DISCLAIMER

All labeling reflected on this website is for informational and promotional purposes only. It is not intended to be used by healthcare professionals or patients for the purpose of prescribing or administering these products. Questions regarding the current content of product labeling should be directed to Akorn's Customer Service department at 800.932.5676.
Fentanyl Citrate Injection, for intravenous or intramuscular use, CII
Initial U.S. Approval: 1968

WARNINGS AND PRECAUTIONS

5 WARNINGS AND PRECAUTIONS

5.11 Increased Risk of Seizures in Patients with Seizure Disorders

5.12 Risks of Driving and Operating Machinery

5.13 Risks due to Interaction with Neuroleptic Agents

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

9 DRUG ABUSE AND DEPENDENCE

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

16 HOW SUPPLIED/STORAGE AND HANDLING

* Sections or subsections omitted from the full prescribing information are not listed.
Fentanyl Citrate Injection 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 Fentanyl Citrate Injection, and monitor all patients regularly for the development of these behaviors and conditions [see Warnings and Precautions (5.1)].

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Fentanyl Citrate Injection. Monitor for respiratory depression, especially during initiation of Fentanyl Citrate Injection or following a dose increase [see Warnings and Precautions (5.2)].

Cytochrome P450 3A4 Interaction
The concomitant use of Fentanyl Citrate Injection with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse 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 fentanyl plasma concentration. Monitor patients receiving Fentanyl Citrate Injection and any CYP3A4 inhibitor or inducer [see Warnings and Precautions (5.3), Drug Interactions (7), Clinical Pharmacology (12.3)].

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 [see Warnings and Precautions (5.4), Drug Interactions (7)].

• Reserve concomitant prescribing of Fentanyl Citrate Injection and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
• Limit dosages and durations to the minimum required.
• Follow patients for signs and symptoms of respiratory depression and sedation.

1 INDICATIONS AND USAGE
Fentanyl Citrate Injection is indicated for:
• Analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises.
• Use as a narcotic analgesic supplement in general or regional anesthesia.
• Administration with a neuroleptic as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.
• Use as an anesthetic agent with oxygen in selected high risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

2 DOSAGE AND ADMINISTRATION
2.1 Important Dosage and Administration Instructions
Fentanyl Citrate Injection should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

• Ensure that an opioid antagonist, resuscitative and intubation equipment, and oxygen are readily available.
• Individualize dosage based on factors such as age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.
• Monitor vital signs routinely.

As with other potent opioids, the respiratory depressant effect of fentanyl may persist longer than the measured analgesic effect. The total dose of all opioid agonists administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia.

If Fentanyl Citrate Injection is administered with a CNS depressant, become familiar with the properties of each drug, particularly each product’s duration of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia.

For open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and the stress response to surgery would be detrimental to the well-being of the patient.

In conjunction with nitrous oxide/ oxygen has been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH and prolactin.

Expect the need for postoperative ventilation and observation due to extended postoperative respiratory depression.

Table 1: Dosage Range Chart

<table>
<thead>
<tr>
<th>TOTAL DOSAGE (expressed as fentanyl base)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose — 2 mcg/kg (0.002 mg/kg) (0.04 mL/kg). For use in minor, but painful, surgical procedures.</td>
</tr>
<tr>
<td>Moderate Dose — 2 to 10 mcg/kg (0.002 to 0.02 mg/kg) (0.04 to 0.4 mL/kg). For use in more major surgical procedures, in addition to adequate analgesia, may abolish some of the stress response.</td>
</tr>
<tr>
<td>High Dose — 20 to 50 mcg/kg (0.02 to 0.05 mg/kg) (0.4 to 1.0 mL/kg). For open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and the stress response to surgery would be detrimental to the well-being of the patient.</td>
</tr>
</tbody>
</table>

For use as a narcotic analgesic supplement in general or regional anesthesia.

Adjunct to Regional Anesthesia
50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 mL) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

Postoperatively (recovery room)
50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 mL) may be administered intramuscularly for the control of pain, tachycardia and emergence delirium. The dose may be repeated in one to two hours as needed.

For Induction and Maintenance in Children 2 to 12 Years of Age
A reduced dose as low as 2 to 3 mcg/kg is recommended.

