HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DSUVIA® safely and effectively. See full prescribing information for DSUVIA®.

DSUVIA® (sufentanil) sublingual tablet, CII
Initial U.S. Approval: 1984

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF DSUVIA

See full prescribing information for complete boxed warning.

- **Accidental exposure to or ingestion of DSUVIA, especially in children, can result in respiratory depression and death. Because of the risk of life-threatening respiratory depression from accidental exposure, DSUVIA is available only through a restricted program called the DSUVIA REMS Program *[see Warnings and Precautions (5.1, 5.2)]*. DSUVIA should only be administered by a healthcare provider in a certified medically supervised healthcare setting. Discontinue use of DSUVIA prior to discharge or transfer from the certified medically supervised setting. (5.1, 5.2)**
- **DSUVIA exposes users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and reassess regularly for these behaviors and conditions. (5.3)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially during initiation. (5.4)**
- **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. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. (5.5, 7)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of sufentanil. (5.6, 7, 12.3)**

----------RECENT MAJOR CHANGES ----------

Indications and Usage (1)	12/2025
Warnings and Precautions (5.3, 5.4, 5.5, 5.13)	12/2025

----------INDICATIONS AND USAGE ----------

DSUVIA contains sufentanil, an opioid agonist, and 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. Discontinue treatment with DSUVIA before patients leave the certified medically supervised healthcare setting. (1)
- Not for use for more than 72 hours.
- Only to be administered by a healthcare provider.
- Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy, reserve opioid analgesics, including DSUVIA, for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1, 5.3)

----------DOSAGE AND ADMINISTRATION ----------

- Recommended dosage is 30 mcg sublingually as needed with a minimum of one hour between doses. (2.2)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve the use of additional doses of DSUVIA for patients in whom a single dose is insufficiently effective and in whom the expected benefits of using additional doses of an opioid clearly outweigh the substantial risks (2.2, 5).
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following additional doses of DSUVIA. Consider this risk when initiating dosing and when making dose adjustments (2.2, 5).
- Do not exceed 12 tablets in 24 hours. (2.2)
- See the Full Prescribing Information for administration information. (2.3)
- Do not rapidly reduce or abruptly discontinue DSUVIA in a physically-dependent patient. (9.3)

----------DOSAGE FORMS AND STRENGTHS ----------

- Sublingual tablet: 30 mcg tablet housed in a disposable, single-dose applicator (SDA). (3)

----------CONTRAINDICATIONS ----------

- Significant Respiratory Depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to sufentanil or components of DSUVIA. (4)

----------WARNINGS AND PRECAUTIONS ----------

- Opioid-Induced Hyperalgesia and Allodynia: Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation. (5.7)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue DSUVIA if serotonin syndrome is suspected. (5.8)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of DSUVIA in patients with circulatory shock. (5.11)
- 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. (5.12)

----------ADVERSE REACTIONS ----------

The most commonly reported adverse reactions (≥ 2%) were nausea, headache, vomiting, dizziness and hypotension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vertical Pharmaceuticals, LLC at 1-855-925-8476 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS ----------

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with DSUVIA because they may reduce analgesic effect of DSUVIA or precipitate withdrawal symptoms. (7)

----------USE IN SPECIFIC POPULATIONS ----------

- Hepatic and/or Renal Impairment: Monitor for signs of sedation and respiratory depression. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2025

FULL PRESCRIBING INFORMATION: CONTENTS *

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF DSUVIA

Accidental Exposure and DSUVIA Risk Evaluation and Mitigation Strategy (REMS) Program
Accidental exposure to or ingestion of DSUVIA, especially in children, can result in respiratory depression and death. Because of the potential for life-threatening respiratory depression due to accidental exposure, DSUVIA is only available through a restricted program called the DSUVIA REMS Program *[see Warnings and Precautions (5.1, 5.2)]*.

- **DSUVIA must only be dispensed to patients in a certified medically supervised healthcare setting.**
- **Discontinue use of DSUVIA prior to discharge or transfer from the certified medically supervised healthcare setting.**

Addiction, Abuse, and Misuse
Because the use of DSUVIA exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient's risk prior to prescribing DSUVIA, and reassess all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.2)]*.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of DSUVIA. Monitor for respiratory depression, especially during initiation of DSUVIA *[see Warnings and Precautions (5.4)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
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. Reserve concomitant prescribing of DSUVIA and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate *[see Warnings and Precautions (5.5) and Drug Interactions (7)]*.

Cytochrome P450 3A4 Interaction
The concomitant use of DSUVIA with all cytochrome P450 3A4 inhibitors may result in an increase in sufentanil plasma concentrations, which could increase or prolong adverse drug reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in sufentanil plasma concentration. Monitor patients receiving DSUVIA and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.6), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

1 INDICATIONS AND USAGE

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. Discontinue treatment with DSUVIA 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, misuse, overdose, and death, which can occur at any dosage or duration and persist over the course of therapy, *[see Warnings and Precautions (5.3)]*, reserve opioid analgesics, including DSUVIA, for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

DSUVIA is only to be administered by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.

