Piramal Critical Care

FentaneX

fentanyl

DOSAGE FORMS AND STRENGTHS

Fentanyl is a sterile, preservative-free, isotonic aqueous solution for intravenous use.
Each mL contains 50 mcg fentanyl (*as fentanyl citrate*).

For excipients, *see List of Excipients*.

CLINICAL INFORMATION

INDICATIONS

Fentanyl is indicated:
For use as an opioid analgesic supplement in general or regional anaesthesia.

For administration with a neuroleptic as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia.

For use as an anaesthetic agent with oxygen in selected high-risk patients undergoing major surgery.

DOSAGE AND ADMINISTRATION

Dosage

The dosage of Fentanyl should be individualized according to age, body weight, physical status, underlying pathological condition, use of other drugs, and type of surgery and anaesthesia.

The initial dose should be reduced in the elderly and in debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

To avoid bradycardia, it is recommended to administer a small intravenous dose of an anti-cholinergic just before induction.

Use as an analgesic supplement to general anaesthesia
Low dose: 2 µg/kg
Fentanyl in small doses is most useful for minor, surgery.

Moderate dose: 2-20 µg/kg
Where surgery becomes more complicated, a larger dose will be required. The duration of activity is dependent on dosage.

High dose: 20-50 µg/kg
During major surgical procedures, in which surgery is longer, and during which the stress response would be detrimental to the well-being of the patient, doses of 20-50 µg/kg of Fentanyl with nitrous oxide/oxygen have been shown to have an attenuating effect. When doses in this range have been used during surgery, post-operative ventilation and observation are essential in view of the possibility of extended post-operative respiratory depression.

Supplemental doses of 25-250 µg (0.5-5 mL) should be tailored to the needs of the patient and to the anticipated time until completion of the operation.

Use as an anaesthetic agent
When attenuation of the response to surgical stress is especially important, doses of 50-100 mcg/kg may be administered with oxygen and a muscle relaxant. This technique provides anaesthesia without necessitating

the use of additional anaesthetic agents. In certain cases, doses up to 150 mcg/kg may be required to produce this anaesthetic effect. Fentanyl has been used on this fashion for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated.

Special populations
Pediatrics
For induction and maintenance in children aged 2-12 years, a dose of 2-3 mcg/kg is recommended.

Elderly and debilitated patients
As with other opioids, the initial dose should be reduced in the elderly (>65 years of age) and in debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

Obese Patients
In obese patients, there is a risk of overdosing if the dose is calculated based on body weight. Obese patients should be dosed based on estimated lean body mass rather than on body weight only.

Renal Impairment
In patients with renal impairment reduced dosing of Fentanyl should be considered and these patients should be observed carefully for signs of fentanyl toxicity (see *Pharmacokinetic properties*).

CONTRAINDICATIONS
Known intolerance to any of its components or to other opioids.

WARNINGS AND PRECAUTIONS
Respiratory depression
As with all potent opioids, respiratory depression is dose related and can be reversed by a specific opioid antagonist, but additional doses may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist. Profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the post-operative period. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and opioid antagonist should be readily available. Hyperventilation during anaesthesia may alter the patient's responses to CO_2, thus affecting respiration postoperatively.

Risk from concomitant use of central nervous system (CNS) depressants, especially benzodiazepines or related drugs
Concomitant use of Fentanyl and CNS depressants especially benzodiazepines or related drugs in spontaneous
breathing patients, may increase the risk of profound sedation, respiratory depression, coma and death. If a decision is made to administer Fentanyl concomitantly with a CNS depressant, especially a benzodiazepine or a related drug, the lowest effective dose of both drugs should be administered, for the shortest period of concomitant use. Patients should be carefully monitored for signs and symptoms of respiratory depression and
profound sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see Interactions).

Muscle rigidity
Induction of muscle rigidity, which may also involve the thoracic muscles, can occur, but can be avoided by the following measures: slow IV injection (ordinarily sufficient for lower doses), premedication with benzodiazepines, and the use of muscle relaxants.

Non-epileptic (myo)clonic movements can occur.