As a General Anesthetic
As a technique to attenuate the responses to surgical stress without the use of additional anesthetic agents, doses of 50 to 100 mcg/kg (0.05 to 0.1 mg/kg) (1 to 2 mL/kg) may be administered with oxygen and a muscle relaxant. In certain cases, doses up to 150 mcg/kg (0.15 mg/kg) (3 mL/kg) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

3 DOSAGE FORMS AND STRENGTHS
Fentanyl Citrate Injection, USP 50 mcg/mL (equivalent to 50 mcg/mL Fentanyl base) is available as: 2 mL, 5 mL, 10 mL and 20 mL ampules.

4 CONTRAINDICATIONS
Fentanyl Citrate Injection is contraindicated in patients with:
• Hypersensitivity to fentanyl (e.g., anaphylaxis) [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS
5.1 Addiction, Abuse, and Misuse
Fentanyl Citrate Injection contains fentanyl, a Schedule II controlled substance. As an opioid, Fentanyl Citrate Injection exposes users to the risks of addiction, abuse, and misuse [see Drug Abuse and Dependence (9)].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when handling Fentanyl Citrate Injection. 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.

5.2 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. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of Fentanyl Citrate Injection. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression. Management of respiratory depression may include close
Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. To reduce the risk of respiratory depression, proper dosing and titration of Fentanyl Citrate Injection are essential. As with other potent opioids, the respiratory depressant effect of Fentanyl Citrate Injection may persist longer than the measured analgesic effect. The total dose of all opioid agonists administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia. Certain forms of conduction anesthesia, such as spinal anesthesia and some peripheral anesthetics, can alter respiration by blocking intercostal nerves through other mechanisms [see Clinical Pharmacology (12.2)]. Fentanyl Citrate Injection can also alter respiration. Therefore, when Fentanyl Citrate Injection is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

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 recommended dosages of Fentanyl Citrate Injection. Elderly, cachectic, or debilitated patients may have altered pharmacokinetics or altered clearance compared to younger, healthier patients resulting in greater risk for respiratory depression. Monitor such patients closely including vital signs, particularly when initiating and titrating Fentanyl Citrate Injection and when Fentanyl Citrate Injection is given concomitantly with other drugs that depress respiration. To reduce the risk of respiratory depression, proper dosing and titration of Fentanyl Citrate Injection are essential [see Dosage and Administration (2.1)].

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

Concomitant use of Fentanyl Citrate Injection 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 fentanyl and prolong opioid adverse reactions, which may exacerbate respiratory depression [see Warnings and Precautions (5.1)]. Fentanyl Citrate Injection may inhibit an inhibitor or induce an inducer of CYP3A4 in other drug products. Such changes in CYP3A4 activity are observed when certain medications are given together. Therefore, the dose of Fentanyl Citrate Injection may need to be modified when used in combination with CYP3A4 inhibitors or inducers. Discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Fentanyl Citrate Injection-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using Fentanyl Citrate Injection with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Fentanyl Citrate Injection-treated patients, monitor closely for adverse reactions including respiratory depression [see Drug Interactions (7)].

Concomitant use of Fentanyl Citrate Injection with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could result in lower than expected fentanyl plasma concentrations and, decrease efficacy. When using Fentanyl Citrate Injection with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the Fentanyl Citrate Injection dosage [see Dosage and Administration (2.1), Drug Interactions (7)].

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

When benzodiazepines or other CNS depressants are used with Fentanyl Citrate Injection, postoperative respiratory depression may be increased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of Fentanyl Citrate Injection are employed, even relatively small dosages of diazepam may cause cardiovascular depression. When Fentanyl Citrate Injection is used with CNS depressants, hypotension can occur. If it occurs, consider the possibility of hypovolemia and manage with appropriate parenteral fluid therapy. When operating conditions permit, consider repositioning the patient to improve venous return to the heart. Exercise care in moving and repositioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, consider administration of pressor agents other than ephedrine. Ephedrine may paradoxically decrease blood pressure in patients treated with a neuroleptic that has antihypotensive activity.

