

These highlights do not include all the information needed to use FENTANYL CITRATE INJECTION safely and effectively. See full prescribing information for FENTANYL CITRATE INJECTION.

FENTANYL CITRATE injection, for intravenous or intramuscular use,

WARNING: RISK OF ADDICTION, ABUSE, AND MISUSE: LIFE-P450 3A4 INTERACTION: and RISKS FROM CONCOMITANT USE

See full prescribing information for complete boxed warning. Fentanyl Citrate Injection exposes users to risks of addiction

- Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase (5.2) Concomitant use with CYP3A4 inhibitors (or discontinuation
- of CYP3A4 inducers) can result in a fatal overdose of fentanyl (5.3. 7. 12.3)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may resul in profound sedation, respiratory depression, coma, and death Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7

- RECENT MAJOR CHANGES -

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Fentanyl Citrate

Injection, USP

- · use as an opioid 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
- · use as an anesthetic agent with oxygen in selected high risk patients, neurological or orthopedic procedures.

- DOSAGE AND ADMINISTRATION -

- · 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.
- ment, and oxygen are readily available (2.1).

Warnings and Precautions (5.2)

- INDICATIONS AND USAGE -

Fentanyl Citrate Injection is indicated for:

- · analgesic action of short duration during the anesthetic periods, premed ication, induction and maintenance and in the immediate postoperative period (recovery room) as the need arises.
- and regional anesthesia.
- such as those undergoing open heart surgery or certain complicated

- · Ensure that an opioid antagonist, resuscitative and intubation equip-

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF ADDICTION, ABUSE, AND MISUSE: LIFE THREATENING RESPIRATORY DEPRESSION: CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT US WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse
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

<u>Life-Threatening Respiratory Depression</u>
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

· Individualize dosing based on the 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. (2.1) Initiate treatment in adults with 50 to 100 mcg (0.05 to 0.1 mg) (1 to

Initiate treatment in children 2 to 12 years of age, with a reduced dose as low as 2 to 3 mcg/kg. (2.2)

— DOSAGE FORMS AND STRENGTHS ——

Fentanyl Citrate Injection, equivalent to 50 mcg (0.05 mg) fentanyl base per mL, is a preservative-free solution, available in 1 mL, 2 mL, 5 mL, 20 mL, 50 mL single-dose glass vials. (3)

concomitant serotonergic drug administration. Discontinue Fentanyl

- CONTRAINDICATIONS -

 Hypersensitivity to fentanvl (4) ----- WARNINGS AND PRECAUTIONS ----

- Risks of Skeletal Muscle Rigidity and Skeletal Muscle Movement: Manage with neuromuscular blocking agent. See full prescribing information for more detail on managing these risks. (5.5)
- Severe Cardiovascular Depression: Monitor during dosage initiation and • Serotonin Syndrome: Potentially life-threatening condition could result
- Citrate Injection if serotonin syndrome is suspected. (5.7) · Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of eroids, and wean patient off of the opioid. (5.8)
- Risks of Use in Patients with Increased Intracranial Pressure. Brain Tumors, or Head Injury: Monitor for sedation and respiratory depression. (5.9)

— ADVERSE REACTIONS ———

Most common serious adverse reactions were respiratory depression, annea rigidity and bradycardia (6) To report SUSPECTED ADVERSE REACTIONS contact

Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. - DRUG INTERACTIONS -

Concomitant Use of CNS Depressants: May decrease pulmonary arterial

- pressure and may cause hypotension. See FPI for management instructions. For post-operative pain, start with the lowest effective dosage and monitor for potentiation of CNS depressant effects. (5.4, 7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Fentanyl Citrate Injection because they may reduce the analgesic effect of Fentanyl Citrate Injection or precipitate withdrawal ----- USE IN SPECIFIC POPULATIONS -----

• Pregnancy: May cause fetal harm. (8.1)

- Lactation: Infants exposed to Fentanyl Citrate Injection through breast milk should be monitored for excess sedation and respiratory depres-Geriatric Patients: Titrate slowly and monitor for CNS and respiratory

See 17 for PATIENT COUNSELING INFORMATION.

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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 con centration. Monitor patients receiving Fentanyl Citrate Injection and (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

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

INDICATIONS AND USAGE

- Fentanyl Citrate Injection is indicated for: analgesic action of short duration during the anesthetic periods
- ate 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.

DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions
Fentanyl Citrate Injection should be administered only by persons Dependence (9)1. 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 of other drugs, type of anesthesia to be used, and the surgical abuse or diversion of this product. 5.2 Life-Threatening Respiratory Depression
- 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 depres

sant, 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 available [see Warnings and Precautions Inspect parenteral drug products visually for particulate matter and

tainer permit.

2.2 Dosage

50 mcg = 0.05 mg = 1 mL Premedication in Adults

50 to 100 mcg (0.05 to 0.1 mg) (1 to 2 mL) may be administered intramuscularly 30 to 60 minutes prior to surgery Adjunct to General Anesthesia

See Dosage Range Charts below. Table 1: Dosage Range Chart

Total Dosage (expressed as fentanyl base)

Low Dose-2 mcg/kg (0.002 mg/kg) (0.04 mL/kg). For use in minor, but painful, surgical procedures.

May also provide some pain relief in the immediate postoperative

Moderate Dose—2 to 20 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 Expect respiratory depression requiring artificial ventilation during anesthesia and careful observation of ventilation postoperatively is

High dose-20 to 50 mcg/kg (0.02 to 0.05 mg/kg) (0.4 to 1 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

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 of postoperative ventilation and observation due to extended post-operative respiratory depression.

Maintenance Dose (expressed as fentanyl base)

Low Dose-2 mcg/kg (0.002 mg/kg) (0.04 mL/kg). Additional dosages infrequently needed in these minor procedures.

lightening of analgesia.

As a General Anesthetic

Moderate Dose—2 to 20 mcg/kg (0.002 to 0.02 mg/kg) (0.04 to 0.4 mL/kg). 25 to 100 mcg (0.025 to 0.1 mg) (0.5 to 2 mL) Administer intravenously or intramuscularly as needed when movement and/or changes in vital signs indicate surgical stress or

High Dose—20 to 50 mcg/kg (0.02 to 0.05 mg/kg) (0.4 to 1 mL/kg). Maintenance dosage [ranging from 25 mcg (0.025 mg) (0.5 mL) to one half the initial loading dose] as needed based on vital signs indicative of stress and lightening of analgesia. Individualize the dosage especially if the anticipated remaining operative time is short

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, tachypnea 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 technique to attenuate the responses to surgical stress without he 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 oxyge 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 anestheti effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocar dium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

DOSAGE FORMS AND STRENGTHS

Single-Dose Vials:

Fentanyl Citrate Injection, USP, equivalent to 50 mcg (0.05 mg) fentanyl base per mL, is a preservative-free solution, available in 1 mL, 2 mL, 5 mL, 20 mL, 50 mL single-dose glass vials.

CONTRAINDICATIONS

Fentanyl Citrate Injection is contraindicated in patients with: Hypersensitivity to fentanyl (e.g., anaphylaxis) [See Adverse

Reactions (6)1 WARNINGS AND PRECAUTIONS

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

Opioids are sought by drug users 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 controlle substances authority for information on how to prevent and detect

Serious, life-threatening, or fatal; respiratory depression has beer reported with the use of opioids, even when used as recommended spiratory 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 degree of respiratory depression. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status (see Overdosage (10)1, Carbon dioxide (CO₂) retention from opioid induced respiratory depression can exacerbate the sedating effects

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 anesthe

sia and some peridural anesthetics can alter respiration by block-ing 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 man-age them in the patients selected for these forms of anesthesia Patients with significant chronic obstructive nulmonary disease or cor pulmonale, and those with a substantially decreased respirator 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 pharmacokine 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 dos ing and titration of Fentanyl Citrate Injection are essential [see Dosage and Administration (2.1)1.

Opioids can cause sleep-related breathing disorders including ce tral 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 decreasing the opioid dosage using best practices for opioid taper [see Dosage and Administration (2.1)

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

oncomitant use of Fentanyl Citrate Injection with a CYP3A4 inhibitor such as macrolide antibiotics (e.g., erythromycin), azole-antifunga 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 (5.2)], particularly when an inhibitor is added after a stable dose of Fentanyl Citrate Injection is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin carbamazenine and phenytoin in Fentanyl Citrate Injection-treater patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using Fentanyl Citrate Injection with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Fentany Citrate Injection-treated patients, monitor patients closely at frequen tervals and consider dosage reduction of Fentanyl Citrate Injection [see Dosage and Administration (2.1), Drug Interactions (7)].