Cardiac disease
Bradycardia, and possibly cardiac arrest, can occur if the patient has received an insufficient amount of

anticholinergic, or when Fentanyl is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.

Opioids may induce hypotension, especially in hypovolemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Special dosing conditions
The use of rapid bolus injections of opioids should be avoided in patients with compromised intracerebral compliance; in such patients, the transient decrease in the mean arterial pressure has occasionally been accompanied by a short-lasting reduction of the cerebral perfusion pressure.

Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses.

It is recommended to reduce the dosage in the elderly and in debilitated patients. Opioids should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism, or impaired hepatic or renal function. Such patients also require prolonged post-operative monitoring.

Interaction with neuroleptics
If Fentanyl is administered with a neuroleptic, the user should be familiar with the special properties of each drug, particularly the difference in duration of action. When such a combination is used, there is a higher incidence of hypotension. Neuroleptics can induce extrapyramidal symptoms that can be controlled with anti-Parkinson agents.

The initial dose of fentanyl should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental dose.
- Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of Fentanyl.
- Fentanyl should be used with caution in patients with chronic obstructive pulmonary disease, patients with decrease respiratory reserve, and others with potentially compromised respiration.
  In such patient, narcotics may additionally decrease respiratory drive and increase air way resistance.
- Fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drug.
- Pediatric use: The safety and efficacy of Fentanyl in children under two years of age has not been established.

Serotonin syndrome
Caution is advised when Fentanyl is co-administered with drugs that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norephinephrine Reuptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose.

Serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

If serotonin syndrome is suspected, rapid discontinuation of Fentanyl should be considered.

INTERACTIONS

Effect of other drugs on Fentanyl

Central Nervous System (CNS) depressants

Drugs such as barbiturates, benzodiazepines, or related drugs neuroleptics, general anaesthetics, and other, non-selective CNS depressants (e.g., alcohol) may potentiate the respiratory depression of opioids.

When patients have received such CNS depressant drugs, the dose of Fentanyl required may be less than usual. Concomitant use with Fentanyl in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death (see *Warnings and Precautions*). Likewise, following the administration of Fentanyl, the dose of other CNS-depressant drugs should be reduced.

Cytochrome P450 3A4 (CYP3A4) inhibitors

Fentanyl, a high clearance drug, is rapidly and extensively metabolized mainly by CYP3A4. When Fentanyl is used, the concomitant use of a CYP3A4 inhibitor may result in a decrease in fentanyl clearance. With single-dose Fentanyl administration, the period of risk for respiratory depression may be prolonged, which may require special patient care and longer observation. With multiple-dose Fentanyl administration, the risk of acute and/or delayed respiratory depression may be increased, and a dose reduction of Fentanyl may be required to avoid accumulation of fentanyl. Oral ritonavir (a potent CYP3A4 inhibitor) reduced the clearance of a single intravenous Fentanyl dose by two thirds, although peak plasma concentrations of fentanyl were not affected. However, itraconazole (another potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of a single intravenous Fentanyl dose. Co-administration of other potent or less potent CYP3A4 inhibitors, such as voriconazole or fluconazole, and Fentanyl may also result in an increased and/or prolonged exposure to fentanyl.

Monoamine Oxidase Inhibitors (MAOI)

It is usually recommended to discontinue MAOIs 2 weeks prior to any surgical or anaesthetic procedure. However, several reports describe the uneventful use of Fentanyl during surgical of anaesthetic procedures in patients on MAOIs.

Serotonergic drugs

Co-administration of Fentanyl with a serotonergic agent, such as a SSRI, or SNRI or MAOI, may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Effect of Fentanyl on other drugs

Following the administration of Fentanyl, the dose of other CNS-depressant drugs should be reduced. This is particularly important after surgery, because profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the postoperative period. Administration of a CNS depressant, such as a benzodiazepine or related drugs, during this period may disproportionally increase the risk for respiratory depression (see *Warnings and Precautions*).