DSUVIA is only to be used in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments.

DSUVIA treatment must be discontinued prior to the patient leaving the certified medically supervised setting.

2.2 Dosage Information

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

Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. Because the risk of overdose increases as opioid doses increase, reserve the use of additional doses of DSUVIA for patients in whom a single dose is insufficiently effective and in whom the expected benefits of using additional doses of an opioid clearly outweigh the substantial risks.

The maximum cumulative daily dose of sufentanil is 360 mcg or 12 tablets (12 tablets x 30 mcg/dose).

Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addition, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

Respiratory depression can occur at any time during opioid therapy, especially when initiating and following additional doses of DSUVIA. Consider this risk when initiating dosing and when making dose adjustments *[see Warnings and Precautions (5)]*.

2.3 Administration of DSUVIA

- Single-use product / Do not reuse.
- Do not use if pouch seal is broken.
- Do not use if the Single-Dose Applicator (SDA) is damaged.
- Wear gloves when administering DSUVIA.
- Instruct the patient to not chew or swallow the tablet.
- Instruct the patient to not eat or drink and minimize talking for 10 minutes after receiving the tablet. If a patient experiences excessive dry mouth, ice chips should be provided prior to administration of DSUVIA.

Administration Instructions

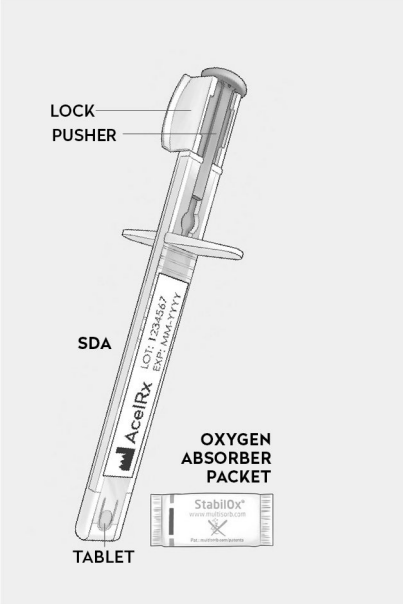
1. Only when ready to administer the medication, TEAR OPEN the notched pouch across the top.

   The pouch contains one clear plastic SDA with a single blue-colored tablet housed in the tip, and an oxygen absorber packet. See *Figure 1*.

   REMOVE SDA from pouch.

   DISCARD the oxygen absorber packet.

Figure 1. DSUVIA Pouch Contents



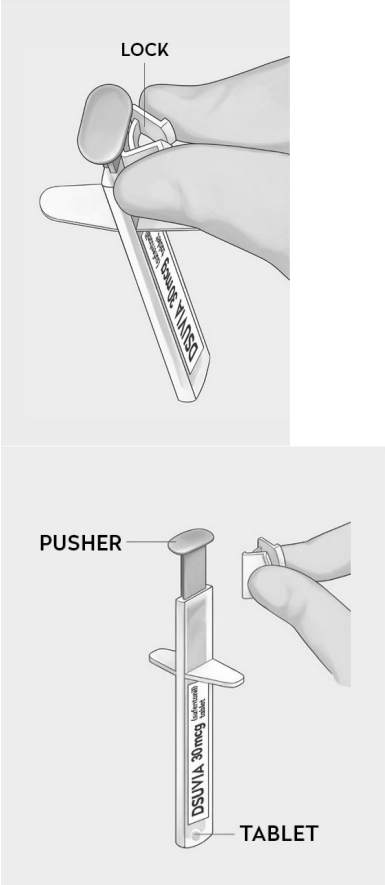
2. REMOVE the white Lock from the green Pusher by squeezing the sides together and detaching from Pusher. See *Figure 2*.

   DISCARD the Lock.

   NOTE: To prevent ejecting the tablet accidentally:

   - Do not remove Lock until ready to administer
   - Avoid touching the green Pusher before placing the SDA in the patient's mouth for administration

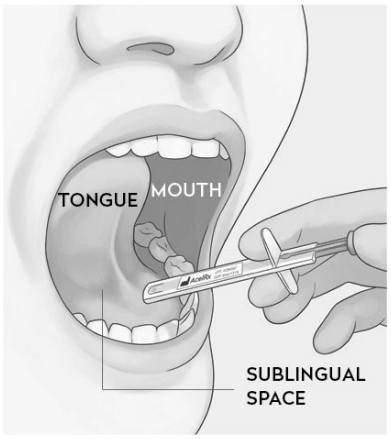
Figure 2. Lock Removal



3. TELL the patient to open their mouth and touch their tongue to the roof of their mouth if possible.
4. REST the SDA lightly on the patient's lower teeth or lips. See *Figure 3.*
5. PLACE the SDA tip under the tongue and aim at the floor of the patient's mouth or sublingual space. See *Figure 3*.

   NOTE: Avoid direct mucosal contact with the SDA tip.
6. GENTLY DEPRESS the green Pusher to deliver the tablet to the patient's sublingual space. See *Figure 3*.