5.5 Risks of Muscle Rigidity and Skeletal Muscle Movement

Fentanyl Citrate Injection may cause muscle rigidity, particularly involving the muscles of respiration. The incidence and severity of muscle rigidity is dose related. These effects are related to the dose and speed of injection. Skeletal muscle rigidity also has been reported to the heart. Exercise care in moving and repositioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, consider administration of pressor agents other than ephedrine. Ephedrine may paradoxically decrease blood pressure in patients treated with a neuroleptic that has antihypotensive activity.

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of Fentanyl Citrate Injection combined with a neuroleptic. This might be due to increased arterial pressure in the presence of risk factors for development of prolonged QT syndrome and torsades de pointes, such as: 1) clinically significant bradycardia (less than 50 bpm), 2) any clinically significant cardiac disease, including baseline prolonged QT interval, 3) treatment with Class I and Class III antiarrhythmics, 4) treatment with monoamine oxidase inhibitors (MAO's), 5) concomitant treatment with other drugs that prolong the QT interval, 6) electrolyte imbalance, in particular hypokalemia and hypomagnesemia, or concomitant treatment with drugs (e.g. diuretics) that may cause electrolyte imbalance.

Monitor these patients for signs of hypotension after initiating or titrating the dosage of Fentanyl Citrate Injection.

5.7 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

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

5.8 Adrenal Insufficiency

During treatment with Fentanyl Citrate Injection, adrenal insufficiency may occur, and symptoms may include nausea, vomiting, diarrhea, and hypotension. Hypoglycemia may occur in patients with existing diabetes. Hypoglycemia may be more likely to occur in patients treated with Fentanyl Citrate Injection and when Fentanyl Citrate Injection is given concomitantly with other opioids. The total dose of all opioid agonists administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia. Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Management of adrenal insufficiency may include non-specific symptoms such 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.

5.9 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, or Head Injury

5.10 Risks of Use in Patients with Gastrointestinal Conditions

Fentanyl 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.

5.11 Increased Risk of Seizures in Patients with Seizure Disorders

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

5.12 Risks of Driving and Operating Machinery

Fentanyl may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery after Fentanyl Citrate Injection administration.

5.13 Risks due to Interaction with Neuroleptic Agents

Many neuroleptic agents have been associated with QT prolongation, torsades de pointes, and cardiac arrest. Administer neuroleptic agents with extreme caution in the presence of increased intracranial pressure or brain tumors), Fentanyl Citrate Injection may cause severe bradycardia, severe hypotension including orthostatic hypotension, and syncope. There is 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., phentazocine or general anesthetics). Fentanyl Citrate Injection given concomitantly with a tricyclic antidepressant (TCA), monoamine oxidase inhibitors (MAO), or tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), 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 melphalan blue) [see Drug Interactions (7)]. This may occur within the recommended dosage range.

Many neuroleptic agents have been associated with QT prolongation, torsades de pointes, and cardiac arrest. Administer neuroleptic agents with extreme caution in the presence of increased intracranial pressure or brain tumors), Fentanyl Citrate Injection may cause severe bradycardia, severe hypotension including orthostatic hypotension, and syncope. There is 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., phentazocine or general anesthetics). Fentanyl Citrate Injection given concomitantly with a tricyclic antidepressant (TCA), monoamine oxidase inhibitors (MAO), or tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), 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 melphalan blue) [see Drug Interactions (7)]. This may occur within the recommended dosage range.

5.7 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of fentanyl 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 serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), 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 melphalan blue) [see Drug Interactions (7)]. This may occur within the recommended dosage range.
• Interactions with Benzodiazepines or Other CNS Depressants [see Warnings and Precautions (5.4)]
• Severe Cardiovascular Depression [see Warnings and Precautions (5.6)]
• Serotonin Syndrome [see Warnings and Precautions (5.7)]
• Gastrointestinal Adverse Reactions [see Warnings and Precautions (5.10)]
• Seizures [see Warnings and Precautions (5.11)]

The following adverse reactions associated with the use of fentanyl were identified in clinical studies or postmarketing reports. Because some of these reactions were 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.

As with opioid agonists, the most common serious adverse reactions reported to occur with fentanyl are respiratory depression, apnea, rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausae, emesis, diaphoresis, pruritus, urticaria, laryngospasm and anaphylaxis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively.