Concomitant use of Fentanyl Citrate Injection with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor, could result in lower than expected fentanyl plasma concentrations and, decrease efficacy When using Fentanyl Citrate Injection with CYP3A4 inducers, or discontinuation of a CYP3A4 inhibitors monitor patients closely at fre quent 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, pulmonary arterial pressure may be decreased. 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

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 operative conditions permit, consider repositioning the patient to improve venous return to the heart. Exercise care in moving and reposition ing 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 epinephrine. Epinephrine may paradoxically decrease blood

may cause cardiovascular depression.

pressure in patients treated with a neuroleptic that blocks alpha drenergic activity.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Fentanyl Citrate Injection with penzodiazepines or other CNS depressants (e.g., nonbenzodiazepine sedatives/hypnotics anxiolytics tranquilizers muscle relaxants gen eral anesthetics, antipsychotics, other opioids, alcohol). If the decision is made to manage postoperative pain with Fentanyl Citrate Injection concomitantly with a benzodiazepine or other CNS depressant, start dosing with the lowest effective dosage and titrate based on clinical esponse. Follow patients closely for signs and symptoms of respiratory depression, sedation, and hypotension. Fluids or other measures o counter hypotension should be available [see Drug Interactions (7)].

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 occur or recur infrequently in the extended postoperative period usually following high dose administration. In addition, skeletal muscle movements of various groups in the extremities, neck, and external eye have been reported during induction of anesthesia with Fentanyl Citrate Injection; these reported movements have, on rare occasions, been strong enough to pose patient management These effects are related to the dose and speed of injection and its

ncidence can be reduced by: 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blockng agent just prior to administration of Fentanyl Citrate Injection; 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when Fentanyl Citrate Injection is used in anesthetic doses titrated by slow intravenous infusion; or, 3) simultaneous administration of Fentanyl Citrate Injection and a full paralyzing dose of a neuromuscular blocking agent when Fentanyl Citrate Injection is used in rapidly administered anesthetic dosage ne neuromuscular blocking agent used should be compatible with the natient's cardiovascular status

Severe Cardiovascular Depression

entanyl 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., phenothiazine or general anesthetics) [see Drug Interactions (7)] In patients with culatory shock, Fentanyl Citrate Injection may cause vasodilation that can further reduce cardiac output and blood pressure. Monitor these patients for signs of hypotension after initiating or titrating the dosage of Fentanyl Citrate Injection. Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

ses of serotonin syndrome, a potentially life-threatening co tion, have been reported during concomitant use of fentanyl with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reupe inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neuotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., 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 within the recommended dosage range. Serotonin syndrome symptoms may include mental status changes

(e.g., agitation, hallucinations, coma), autonomic instability (e.g. achycardia, labile blood pressure, hyperthermia), neuromuscula aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gas trointestinal 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 Fentanvl Citrate Injection if serotonin syndrome is suspected.

5.8 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 of the opioid to allow adrenal

unction 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. Risks of Use in Patients with Increased Intracranial Pressure. Brain Tumors, or Head Injury
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), Fentanyl Citrate Injection may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of increasing intracranial

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

5.11 Increased Risks of Seizures in Patients with Seizure Disorders entanyl may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical setting associated with seizures. Monitor natients with a history of seizure disorders for worsened seizure control during Fentanyl Citrate Injection therapy.

lisease, including acute pancreatitis for worsening symptoms.

Fentanyl Citrate Injection may impair the mental or physical abilities

needed to perform potentially hazardous activities such as driving a car

or operating machinery after Fentanyl Citrate Injection administration. 5.13 Risks due to Interaction with Neuroleptic Agents

5.12 Risks of Driving and Operating Machinery

Many neuroleptic agents have been associated with QT prolonga tion, torsades de pointes, and cardiac arrest. Administer neuroleptic agents with extreme caution in the presence of risk factors for devel opment 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 treatment with monoamine oxidase inhibitors (MAOI's), 5) con comitant treatment with other drug products known to prolong the QT interval and 6) electrolyte imbalance, in particular hypokalemia diuretics) that may cause electrolyte imbalance.