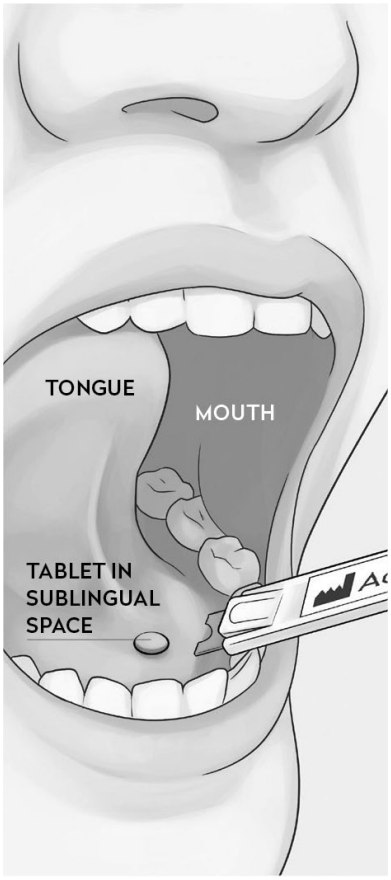
Figure 3. SDA Placement for Administration



7. VISUALLY CONFIRM tablet placement in the sublingual space. See *Figure 4*.

   NOTE: If the tablet is NOT in the patient's mouth, it is important to retrieve and dispose of the tablet according to institutional CII waste procedures.
8. DISCARD the used SDA in biohazard waste after administration.

Figure 4. Tablet Placement in Sublingual Space



3 DOSAGE FORMS AND STRENGTHS

Sublingual tablets: DSUVIA is a single 30 mcg sufentanil tablet housed in a disposable, single-dose applicator (SDA). The tablet is blue-colored, flat-faced with rounded edges and is 3 mm in diameter.

4 CONTRAINDICATIONS

Use of DSUVIA is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.4)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.9)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.13)]*
- Known hypersensitivity to sufentanil or components of DSUVIA *[see Adverse Reactions (6.1, 6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Respiratory Depression and Death Due to Accidental Exposure

Accidental ingestion or exposure to even one dose of DSUVIA, especially in children, can result in respiratory depression and death due to an overdose of sufentanil.

DSUVIA is for use in adult patients only in a certified medically supervised healthcare setting. Use of DSUVIA outside of this setting can increase the risk of accidental exposure in others for whom it is not prescribed, causing fatal respiratory depression. Discontinue use of DSUVIA prior to discharge or transfer from the certified medically supervised healthcare setting. DSUVIA is not for home or pediatric use.

Following accidental ingestion of DSUVIA, monitor patients for opioid-related adverse events, such as respiratory depression.

5.2 DSUVIA Risk Evaluation and Mitigation Strategy (REMS)

Because of the potential for life-threatening respiratory depression due to accidental exposure, DSUVIA is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the DSUVIA REMS Program.

The goal of the DSUVIA REMS is to mitigate the risk of respiratory depression resulting from accidental exposure by:

- Ensuring that DSUVIA is dispensed only to patients in certified medically supervised healthcare settings.

The requirements of the DSUVIA REMS are as follows:

- Healthcare settings that dispense DSUVIA must:
  - Be able to manage an acute opioid overdose including respiratory depression
  - Train all relevant staff that DSUVIA must not be dispensed for use outside of the certified healthcare setting
  - Train all relevant staff involved in administration of DSUVIA to refer to the Directions for Use prior to administration
    Establish processes and procedures to verify that DSUVIA is not dispensed for use outside of the certified healthcare setting.
- Wholesalers that distribute DSUVIA must:
  - Establish processes and procedures to ensure that DSUVIA is distributed only to certified medically supervised healthcare settings.
  - Distribute only to certified medically supervised healthcare settings.

Further information about the DSUVIA REMS Program is available at www.DSUVIAREMS.com, or by calling 1-855-925-8476.

5.3 Addiction, Abuse and Misuse

DSUVIA contains sufentanil, a Schedule II controlled substance. As an opioid, DSUVIA exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed

DSUVIA. Addiction can occur at recommended dosages and if the drug is misused or abused. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use *[see Adverse Reactions (6.2)]*.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing DSUVIA, and monitor all patients receiving DSUVIA for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as DSUVIA but use in such patients necessitates intensive counseling about the risks and proper use of DSUVIA along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought for nonmedical use and are subject to diversion from legitimate prescribed use. Consider these risks when prescribing or dispensing DSUVIA. Strategies to reduce these risks include proper product storage and control practices for a C-II drug. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.4 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid overdose reversal agents (e.g., naloxone, nalmefene), depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of DSUVIA, the risk is greatest during the initiation of therapy. Monitor patients closely for respiratory depression while on treatment with DSUVIA.

Accidental exposure to or ingestion of even one dose of DSUVIA, especially in children, can result in respiratory depression and death due to an overdose of sufentanil.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider minimizing the use of DSUVIA and carefully monitor the patient for signs of respiratory depression *[see Dosage and Administration (2.2)]*.