The total plasma clearance and volume of distribution of etomidate is decreased by a factor of 2 to 3 without a change in half-life when administered with Fentanyl. Simultaneous administration of Fentanyl and intravenous midazolam results in an increase in the terminal plasma half-life and a reduction in the plasma clearance of midazolam. When these drugs are co-administered with Fentanyl their dose may need to be reduced.

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no adequate data from the use of Fentanyl in pregnant women. Fentanyl can cross the placenta in early pregnancy. Studies in animals have shown some reproductive toxicity (see *Non-Clinical Information*). The potential risk for humans is unknown. Fentanyl should not be used during pregnancy.

Analgesics of the morphine type may cause respiratory depression in the newborn infant. During 2-3 hours before expected partus these products should therefore only be used on strict indications and after weighing the mother's needs against the risks to the child.

Administration (intramuscular (IM) or IV) during childbirth (including cesarean section) is not recommended because Fentanyl crosses the placenta and may suppress spontaneous respiration in the newborn period. If Fentanyl is administered, assisted ventilation equipment must be immediately available for the mother and infant if required. An opioid antagonist for the child must always be available.

Breast-feeding
Fentanyl is excreted into human milk. Therefore, breast-feeding or use of expressed breast milk is not recommended for 24 hours following the administration of this drug. The risk/benefit of breastfeeding following fentanyl administration should be considered.

Fertility
There are no clinical data on the effects of fentanyl on male or female fertility. In animal studies, some tests on rats showed reduced female fertility at maternal toxic doses (see Non-Clinical Information).

Effects on driving ability and use machines
Patients should only drive or operate a machine if sufficient time has elapsed (at least 24 hours) after the administration of Fentanyl.

ADVERSE REACTIONS
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of fentanyl citrate based on the comprehensive assessment of the available adverse event information. A causal relationship with fentanyl citrate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data
The safety of Fentanyl was evaluated in 376 subjects who participated in 20 clinical trials evaluating Fentanyl used as an anaesthetic. These subjects took at least one dose of Fentanyl and provided safety data. Adverse reactions, as identified by the investigator, reported for ≥ 1% of Fentanyl treated subjects in these studies are shown in Table 1.

Table 1. Adverse Reactions Reported by ≥ 1% of Fentanyl treated Subjects in 20 Clinical Trials of Fentanyl

System/Organ Class Adverse Reaction	**FENTANYL(n=376)** **%**
Nervous System Disorders	
Sedation	5.3
Dizziness	3.7
Dyskinesia	3.2
Eye Disorders	
Visual disturbance	1.9
Cardiac Disorders	
Bradycardia	6.1
Tachycardia	4.0
Arrhythmia	2.9
Vascular Disorders	
Hypotension	8.8
Hypertension	8.8
Vein pain	2.9
Respiratory, Thoracic and Mediastinal Disorders	
Apnea	3.5
Bronchospasm	1.3
Laryngospasm	1.3
Gastrointestinal Disorders	

Nausea	26.1
Vomiting	18.6
Skin and Subcutaneous Tissue Disorders	
Dermatitis allergic	1.3
Musculoskeletal and Connective Tissue Disorders	
Muscle rigidity (which may also involve the thoracic muscles)	10.4
Injury, Poisoning and Procedural Complications	
Confusion postoperative	1.9
Anaesthetic complication neurological	1.1

Additional adverse reactions that occurred in < 1% of Fentanyl treated subjects in the 20 clinical trials are listed below in Table 2.

Table 2. Adverse Reactions Reported by < 1% of Fentanyl treated Subjects in 20 Clinical Trials of Fentanyl

System/Organ Class
Adverse Reaction
Psychiatric Disorders
Euphoric mood
Nervous System Disorders
Headache
Vascular Disorders
Blood pressure fluctuation
Phlebitis
Respiratory, Thoracic and Mediastinal Disorders
Hiccups
Hyperventilation
General Disorders and Administration Site Conditions
Chills
Hypothermia
Injury, Poisoning and Procedural Complications
Agitation postoperative
Procedural complication
Airway complication of anaesthesia

Post-marketing Data

Adverse reactions first identified during post-marketing experience with Fentanyl are included in Table 3. In each table, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1,000 and < 1/100
Rare	≥ 1/10,000 and < 1/1,000
Very rare	< 1/10,000, including isolated reports

In Table 3, adverse reactions are presented by frequency category based on spontaneous reporting rates, while in Table 4, the same adverse reactions are presented by frequency category based on incidence in clinical trials or epidemiology studies, when known. The frequency category "not known" is used for adverse reactions for which no valid estimate of the incidence rate can be derived from clinical trials.