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 unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

ECG monitoring is indicated when a neuroleptic agent is used in conjunction with Fentanyl Citrate Injection as an anesthetic premedication, for the induction of anesthesia, or as an adjunct in the maintenance of general or regional anesthesia. When fentanyl Citrate Injection is used with a neuroleptic and an EEG

is used for postoperative monitoring, the EEG pattern may return to normal slowly

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 (5.1)]
- Precautions (5.2) Interactions with Benzodiazepines and Other CNS Depressants [see Warnings and Precautions (5.4)]
- Serotonin Syndrome [see Warnings and Precautions (5.7)]
 Severe Cardiovascular Depression [see Warnings and Precautions strointestinal Adverse Reactions (see Warnings and Precautions
- 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 other 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, nausea, emesis, larvngo spasm, diaphoresis, serotonin syndrome, adrenal insufficiency, 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 hal lucinatory episodes (sometimes associated with transient periods of

mental depression); extrapyramidal symptoms (dystonia, akathisia and oculogyric crisis) have been observed up to 24 hours postop-

eratively. 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

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 fe-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Fentanyl Citrate Injection

DRUG INTERACTIONS Table 2 includes clinically significant drug interactions with Fentanyl

Table 2: Clinically Significant Drug Interactions with Fentanyl Citrate

	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)].
	After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease [see Clinical Pharmacology (12.3) resulting in decreased opioid efficacy or a withdraw syndrome in patients who had developed physical dependence to fentanyl.
Intervention:	If concomitant use is necessary, consider dosage reduction of Fentanyl Citrate Injection until stable drug effects are achieved <i>[see Dosage and Administration (2.1)]</i> . Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the Fentanyl Citrate Injection dosage unt stable drug effects are achieved. Monitor for signs opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole- antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CVP3A4 Induce	7.01

Clinical Impact: The concomitant use of Fentanyl Citrate Injection

Inhibitors of CYP3A4

(12.3)], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl [see Warnings and Precautions (5.3)]. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentra-tion 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

Table 2: Clinically Significant Drug Interactions with Fentanyl Citrate Injection (Cont'd.)

CYP3A4 Inducers If concomitant use is necessary consider increasing the Fentanyl Citrate Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider Fentanyl Citrate Injection dosage reduction nd monitor for signs of respiratory depression. Rifampin, carbamazepine, phenytoin Benzodiazepines and Other Central Nervous System (CNS) Clinical Impact: The concomitant use of Fentanyl Citrate Injection with CNS depressants my result in decreased pulmonary artery pressure and may cause hypotension Even small dosages of diazepam may cause cardio vascular depression when added to high dose or anesthetic dosages of Fentanyl Citrate Injection. As postoperative analgesia, concomitant use of Fentanyl Citrate Injection can increase the risk of hypotension respiratory depression, profound sedation, coma. Intervention: 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

otension should be available (see Warnings and

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 (5.7)1.

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., mirtazapin trazodone, tramadol), certain muscle relaxants (i.e. cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month Intervention: The use of Fentanyl Citrate Injection is not recommended for patients taking MAOIs or within 14 days

with chronic use of opioids [see Clinical Pharmacology (12.2)].

Clinical Impact: The concomitant use of 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)]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl 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 fentanyl.
Intervention:	If concomitant use is necessary, consider dosage reduction of Fentanyl Citrate Injection until stable drug effects are achieved [see Dosage and Administration (2.1)]. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the Fentanyl Citrate Injection dosage until

and CYP3A4 inducers can decrease the plasma concentration of fentanyl /see Clinical Pharmacology

Life-Threatening Respiratory Depression [see Warnings and

Examples: Benzodiazepines and other sedatives/hypnotics. anxiolytics, barbiturates, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other

Intervention: If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Fentanyl Citrate Injectio n if serotonin syndrome is suspected.

Monoamine Oxidase Inhibitors Clinical Impact: MAOI interactions with opioids may manifest as serotonin syndrome [see Warnings and Precautions (5.7)] or opioid toxicity (e.g., respiratory depression, comá) [see Warnings and Precautions (5.2)]

of stopping such treatment. Examples: Phenelzine, tranylcypromine, linezolid Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics Androgen deficiency: Cases of androgen deficiency have occurred Clinical Impact: May reduce the analgesic effect of Fentanyl Citrate Injection and/or precipitate withdrawal symptoms.