5.5 Risks from Concomitant Use with Benzodiazepines or other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of DSUVIA with benzodiazepines or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Monitor patients closely for signs and symptoms of respiratory depression and sedation.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory

depression and sedation.

5.6 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of DSUVIA with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g. erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of sufentanil and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.4)]*, particularly when an inhibitor is added after a stable dose of DSUVIA is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in DSUVIA-treated patients may increase sufentanil plasma concentrations and prolong opioid adverse reactions. When using DSUVIA with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in DSUVIA-treated patients, monitor patients closely at frequent intervals for respiratory depression and sedation *[see Drug Interactions (7)]*.

Concomitant use of DSUVIA with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease sufentanil plasma concentrations, decrease opioid efficacy or, possibly lead to a withdrawal syndrome in a patient who had developed physical dependence to sufentanil. When using DSUVIA with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals for adequate analgesia and for symptoms of opioid withdrawal *[see Drug Interactions (7)]*.

5.7 Opioid-Induced Hyperalgesia and Allodynia

Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect *[see Dependence (9.3)]*. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safely switching the patient to a different opioid moiety).

5.8 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of sufentanil, the active opioid ingredient of DSUVIA, with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (e.g., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur at the recommended dosage.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) and can be fatal. The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue DSUVIA if serotonin syndrome is suspected.

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of DSUVIA in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: DSUVIA-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at the recommended dosage of DSUVIA *[see Warnings and Precautions (5.4)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely; particularly when initiating DSUVIA and when DSUVIA is used concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.4)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.11 Severe Hypotension

DSUVIA may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating DSUVIA. In patients with circulatory shock, DSUVIA may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of DSUVIA in patients with circulatory shock.

5.12 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), DSUVIA may reduce respiratory drive, and the resultant CO2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with DSUVIA.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of DSUVIA in patients with impaired consciousness or coma. DSUVIA is not suitable for use in patients who are not alert and able to follow directions.

5.13 Risks of Use in Patients with Gastrointestinal Conditions

DSUVIA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The sufentanil in DSUVIA may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g. dysphagia, regurgitation, non-cardiac chest pain), and if necessary, adjust opioid therapy as clinically appropriate *[see Clinical Pharmacology (12.2)]*.

5.14 Increased Risk of Seizures in Patients with Seizure Disorders

The sufentanil in DSUVIA may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during DSUVIA therapy.

5.15 Bradycardia

DSUVIA may produce bradycardia in some patients. Monitor patients with bradyarrhythmias closely for changes in heart rate, particularly when initiating therapy with DSUVIA.

5.16 Neonatal Opioid Withdrawal Syndrome

Use of opioids for an extended period of time during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.3)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.4)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.7)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.10)]*
- Severe Hypotension *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.13)]*
- Seizures *[see Warnings and Precautions (5.14)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.16)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In controlled and uncontrolled studies, the safety of DSUVIA was evaluated in a total of 646 patients with moderate-to-severe acute postoperative pain or pain due to trauma which required opioid analgesia.

The most frequently reported adverse reactions ≥ 2% that were probably or possibly related to study treatment in the one pivotal, placebo-controlled trial (Study SAP301) are presented in *Table 1.*

Discontinuation of study drug due to adverse events occurred in 0.9% of DSUVIA-treated patients (1 out of 107 patients) and 3.7% of placebo-treated patients (2 out of 54 placebo treated patients). The most common reasons for discontinuation of study drug due to adverse reactions in SAP301 were oxygen saturation decreased (0.9% in the DSUVIA group), and dizziness, hemiparesis, somnolence and syncope in the placebo group (1.9% each).

Table 1: Adverse Reactions Occurring in ≥ 2% of Patients and for Which Rate is Higher in DSUVIA than Placebo Group: Placebo-Controlled Study SAP301

Possibly or Probably Related Adverse Reactions	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%

*Morphine 1 mg IV was permitted as rescue medication

Other Reported Adverse Reactions

Additional treatment related adverse drug reactions which occurred in at least 0.1% of the patients exposed to 30 mcg or higher of sublingual sufentanil are described below.

Cardiac Disorders: sinus tachycardia, bradycardia.

Gastrointestinal Disorders: constipation, dyspepsia, flatulence, diarrhea, dry mouth, eructation, retching, abdominal discomfort, abdominal distension, abdominal pain upper, gastritis, postoperative ileus, hypoesthesia oral.

Investigations: oxygen saturation decreased, respiratory rate decreased, urine output decreased, aspartate aminotransferase increased, electrocardiogram abnormal, hepatic enzyme increased.

Musculoskeletal and Connective Tissue Disorders: muscle spasms.

Nervous System Disorders: somnolence, sedation, presyncope, lethargy, memory impairment.

Psychiatric Disorders: insomnia, confusional state, anxiety, agitation, disorientation, euphoric mood, hallucination, mental status changes.

Renal and Urinary Disorders: urinary retention, urinary hesitation, oliguria, renal failure.

