Drug Monograph

Drug/Drug Class:	**Dsuvia™ (sufentanil) sublingual tablets / Short Acting Single Agent Opioids**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Dsuvia is available as a sublingual tablet containing 30 mcg sufentanil housed in a disposable single-dose applicator. Distributed by: AcelRx Pharmaceuticals, Inc., Redwood City, CA 94063
Summary of Findings:	The efficacy and safety of Dsuvia were evaluated in a randomized, double blind, placebo-controlled trial that enrolled 161 patients with acute postoperative pain after abdominal surgery (studied up to 48 hours). Patients were dosed with Dsuvia or placebo as needed with a minimum of 60 minutes between doses. Morphine sulfate 1 mg IV was available as rescue medication. The primary efficacy endpoint was the time-weighted summed pain intensity difference over 12 hours (SPID12). Patients using Dsuvia had a statistically significantly higher SPID12 than patients using placebo. The median time to onset of meaningful pain relief was 54 minutes for Dsuvia vs. 84 minutes for placebo. Approximately 27% of patients in the Dsuvia group and 65% of patients in the placebo group took rescue medication during the treatment phase.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☒ Increased Risk of ADE ☐ Non-Preferred Agent ☒ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Acute pain management may present a challenge in certain special circumstances where patients are not able to swallow oral medication or where access to intravenous (IV) pain relief is not possible (ex: use on the battlefield, needle-phobic patients).

Dosage Form [1]

Dsuvia is available as a sublingual tablet containing 30 mcg sufentanil housed in a disposable single-dose applicator.

Manufacturer [1]

Distributed by: AcelRx Pharmaceuticals, Inc., Redwood City, CA 94063

Indication(s) [1]

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.

Limitations of Use

- Not for home use or for use in children. Treatment with Dsuvia should be discontinued before patients leave the certified medically supervised healthcare setting.
- Not for use for more than 72 hours. The use of Dsuvia beyond 72 hours has not been studied.
- Only to be administered by a healthcare provider.
- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, Dsuvia should be reserved for use in patients for whom alternative treatment options (ex: non-opioid analgesics or opioid combination products):
    - Have not been tolerated, or are not expected to be tolerated.
    - Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

Clinical Efficacy [1-3] (mechanism of action/pharmacology, comparative efficacy)

Dsuvia is an opioid agonist that is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principle therapeutic action of Dsuvia is analgesia and sedation, thought to be mediated through opioid-specific receptors throughout the CNS. Like all full opioid agonists, there is no ceiling effect to analgesia.

Pharmacokinetics:

	Dsuvia
Protein Binding	91% to 93%; primarily to alpha 1-acid glycoprotein
Absorption	Sublingual: 53%
Volume of Distribution	1.7 to 2.9 l/kg
Metabolism	Liver and small intestine
Excretion	~80% within 24 hours, 2% unchanged
Half-life	13.4 hours

Clinical Trials Experience

STUDY DESIGN	Phase-3, prospective, randomized, double-blind, placebo-controlled trial (N=161)
INCLUSION CRITERIA	• ≥18 years of age • Acute postoperative pain after abdominal surgery (pain intensity of ≥ 4 on a 0-10 Numeric Rating Scale) • Expected to have moderate-to-severe post-operative pain for at least 24 hours
EXCLUSION CRITERIA	• Opioid use for more than 30 consecutive days, at a daily dose of more than 15 mg of morphine (or equivalent), within the past 3 months prior to surgery
TREATMENT REGIMEN	Patients were dosed with Dsuvia 30 mcg or placebo as needed with a minimum of 60 minutes between doses for up to 48 hours. Morphine sulfate 1 mg IV was available as rescue medication.
RESULTS	The primary efficacy endpoint was the time-weighted summed pain intensity difference over 12 hours (SPID 12). Secondary endpoints included onset of analgesia, termination due to inadequate analgesia and rescue medication use. SPID 12 was higher (greater pain intensity reduction from baseline) in the Dsuvia group compared with placebo (25.8 vs. 13.1; $P < 0.001$, with a difference of 12.7 [95% confidence interval 7.16, 18.23]). The median time to onset of meaningful pain relief was 54 minutes for Dsuvia vs. 84 minutes for placebo. A significantly higher proportion of patients in the placebo group (18.5%; 10/54) compared with the Dsuvia group (3.7%; 4/107) discontinued treatment ($P = 0.002$) or terminated the study early ($P = 0.001$) due to inadequate analgesia. A significantly higher proportion of patients in the placebo group (64.8%; 35/54) compared with the Dsuvia group (27.1%; 29/107) required rescue medication due to inadequate analgesia ($P < 0.001$)
SAFETY	The most frequently (≥ 2%) reported adverse events were nausea (26.7%) and headache (11.8%). There were no significant differences

	between treatment groups for the incidence of any type of adverse event.