Table 3. Adverse Reactions Identified during Post-Marketing Experience with Fentanyl by Frequency Category Estimated from Spontaneous Reporting Rates

Immune system disorders	
Very rare	Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Nervous system disorders	

Very rare Convulsions, Loss of consciousness, myoclonus

Cardiac disorders

Very rare Cardiac arrest (see *Warnings & Precautions*)

Respiratory, Thoracic and Mediastinal Disorders

Very rare Respiratory depression (see *Warnings & Precautions*)

Skin and subcutaneous Tissue Disorders

Very rare Pruritus

Table 4. Adverse Reactions Identified during Post-Marketing Experience with Fentanyl by Frequency Category Estimated from Clinical Trials or Epidemiologic Studies

Immune system disorders

Not known Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)

Nervous system disorders

Not known Convulsions, Loss of consciousness, myoclonus

Cardiac disorders

Not known Cardiac arrest (see *Warnings & Precautions*)

Respiratory, Thoracic and Mediastinal Disorders

Not known Respiratory depression (see Warnings & Precautions)

Skin and subcutaneous Tissue Disorders

Very rare Pruritus

When a neuroleptic is used with Fentanyl, the following adverse reactions may be observed: chills and/or shivering; restlessness, post-operative hallucinatory episodes; and extrapyramidal symptoms (see *Warnings and Precautions*).

Overdose

Symptoms and signs

An overdosage of Fentanyl manifests itself as an extension of its pharmacologic actions. Respiratory depression which can vary in severity from bradypnea to apnea may occur.

Treatment

In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific opioid antagonist, should be used as indicated to control respiratory depression. This does not preclude the use of more immediate respiratory countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.

If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration.

The patient should be carefully observed; body warmth and adequate fluid intake should be maintained. If hypotension is severe or if it persists, the possibility of hypovolemia should be considered, and if present, should be controlled with appropriate parental fluid administration.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: anaesthetics general, opioid anaesthetics. ATC Code N01AH01

Mechanism of action

Fentanyl is a potent, narcotic analgesic.

Pharmacodynamic effects

Fentanyl is an opioid analgesic, interacting predominantly with the μ-opioid receptor. Fentanyl can be used as an analgesic supplement to general anaesthesia or as the sole anaesthetic. Fentanyl preserves cardiac

stability and obtunds stress-related hormonal changes at higher doses. A dose of 100 mcg (2.0 mL) is approximately equivalent in analgesic activity to 10 mg of morphine. The onset of action is rapid. However, the maximum analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is approximately 30 minutes after a single I.V. dose of up to 100mcg. Depth of analgesia is dose-related and can be adjusted to the pain level of the surgical procedure.

Like other opioid analgesics, Fentanyl, depending upon the dose and speed of administration, can cause muscle rigidity, as well as euphoria, miosis and bradycardia.

Histamine assays and skin-wheal testing have indicated that clinically significant histamine release is rare with Fentanyl.

All actions of Fentanyl are reversed by a specific opioid antagonist.

Pharmacokinetic properties
Distribution
After intravenous injection, fentanyl plasma concentrations fall rapidly, with sequential distribution half-lives of about 1 minute and 18 minutes and a terminal elimination half-life of 475 minutes. Fentanyl has a Vc (volume of distribution of the central compartment) of 13 L, and a total Vdss (distribution volume at steady-state) of 339 L. The plasma-protein binding of Fentanyl is about 84%.

Metabolism
Fentanyl is rapidly metabolized, mainly in the liver by CYP3A4. The major metabolite is norfentanyl. Fentanyl clearance is 574 mL/min.

Excretion
Approximately 75% of the administered dose is excreted in the urine within 24 hours and only 10% of the dose eliminated in urine is present as unchanged drug.