Respiratory, Thoracic and Mediastinal Disorders: hypoxia, bradypnea, hiccups, apnea, atelectasis, hypoventilation, respiratory distress, respiratory failure.

Skin and Subcutaneous Tissue Disorders: pruritus, hyperhidrosis, rash.

Vascular Disorders: hypotension, hypertension, orthostatic hypotension, flushing.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of sufentanil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in DSUVIA.

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time.

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see Warnings and Precautions (5.7)]*.

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids, and may occur more frequently in patients taking higher doses of opioids, and/or in patients taking opioids longer term *[see Warnings and Precautions (5.13)]*.

Adverse Reactions from Observational Studies

A prospective, observational cohort study estimated the risks of addiction, abuse, misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either: 1) filled multiple extended-release/long acting opioid analgesic prescriptions during a 90-day period (n=978); or 2) filled

any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months.

Over 12 months:

- approximately 15 to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and
- approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse *[defined in Drug Abuse and Dependence (9.2)]*, respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. *New long-term* use was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

7 DRUG INTERACTIONS

Table 2 includes clinically significant drug interactions with DSUVIA.

Table 2: Clinically Significant Drug Interactions with DSUVIA

Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of DSUVIA and CYP3A4 inhibitors can increase the plasma concentration of sufentanil, resulting in increased or prolonged opioid effects. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the sufentanil plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to sufentanil.
Intervention:	If concomitant use is necessary, consider an alternate medication that permits dose titration. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider an alternate medication that permits dose titration. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	

Clinical Impact:	The concomitant use of DSUVIA and CYP3A4 inducers can decrease the plasma concentration of sufentanil *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to sufentanil *[see Warnings and Precautions (5.6)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the sufentanil plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider an alternate medication that permits dose titration. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider less frequent dosing of DSUVIA and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death *[see Warnings and Precautions (5.5)]*.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.5)]*.
Examples:	Alcohol, benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), other opioids.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.8)]*.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue DSUVIA if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (e.g., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.4)]*.
Intervention:	The use of DSUVIA is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of DSUVIA and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	Butorphanol, nalbuphine, pentazocine, buprenorphine

Muscle Relaxants	
Clinical Impact:	Sufentanil may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Because respiratory depression may be greater than otherwise expected, decrease the dosage of the muscle relaxant as necessary or consider discontinuing use of DSUVIA.
Examples:	Cyclobenzaprine, metaxolone.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when DSUVIA is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.16)]*. There are no available data with sufentanil in pregnant women to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, embryolethality and maternal toxicity were noted in rabbits when sufentanil was administered intravenously at 4.4 times the maximum human daily dose of 360 mcg/60 kg/day, based on a body surface area comparison during organogenesis. Decreased live fetuses and pup survival were noted in rats treated with sufentanil late in gestation and throughout lactation at doses below the human daily dose of 360 mcg. No malformations were observed in either rats or rabbits at doses below the human daily dose of 360 mcg *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Use of opioid analgesics for an extended period of time during pregnancy for medical or non-medical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.16)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid overdose reversal agent, such as naloxone or nalmefene, must be available for reversal of opioid-

induced respiratory depression in the neonate. DSUVIA is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including DSUVIA, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Pregnant rats were treated with intravenous sufentanil doses of 0.005, 0.02, or 0.08 mg/kg/day (0.14, 0.6, or 2.2 times the maximum human daily dose of 360 mcg/60 kg, based on body surface area, respectively). No malformations or embryotoxic effects were noted despite maternal toxicity (increased mortality in the mid- and high-dose group).

Pregnant rabbits were treated with intravenous sufentanil doses of 0.005, 0.02, or 0.08 mg/kg/day (0.2, 1.0, or 4.4 times the maximum human daily dose of 360 mcg/60 kg, based on body surface area, respectively). Decreased live fetuses per litter and decreased litter size in the high dose group were noted in the presence of maternal toxicity (decreased body weight gain and mortality in the high-dose group).

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered 10, 50, or 100 mcg/kg/day sufentanil (0.2, 1.4, or 2.8 times the maximum human daily dose of 360 mcg/60 kg, based on body surface area) continuously from Gestation Day 5 through Gestation Day 20 via subcutaneously implanted osmotic minipumps.

Pregnant rats were treated intravenously with sufentanil 0.005, 0.02, or 0.08 mg/kg/day (0.14, 0.6, or 2.2 times the maximum human daily dose of 360 mcg/60 kg, based on body surface area, respectively) from Gestation Day 16 through Lactation Day 21. Sufentanil reduced birth weights in the mid- and high-dose groups, decreased live fetuses in the high-dose group, and decreased pup survival in all groups in the presence of maternal toxicity (decreased weight gain and increased mortality in all groups).

8.2 Lactation

Risk Summary

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DSUVIA and any potential adverse effects on the breastfed infant from DSUVIA or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to DSUVIA through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible. DSUVIA is not intended for chronic use *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of the use of DSUVIA in pediatric patients has not been established.