Intervention: Avoid concomitant use Examples: Butorphanol, nalbuphine, pentazocine, buprenor-

> Muscle Relaxants Clinical Impact: Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Intervention: Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of Fentanyl Citrate Injection

and/or the muscle relaxant as necessary

Clinical Impact: Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Intervention: Monitor patients for signs of diminished digresis 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

constination, which may lead to paralytic ileus. Intervention: Monitor patients for signs of urinary retention or reduced gastric motility when Fentanyl Citrate Injection is used concomitantly with anticholinergic Neuroleptics Clinical Impact: Elevated blood pressure, with and without pre-existing

hypertension, has been reported following adminis-tration of Fentanyl Citrate Injection combined with a neuroleptic see Warnings and Precautions (5.13)]. Intervention: ECG monitoring is indicated when a neuroleptic agent is used in conjunction with Fentanyl Citrate Injection as an anesthetic premedication, for the induction of anesthesia, or as an adjunct in the maintenance of general or regional anesthesia. Nitrous oxide

Clinical Impact: Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of Fentanyl Citrate Injection. Intervention: | Monitor patients for signs of cardiovascular depression that may be greater than otherwise expected.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with Fentany Citrate Injection in pregnant women are insufficient to inform a drugassociated risk for major birth defects and miscarriage. In anima eproduction studies, fentanyl administration to pregnant rats du organogenesis was embryocidal at doses within the range of the uman recommended dosing. No evidence of malformations was

The estimated 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. Ir the U.S. general population, the estimated background risk of major rth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

noted in animal studies completed to date [see Data].

Clinical Considerations etal/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. for symptoms of neonatal opioid withdrawal syndrome and manage

Labor or Delivery

There are insufficient data to support the use of fentanyl in labor or delivery. Therefore, such use is not recommended. Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone sion in the neonate. Fentanyl Citrate Injection is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic 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.

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 which pregnant rats 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

8.2 Lactation

Risk Summary Fentanyl is present in breast milk. One published lactation study

reports a relative infant dose of fentanyl of 0.38%. 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 materna administration of an opioid analgesic is stopped, or when breasteeding is stopped

8.3 Females and Males of Reproductive Potential

<u>Chronic use of opioids may cause reduced fertility in females and</u> males of reproductive potential. It is not known whether these

effects on fertility are reversible [see Adverse Reactions (6), Clinical harmacology (12.2), Nonclinical Toxicology (13.1)] 8.4 Pediatric Use The safety and efficacy of Fentanyl Citrate Injection in pediatric

patients under two years of age has not been established

Rare cases of unexplained clinically significant methemoglobinemia have been reported in premature neonates undergoing emergency anesthesia and surgery which included combined use of fentanyl ancuronium and atropine. A direct cause and effect relationsh 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 fentany). 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. rena 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 coadministered with other agents that depress respiration. Titrate the dosage of Fentanyl Citrate Injection slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory epression [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 ave decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. 8.6 Hepatic Impairment

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

DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl Citrate Injection contains fentanyl, a Schedule II controlled

Fentanyl Citrate Injection contains fentanyl, a substance with a high potential for abuse similar to other opioids including hydrocodor hydromorphone, 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)]

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects Drug addiction is a cluster of behavioral, cognitive, and physiological

phenomena that develop 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 record-keeping 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 ction with alcohol and other central nervous system depres Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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 and 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.

10 OVERDOSAGE

<u>Clinical Presentation</u> Acute overdose with Fentanyl Citrate Injection 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, 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)]

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 measured (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques. The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to opioid overdose. Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in Fentanyl Citrate Injection, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

DESCRIPTION

Fentanyl Citrate Injection is an opioid agonist, available as a stergenic solution containing fentanyl citrate equivalent to 50 mcg (0.05 mg) fentanyl base per mL for intravenous or intramuscular administration. Fentanyl citrate is chemically identified as N-(1-Phenethyl-4-piperidyl)propionanilide citrate (1:1) with the following structural formula