Special Populations
Renal impairment
Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive Fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see *Dosage and Administration*).

Obese Patients
An increase in clearance of fentanyl is observed with increased body weight. In patients with a BMI>30, clearance of fentanyl increases by approximately 10% per 10 kg increase of the fat free mass (lean body mass).

NON-CLINICAL INFORMATION
Fentanyl has a broad safety-margin. In rats the ratio LD_{50}/ED_{50} for the lowest level of analgesia is 281.8, as compared with 69.5 and 4.8 for morphine and pethidine respectively.

Carcinogenicity and Mutagenicity
In vitro fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in in vivo rodent studies and bacterial assays. In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 mcg/kg/day in males or 100 mcg/kg/day in females, which were the maximum tolerated doses for males and females.

Reproductive Toxicology
Fertility

Some tests on female rats showed reduced fertility as well as embryo mortality. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. There was no evidence of teratogenic effects.

PHARMACEUTICAL INFORMATION

List of Excipients

Sodium chloride
Water for injection

Incompatibilities

The injectable solution must not be mixed with other products.
If desired, Fentanyl may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with plastic infusion sets. These should be used within 24 hours of preparation.

Shelf life

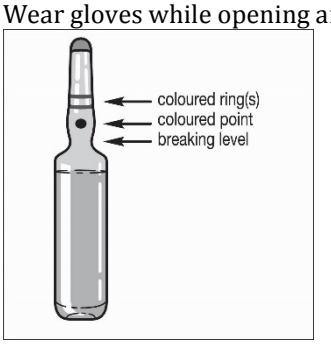
3 (three) years

Storage Conditions

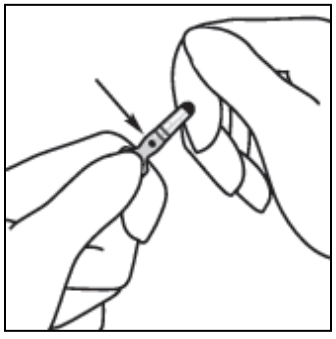
Protect from the light.
Store below 30°C.
Keep out of sight and reach of children.

Instructions for use/handling

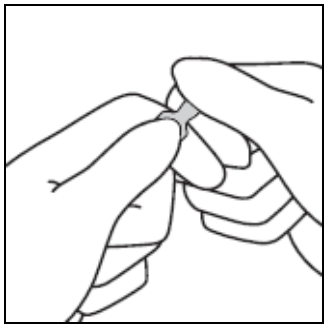
Wear gloves while opening ampoule.



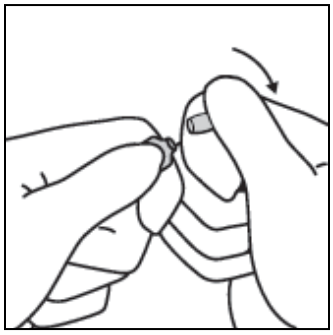
Maintain the ampule between thumb and index finger, leaving the tip of the ampule free.



With the other hand, hold the tip of ampoule putting the index finger against the neck of ampoule, and the thumb on the colored point, in parallel to the identification colored ring(s).



Keeping the thumb on the point, sharply break the tip of ampoule while holding firmly the other part of the ampoule in the hand.



Accidental dermal exposure should be treated by rinsing the affected area with water. Avoid use of soap, alcohol, and other cleaning materials that may cause chemical or physical abrasions to the skin.

HOW SUPPLIED
Fentanyl injection 50 mcg
Box 5 ampoules @ 2 ml
Reg. No.:

Fentanyl injection 50 mcg
Box 5 ampoules @ 10 ml
Reg. No.:

HARUS DENGAN RESEP DOKTER

Manufactured by DEMO S.A. Pharmaceutical Industry, Attiki, Greece
Imported and distributed by PT Kimia Farma Tbk, Jakarta, Indonesia for Piramal Critical Care Limited, UK
For adverse event and product quality complaint, please contact: pv.kf@kimiafarma.co.id; medical.information@piramal.com or call 1500 255 / 0018030160017

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