When a tranquilizer is used with Fentanyl Citrate Injection, the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of neuroleptics with fentanyl citrate.

Cases of cardiac dysrhythmias, cardiac arrest, and death have been reported following the use of fentanyl citrate with a neuroleptic agent.

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 Fentanyl Citrate Injection.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see Clinical Pharmacology (12.2)].

7 DRUG INTERACTIONS

Table 2 includes clinically significant drug interactions with Fentanyl Citrate Injection.

Table 2: Clinically Significant Drug Interactions with Fentanyl Citrate Injection

<table>
<thead>
<tr>
<th>Inhibitors of CYP3A4</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl Citrate Injection and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of Fentanyl Citrate Injection is achieved [see Warnings and Precautions (5.3)].</td>
<td>As postoperative analgesia, start with a lower dose of Fentanyl Citrate Injection and monitor patients for signs of respiratory depression, sedation, and hypotension. Fluids or other measures to counter hypotension should be available. [see Warnings and Precautions (5.4)].</td>
<td>Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.</td>
<td></td>
</tr>
<tr>
<td>Fentanyl Citrate Injection and CYP3A4 inhibitors can decrease the plasma concentration of fentanyl [see Clinical Pharmacology (12.3)], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl 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.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Examples: Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice

<table>
<thead>
<tr>
<th>CYP3A4 Inducers</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>The concomitant use of Fentanyl Citrate Injection and CYP3A4 inducers can decrease the plasma concentration of fentanyl [see Clinical Pharmacology (12.3)], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl.</td>
<td></td>
<td>Rifampin, carbamazepine, phenytoin</td>
<td></td>
</tr>
<tr>
<td>After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl 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.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If a CYP3A4 inducer is discontinued, consider increasing the Fentanyl Citrate Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Examples: Rifampin, carbamazepine, phenytoin

<table>
<thead>
<tr>
<th>Benzodiazepines and Other Central Nervous System (CNS) Depressants</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>The concomitant use of Fentanyl Citrate Injection with CNS depressants may result in decreased pulmonary artery pressure and may cause hypotension. Even small doses of diazepam may cause cardiovascular depression when added to high dose or anesthetic dosages of Fentanyl Citrate Injection.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical 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.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Fentanyl Citrate Injection is not recommended for use in pregnant women during or immediately prior to labor, when other anesthetic techniques are more appropriate. Opioid analgesics, including Fentanyl Citrate Injection, 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

Fentanyl has been shown to embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.05 times the human dose of 100 mcg/kg on a mg/m² basis) and 160 mcg/kg subcutaneously (0.26 times the human dose of 100 mcg/kg on a mg/m² basis). There was no evidence of teratogenicity reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in pregnant rabbits. Pregnant rabbits were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 0.81 times the human dose of 100 mcg/kg on a mg/m² basis.

8.2 Lactation

Risk Summary

Fentanyl is present in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.39%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production.

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

Clinical Considerations

Monitor infants exposed to fentanyl 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

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and efficacy of Fentanyl Citrate Injection in children under two years of age have not been established.

Rare cases of unexplained clinically significant methemoglobinemia have been reported in premature neonates undergoing emergency anesthesia and surgery which included the combined use of fentanyl, pancuronium, and atropine. A direct cause and effect relationship between the combined use of these drugs and the reported cases of methemoglobinemia has not been established.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to fentanyl. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

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. Titrated the dosage of Fentanyl Citrate Injection slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see Warnings and Precautions (5.2)].

Fentanyl is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Fentanyl Citrate Injection should be administered with caution to patients with liver dysfunction because of the extensive hepatic metabolism. Reduce the dosage as needed and monitor closely for signs of respiratory depression, sedation, and hypotension.

8.7 Renal Impairment

Fentanyl Citrate Injection should be administered with caution to patients with kidney dysfunction because of the renal excretion of fentanyl citrate and its metabolites. Reduce the dosage as needed and monitor for signs of respiratory depression, sedation, and hypotension.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl Citrate Injection contains fentanyl, a Schedule II controlled substance.