C22H28N2O • C6H8O7 Molecular Weight is 528.59

Each mL contains fentanyl citrate equivalent to 50 mcg (0.05 mg) fentanyl base in Water for Injection, Sodium hydroxide and/or hydroxide oric acid added, if needed, for pH adjustment. The pH range is 4.0 to 7.5. Contains no preservative

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl Citrate Injection is an opioid agonist, whose principal actions of therapeutic value are analgesia and sedation

12.2 Pharmacodynamics

Effects on the Central Nervous System entanyl produces respiratory depression by direct action on brain respiratory centers. The respiratory depression involves a redu

tion 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 pathognomic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to vpoxia in overdose situations Effects on the Gastrointestinal Tract and Other Smooth Muscle

Fentanyl causes a reduction in motility associated with an increas 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 esulting 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 pruritis, flushing, red eyes, weating, 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 glucago Chronic use of opioids may influence the hypothalamic-pituitary-

gonadal axis, leading to androgen deficiency that may manifest as ow libido impotence erectile dysfunction amenorrhea or infertilty. 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 compo-

nents of the immune system in in vitro and animal models clinical significance of these findings is unknown. Overall, the effects f 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

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 (2.1) [see Dosage and Administration

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 adminstration, 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)].

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 narcotic analgesics, the duration of the respiratory depre of fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respirator esponse to CO₂ stimulation following administration of fentanyl

- Diminished sensitivity to CO₂ stimulation may persist longer than depression of respiratory rate. (Altered sensitivity to CO stimulation has been demonstrated for up to four hours fol lowing a single-dose of 600 mcg [0.6 mg] [12 mL] fentanyl 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 is noted 5 to 15 minutes following injection [see Warnings and Precautions (5.2)].

Pharmacokinetics 5 4 1

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

Fentanyl plasma protein binding capacity increases 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

<u>Elimination</u> 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.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Mutagenesis
No formal studies to assess the mutagenic potential of fentanyl citrate have been conducted. Impairment of Fertility Decreased pregnancy rates occurred in a multigenerational study in

which pregnant rats were treated subcutaneously during the first 2 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 characterized the effect of fentanyl on male ertility have not been conducte 16 HOW SUPPLIED/STORAGE AND HANDLING

Fentanyl Citrate Injection is supplied as a sterile, clear, and color-

Fentanyl Citrate Injection, equivalent to 50 mcg (0.05 mg) fentanyl

base per mL, is a preservative-free solution, supplied as follows:

uct No.	NDC No.	Strength	Each
01	63323-806-01	50 mcg in 1 mL	63323-806-11
	25 vials per	(50 mcg per mL)	1 mL fill in a 2 mL
	carton	(0.05 mg per mL)	single-dose vial
02	63323-806-02	100 mcg in 2 mL	63323-806-12
	25 vials per	(50 mcg per mL)	2 mL single-dose
	carton	(0.05 mg per mL)	vial
05	63323-806-05	250 mcg in 5 mL	63323-806-13
	25 vials per	(50 mcg per mL)	5 mL single-dose
	carton	(0.05 mg per mL)	vial
_			

For Intravenous Use by Hospital Personnel Specifically Trained in the Use of Narcotic Analgesics:

roduct No.	NDC No.	Strength	Each			
06120	63323-806-20 25 vials per carton	1,000 mcg in 20 mL (50 mcg per mL) (0.05 mg per mL)	63323-806-14 20 mL single- dose vial			
06150	63323-806-50 1 vial per individual carton	2,500 mcg in 50 mL (50 mcg per mL) (0.05 mg per mL)	63323-806-50 50 mL single- dose vial			
OTEOT EDOM HOUT 1/2						

PROTECT FROM LIGHT. Keep covered in carton until time of use. Store at 20° to 25°C (68° to 77°F), excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Contains no preservative. DISCARD ANY UNUSED CONTENTS. This container closure is not made from natural rubber latex.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

o report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

17 PATIENT COUNSELING INFORMATION

Serotonin Syndrome Inform patients that Fentanyl Citrate Injection could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Instruct patients to inform their healthcare provider if they are taking, or plan to take sero-tonergic medications [see Warnings and Precautions (5.7), Drug Interactions (7)1

Advise patients of the potential for severe constipation, [see Clinical



For Product Inquiry:

www.fresenius-kabi.com/us 451610B Revised: March 2020