Contraindications [1]

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Known hypersensitivity to sufentanil or components of Dsuvia

Warnings and Precautions [1]

- **Black Box Warning**:
  - **Accidental exposure to or ingestion of Dsuvia, especially in children, can result in respiratory depression and death. Because of this life-threatening risk, Dsuvia is available only through the Dsuvia Risk Evaluation and Mitigation Strategy (REMS) Program. Dsuvia should only be administered by a healthcare provider in a certified medically supervised healthcare setting.**
  - **Serious, life-threatening, or fatal respiratory depression may occur.**
  - **There is risk of opioid addiction, abuse, and misuse, which can lead to overdose and death.**
  - **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of sufentanil.**
  - **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.**
- Life-threatening respiratory depression may occur in patients with chronic pulmonary disease or in elderly, cachectic, or debilitated patients. Monitor closely, particularly during initiation and titration.
- Serotonin Syndrome could result from concomitant serotonergic drug administration. Discontinue Dsuvia if serotonin syndrome is suspected.
- Adrenal insufficiency may occur. If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off the opioid.
- Severe hypotension may occur. Monitor during dosage initiation and titration. Avoid use of Dsuvia in patients with circulatory shock.
- Risks of use in patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness: monitor for sedation and respiratory depression. Avoid use of Dsuvia in patients with impaired consciousness or coma.
- Increased Risk of Seizures in Patients with Seizure Disorders: monitor patients with a history of seizure disorders for worsened seizure control during Dsuvia therapy.
- Bradycardia: monitor patients with bradyarrhythmias closely for changes in heart rate, particularly when initiating therapy with Dsuvia.
- Prolonged use of Dsuvia during pregnancy can result in neonatal opioid withdrawal syndrome. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly.

Adverse Effects [1]

Most common, ≥ 2%	Dsuvia (n = 107) %	Placebo (n = 54) %
Nausea	29.0	22.2
Headache	12.1	11.1
Vomiting	5.6	1.9
Dizziness	5.6	3.7
Hypotension	4.7	3.7

Drug Interactions [1]

- CYP3A4 inhibitors (ex: macrolide antibiotics, azole antifungal agents, protease inhibitors): may increase the plasma concentration of Dsuvia, resulting in increased or prolonged opioid effects.
- CYP3A4 inducers (ex: rifampin, carbamazepine, phenytoin): may decrease the plasma concentration of Dsuvia resulting in decreased efficacy or onset of a withdrawal syndrome.
- Benzodiazepines and other CNS depressants (ex: alcohol, benzodiazepines, sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids): may increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
- Serotonergic drugs (ex: SSRIs, SNRIs, TCAs, triptans, 5-HT3 receptor antagonists, mirtazapine, trazodone, tramadol, MAOIs): may manifest as serotonin syndrome or opioid toxicity.
- Mixed agonist/antagonist and partial agonist opioid analgesics (ex: butorphanol, nalbuphine, pentazocine, buprenorphine): may reduce analgesic effect of Dsuvia or precipitate withdrawal symptoms.
- Muscle relaxants: Dsuvia may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
- Diuretics: Dsuvia may reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
- Anticholinergic Drugs: may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Dosage and Administration [1]

The recommended dosage is 30 mcg sublingually as needed with a minimum of 1 hour between doses. Do not exceed 360 mcg or 12 tablets in 24 hours.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
sufentanil	Dsuvia	AceIRx	30 mcg tablet	$58.31 per tablet

** Wholesale Acquisition Cost

Conclusion

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. Dsuvia carries a boxed warning for accidental exposure; life-threatening respiratory depression; addiction, abuse, and misuse; cytochrome P450 3A4 interaction; and risks from concomitant use with benzodiazepines or other central nervous system depressants and is only available through the Dsuvia REMS Program. The safety and efficacy of Dsuvia were demonstrated in a randomized, double blind clinical trial that enrolled 161 adults with acute post-operative pain following abdominal surgery. Treatment with Dsuvia resulted in greater pain intensity reduction from baseline compared with placebo. The most commonly reported adverse reactions associated with Dsuvia use are nausea, headache, vomiting, dizziness and hypotension.

Recommendation

The Division recommends adding this drug to the current Short Acting Single Agent Opioids clinical edit.

References

1) Product Information: Dsuvia® (sufentanil). AcelRx Pharmaceuticals, Inc., Redwood City, CA 94063.
2) Sufentanil: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
3) Minkowitz HS, Leiman D, Melson T, et al. Sufentanil sublingual tablet 30 mcg for the management of pain following abdominal surgery: a randomized, placebo-controlled, phase-3 study. *Pain Pract.* 2017 Sep;17(7):848-858.

Prepared by: Carrie Gatzke PharmD
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