9.2 Abuse

Fentanyl Citrate Injection contains a substance with a high potential for abuse similar to other opioids including hydrocodone, hydroxypropone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Fentanyl Citrate Injection can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.1)].

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develops after repeated substance use and includes; a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

Fentanyl Citrate Injection, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Risks Specific to Abuse of Fentanyl Citrate Injection

Abuse of Fentanyl Citrate Injection poses a risk of overdose and death. The risk is increased with concurrent use of Fentanyl Citrate Injection with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired effects and the undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also 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 opioid usage.
12.2 Pharmacokinetics

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

Fentanyl 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
Fentanyl 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, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Fentanyl 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, 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.

Chronic use of opioids 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)].

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

Concentration–Efficacy Relationships
A dose of 100 mcg (0.1 mg) (2.0 mL) of Fentanyl Citrate Injection is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of meperidine. The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see Dosage and Administration (2.1)].

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, the maximal analgesic effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single intravenous dose of up to 100 mcg (0.1 mg) (2 mL). Following intramuscular administration, the onset of action is from seven to eight minutes and the duration of action is one to two hours.

Concentration–Adverse Reaction Relationships
There is a relationship between increasing fentanyl plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see Dosage and Administration (2.1, 2.2)].

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, the maximal respiratory depressant effect may not be noted for several minutes. As with longer acting opioid analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO₂ stimulation following administration of fentanyl citrate:

- Diminished sensitivity to CO₂ stimulation may persist longer than depression of respiratory rate. (Altered sensitivity to CO₂ stimulation has been demonstrated for up to four hours following a single dose of 400 mcg (0.6 mg) (12 mL) fentanyl citrate to healthy volunteers). Fentanyl frequently slows the respiratory rate, duration and degree of respiratory depression being dose-related.
- The peak respiratory depressant effect of a single intravenous dose of Fentanyl Citrate Injection is noted 5 to 15 minutes following injection [see Warnings and Precautions (5.2)].

12.3 Pharmacokinetics

Fentanyl Citrate Injection is administered by the intravenous or intramuscular route. The pharmacokinetics of fentanyl can be described as a three-compartment model.

Distribution
Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. It accumulates in skeletal muscle and fat, and is released slowly into the blood. The volume of distribution for fentanyl is 4 L/kg. It has a distribution time of 1.7 minutes and redistribution time of 13 minutes.

Elimination
The terminal elimination half-life is 219 minutes. Fentanyl, which is primarily transformed in the liver, demonstrates a high first pass clearance and releases approximately 75% of an intravenous dose in urine, mostly as metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term studies in animals to evaluate the carcinogenic potential of fentanyl citrate injection have not been conducted.

Mutagenesis
Studies in animals to evaluate the mutagenic potential of fentanyl have not been conducted.

Impairment of Fertility
Decreased pregnancy rates occurred in a multigenerational study in which pregnant rats were treated subcutaneously during the first 21 days of pregnancy with 160 mcg/kg to 1250 mcg/kg fentanyl (0.26 times to 2.0 times a human dose of 100 mcg/kg based on body surface area).

Studies in animals to characterize the effect of fentanyl on male fertility have not been conducted.

16 HOW SUPPLIED/STORAGE AND HANDLING

Fentanyl Citrate Injection, USP equivalent to 50 mcg fentanyl base per mL is available in single-dose glass containers as follows:

- NDC 17478-030-02 100 mcg/2 mL (50 mcg/mL) in packages of 10
- NDC 17478-030-05 250 mcg/5 mL (50 mcg/mL) in packages of 10
- NDC 17478-030-10 500 mcg/10 mL (50 mcg/mL) in packages of 5
- NDC 17478-030-20 1,000 mcg/20 mL (50 mcg/mL) in packages of 5
- NDC 17478-030-25 100 mcg/2 mL (50 mcg/mL) in packages of 25
- NDC 17478-030-55 250 mcg/5 mL (50 mcg/mL) in packages of 25
- NDC 17478-031-50 2,500 mcg/50 mL (50 mcg/mL) in single pack

Storage: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light.

Manufactured by: Akorn, Inc.
Lake Forest, IL 60045

AFCA0N Rev. 11/17
P103 Rev. 03/18