The ability of pediatric patients to comply with the sublingual dosing instructions for DSUVIA has not been evaluated. Use of DSUVIA in younger children is not recommended as younger children may not be able to comply with the sublingual dosing instructions for DSUVIA and could swallow the tablet or spit it out, which could impact the efficacy and safety of DSUVIA.

8.5 Geriatric Use

No special population studies were performed using DSUVIA in elderly patients.

Of the 646 patients exposed to 30 mcg sufentanil or higher in the first hour of treatment, approximately 11% (72) of patients were ≥ 75 years of age and approximately 20% (126) patients were 65 to 75 years of age. The overall rate of adverse events and most common adverse events, such as nausea, tended to increase with age in patients who received sublingual sufentanil, although vomiting was less common in patients aged ≥ 75 years than in younger patients.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. As the dose of DSUVIA cannot be titrated, monitor geriatric patients closely for signs of central nervous system and respiratory depression or consider an alternate medication that can be titrated *[see Warnings and Precautions (5.4)]*.

8.6 Hepatic Impairment

Because sufentanil is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Sufentanil and its metabolites are known to be excreted by the kidney. No significant changes have been observed in subjects with mild or moderate renal impairment. Monitor closely for adverse events such as respiratory depression, sedation, and hypotension in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

DSUVIA contains sufentanil citrate, a Schedule II controlled opioid agonist that can be abused and may produce drug dependence.

9.2 Abuse

DSUVIA contains sufentanil, a substance with a high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.3)]*.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of DSUVIA increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of DSUVIA with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of DSUVIA abuse include those with a history of prolonged use of any opioid, including products containing sufentanil, those with a history of drug or alcohol abuse, or those who use DSUVIA in

combination with other abused drugs.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating health care provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

DSUVIA, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with sufentanil can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support measures.

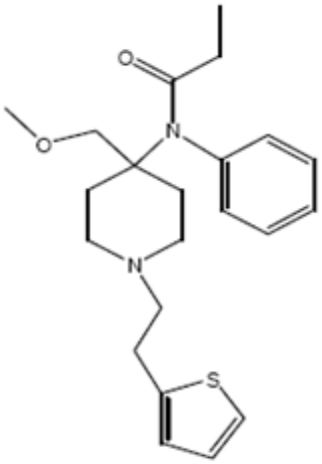
For clinically significant respiratory or circulatory depression secondary to sufentanil overdose, administer an opioid overdose reversal agent, such as naloxone or nalmefene.

Because the duration of opioid reversal is expected to be less than the duration of action of sufentanil in DSUVIA, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid overdose reversal agent is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

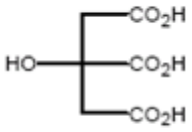
11 DESCRIPTION

DSUVIA contains one 30 mcg sufentanil tablet housed in a disposable single-dose applicator (SDA). The DSUVIA tablet is an immediate release formulation intended for sublingual administration. Each tablet is blue, flat-faced with a diameter of 3 mm.

The IUPAC chemical name for sufentanil is N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide citrate. Sufentanil citrate has a molecular weight of 578.4 (molecular weight of free sufentanil base is 386.55), its empirical formula is C28H38N2O9S ● C6H8N2O7, and its chemical structure is shown below:



Sufentanil



Citrate

DSUVIA tablets inactive ingredients are: mannitol; dicalcium phosphate anhydrous; hypromellose; croscarmellose sodium; FD&C Blue #2; stearic acid and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sufentanil is an opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses.

The principle therapeutic action of sufentanil 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.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Sufentanil produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Sufentanil causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Sufentanil causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, transient elevations in serum amylase, and opioid-induced esophageal dysfunction (OIED).

Effects on the Cardiovascular System

Sufentanil produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[see Adverse Reactions (6.2)]*.

Use of opioids for an extended period of time may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Effects on the Respiratory System

All opioid mu-receptor agonists, including DSUVIA, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects.

