. Couch and Ruan on behalf of Insys. …

In February 2017, following a seven-week federal criminal trial, a jury in Alabama found Drs. Couch and Ruan guilty of several federal criminal offenses, including (1) illegally prescribing fentanyl and other opioid drugs outside the usual course of professional practice and not for a legitimate medical purpose, and (2) accepting kickbacks from Insys. In May 2017, they were sentenced to 20 and 21 years in prison, respectively.”