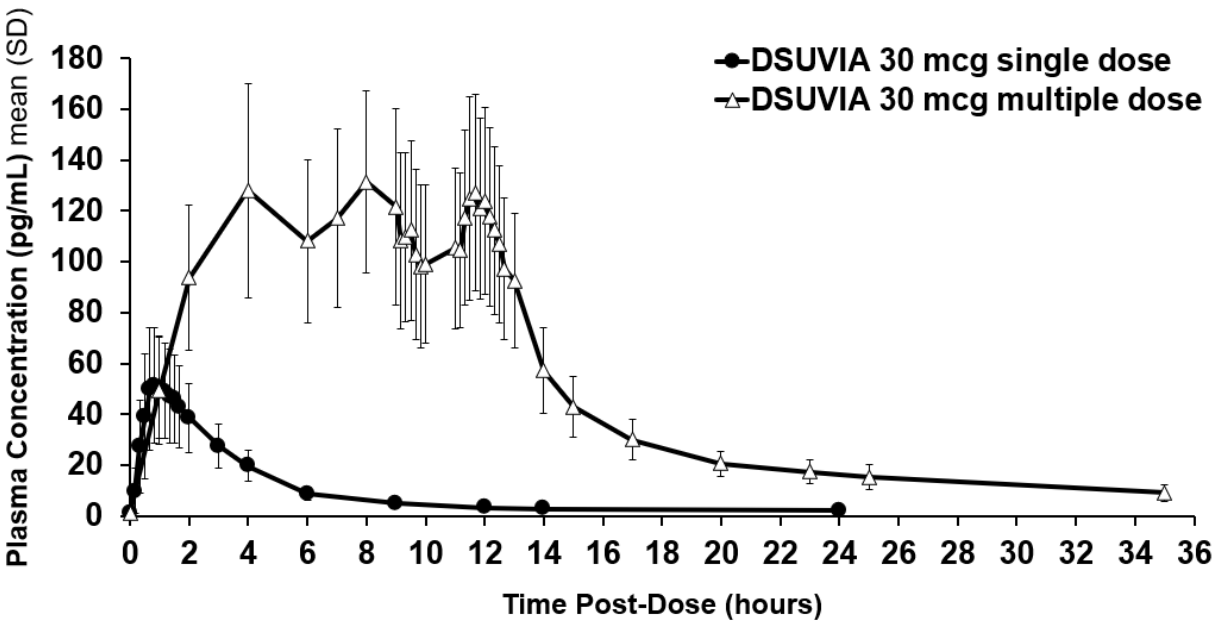
Serious or fatal respiratory depression can occur even at recommended doses. Although not observed with DSUVIA in the clinical trial, sufentanil given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration *[see Warnings and Precautions (5.4)]*.

12.3 Pharmacokinetics

Absorption

A single sublingual administration of DSUVIA has a bioavailability of approximately 53% relative to a one-minute IV sufentanil infusion of 30 mcg. Compared to IV administration, sublingual C_{max} values were 17-fold lower. The sublingual route of administration of sufentanil avoids intestinal and hepatic first-pass effects, both which severely limit bioavailability of swallowed (oral) sufentanil sublingual tablet (9%). Following a single dose of DSUVIA, the mean $AUC_{0\text{-}inf}$ is 278 h*pg/mL, the average C_{max} of 63.1 pg/mL occurs at a median T_{max} of 1.00 hour. After 12 multiple hourly doses over 11 hours, the geometric mean for the AUC within a dosing interval ($AUC_{0\text{-}60min}$) and C_{max} values were increased by 3.7-fold and 2.3-fold greater compared to single-dose administration, respectively. Steady-state plasma concentrations were achieved after 7 doses (*Figure 1*).

Figure 1: Sufentanil Concentration-Time Values: Single vs. Consecutive Repeat Doses (12 DSUVIA Doses)



Distribution

Plasma protein binding of sufentanil, related to the alpha acid glycoprotein concentration, was approximately 93% in healthy males, 91% in mothers and 79% in neonates.

Elimination

Following a single dose of DSUVIA, the mean terminal half-life is 13.4 hours, and the mean apparent plasma clearance is 108 L/hour.

Metabolism: The liver and small intestine are the major sites of biotransformation

Excretion: Approximately 80% of the IV administered dose of sufentanil is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug.

Specific Populations

Clearance is not significantly affected by race, sex, mild or moderate renal impairment based on the population pharmacokinetics.

Drug Interaction Study

Co-administration of a single dose of sufentanil sublingual tablet 15 mcg with a strong CYP3A4 inhibitor, ketoconazole, resulted in 77% and 19% greater $AUC_{0\text{-}inf}$ and C_{max} values of sufentanil, respectively, compared to its administration alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of sufentanil have not been conducted.

Mutagenesis:

Sufentanil was not genotoxic in the in vitro bacterial reverse mutation assay (Ames assay) or in the in vivo rat bone marrow micro-nucleus assay.

Impairment of Fertility

Fertility and early embryonic development studies were conducted in male and female rats treated with 0.005, 0.02 or 0.08 mg/kg sufentanil IV for 56 days and 14 days prior to mating through gestation respectively. Increased

mortality was noted in all treatment groups.

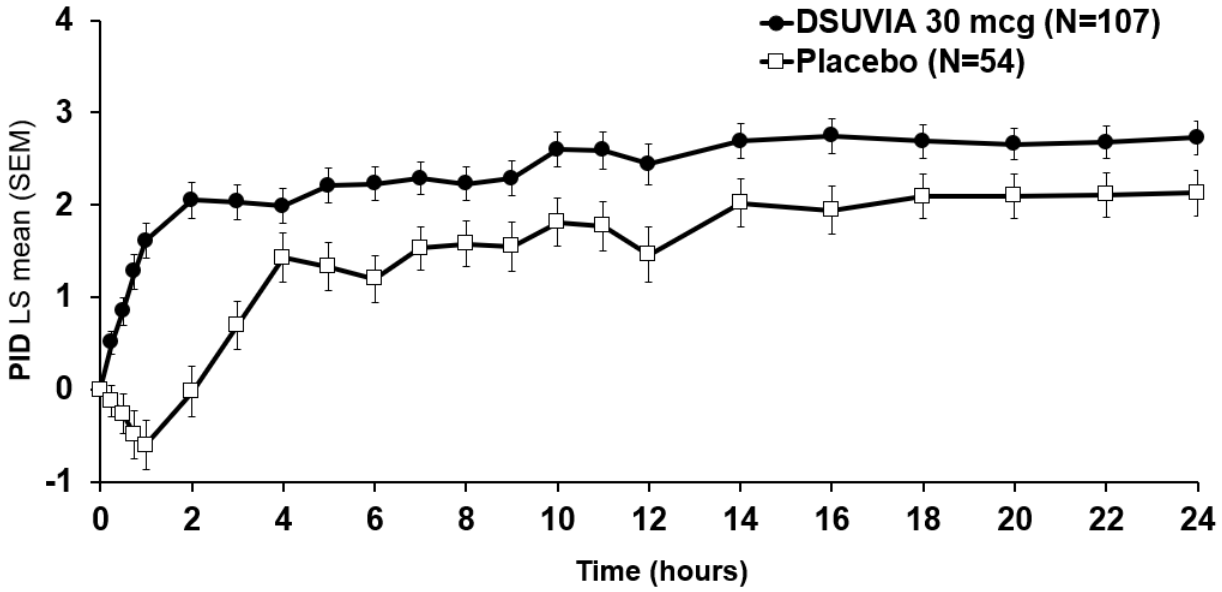
Lower pregnancy rates were noted following treatment of males at doses of 0.02 and 0.08 mg/kg (0.6 and 2.2 times the maximum human daily dose of 360 mcg/60 kg, based on a body surface area comparison), suggesting the potential for an adverse effect on fertility in males. Increased resorption of fetuses and reduced litter size was noted in the high dose females (2.2 times the maximum human daily dose of 360 mcg/60 kg, based on a body surface area comparison) suggesting the potential for fetotoxicity, likely due to maternal toxicity.

14 CLINICAL STUDIES

The efficacy and safety of DSUVIA were evaluated in one randomized, double-blind, placebo-controlled trial which enrolled 161 patients (age 18 to 69 years) with acute postoperative pain (pain intensity of ≥ 4 on a 0-10 Numeric Rating Scale [NRS]) after abdominal surgery (studied up to 48 hours) (Study SAP301, NCT# 02356588). Patients were dosed with DSUVIA 30 mcg 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. Least squares means of pain intensity difference from baseline over 24 hours for the abdominal surgery study are shown in *Figure 2*. Median time to onset of meaningful pain relief (measured using the double stopwatch method) was 54 minutes for the DSUVIA group and 84 minutes for the placebo group. Approximately 22% of patients in the DSUVIA group and 65% of patients in the placebo group took rescue medication within the first 12 hours of the treatment phase.

Figure 2: Least Squares Mean of Pain Intensity Difference by Evaluation Time Point over the 24-Hour Study Period: Abdominal Surgery ITT Population



PID = pain intensity difference; ITT = intent-to-treat; LS = least squares; SEM = standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Each DSUVIA tablet 30 mcg is housed in a single-dose applicator (SDA) and packaged within a tamper-evident laminate foil pouch. For distribution there is one presentation:

- NDC 61621-430-11 (10 pouches per carton)

The SDA should be disposed in biohazard waste after administration of DSUVIA.

Instruct the healthcare provider to take steps to store DSUVIA securely and to dispose of any dropped or misplaced DSUVIA tablets according to institutional CII procedures.

16.2 Storage and Handling

Store DSUVIA at room temperature 20-25 ºC, excursions allowed 15-30 ºC in a secure, limited access location, in accordance with institutional procedures for CII products.

17 PATIENT COUNSELING INFORMATION

Increased Risk of Overdose and Death in Children Due to Accidental Exposure

Inform patients that accidental exposure, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.1)]*.

Addiction, Abuse, and Misuse

Inform patients that the use of DSUVIA, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.4)]*. Instruct patients not to share DSUVIA with others and to take steps to protect DSUVIA from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting DSUVIA *[see Warnings and Precautions (5.4)]*.

Hyperalgesia and Allodynia

Advise patients to inform their healthcare provider if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.7), and Adverse Reactions (6.2)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition called serotonin syndrome resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop after discharge from the hospital. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications. *[see Warnings and Precautions (5.8), and Drug Interactions (7)]*.

Important Administration Instructions

Advise patients to allow DSUVIA to dissolve under the tongue and not to chew or swallow the tablet. Advise patients not to eat or drink and to minimize talking for 10 minutes after each dose of DSUVIA.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.10)]*.

Hypotension

Inform patients that DSUVIA may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Contraindications (4), and Warnings and Precautions (5.11)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in DSUVIA. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), and Adverse Reactions (6)]*.

Pregnancy

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that DSUVIA can (or may) cause fetal harm and to inform the prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.3)]*.

Lactation

Advise nursing mothers to carefully observe infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

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