

Rx

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Fentanyl Citrate Injection IP

OPIFENT® 100/500

Each ml contains:

Fentanyl Citrate IP
Equivalent to Fentanyl 50 mcg
Water for injections IP q.s.

DESCRIPTION:

Fentanyl is an opioid analgesic. The chemical name of Fentanyl citrate is N-(phenylethyl-4-piperidyl)-N-phenylpropionamide citrate. The empirical formula is $C_{22}H_{28}N_2O_3$, and the molecular weight is 528.6 g/mol.

THERAPEUTIC INDICATIONS:

Fentanyl is an opioid analgesic used in:
- Low doses to provide analgesia during short surgical procedures.
- High doses as an analgesic/respiratory depressant in patients requiring assisted ventilation.
- Combination with a neuroleptic drug as part of the technique of neuroleptanalgesia.
- The treatment of severe pain, such as the pain of myocardial infarction.

PHARMACOLOGY AND METHOD OF ADMINISTRATION

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with fentanyl in order to minimise the risk of addiction and drug withdrawal syndrome (see section Special warnings and precautions for use).

Route of administration

Intravenous administration either as a bolus or by infusion. Intramuscular administration. Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway (see section Special warnings and precautions for use).

To avoid bradycardia, it is recommended to administer a small intravenous dose of an anti-cholinergic just before anaesthetic induction. It is recommended to wear gloves while opening the ampoule.

The injection should not be used if particles are present. Any unused portion should be discarded.

Posology

Fentanyl, by the intravenous route, can be administered to both adults and children. The dose of fentanyl should be individualised according to age, body weight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.

Adults

The usual dosage regimen in adults is as follows:

	Initial	Supplemental
Spontaneous Respiration	50-200 micrograms	50 micrograms
Assisted Ventilation	300-3500 micrograms	100-200 micrograms

Doses in excess of 200 micrograms are for use in anaesthesia only. As a premedicant, 1-2 ml fentanyl may be given intramuscularly 45 minutes before induction of anaesthesia.

After intravenous administration in unpremedicated adult patients, 2 ml fentanyl may be expected to provide sufficient analgesia for 10-20 minutes in surgical procedures involving low pain intensity. 10 ml fentanyl injected as a bolus gives analgesia lasting about one hour. The analgesia produced is sufficient for surgery involving moderately painful procedures. Giving a dose of 50 micrograms/kg fentanyl will provide intense analgesia for some four to six hours, for intensely stimulating surgery.

Fentanyl may also be given as an infusion. In ventilated patients, a loading dose of fentanyl may be given as a fast infusion of approximately 1 microgram/kg/min for the first 10 minutes followed by an infusion of approximately 0.1 micrograms/kg/min.

Alternatively the loading dose of fentanyl may be given as a bolus. Infusion rates should be titrated to individual patient response; lower infusion rates may be adequate. Unless it is planned to ventilate post-operatively, the infusion should be terminated at about 40 minutes before the end of surgery.

Lower infusion rates, e.g. 0.05-0.08 micrograms/kg/minute are necessary if spontaneous ventilation is to be maintained. Higher infusion rates (up to 3 micrograms/kg/minute) have been used in cardiac surgery.

Fentanyl is chemically incompatible with the induction agents pentobarbital sodium, thiopentone and methohexitone because of wide differences in pH.

Paediatric population

Children aged 12 to 17 years old: Follow adult dosage.

Children aged 2 to 11 years old: The usual dosage regimen in children is as follows:

	Age	Initial	Supplemental
Spontaneous Respiration	2-11 yrs	1-3 micrograms/kg	1-1.25 micrograms/kg
Assisted Ventilation	2-11 yrs	1-3 micrograms/kg	1-1.25 micrograms/kg

Use in children:

Analgesia during operation, enhancement of anaesthesia with spontaneous respiration. Techniques that involve analgesia in a spontaneous breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/analgesia technique with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support (see section Special warnings and precautions for use).

Use in 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 have dosage calculated according to their estimated lean body mass.

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.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients of this formulation or other opioids.
- Respiratory depression, obstructive airways disease.
- Concurrent administration with monoamine oxidase inhibitors or within 2 weeks of their discontinuation.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Warnings: Following intravenous administration of fentanyl, a transient fall in blood pressure may occur, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Tolerance and Opioid use disorder (abuse and dependence)

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. Repeated use of opioids may lead to Opioid use disorder (OUD). Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders). Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse. Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with fentanyl. Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months. The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women receive this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Respiratory Depression: As with all potent opioids, profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early postoperative period. Care should be taken after large doses or infusions of fentanyl to ensure that adequate spontaneous breathing has been established and maintained before discharging the patient from the recovery area. Significant respiratory depression will occur following the administration of fentanyl in doses in excess of 200 micrograms.

Resuscitation equipment and opioid antagonists should be readily available.

Hyperventilation during anaesthesia may alter the patient's response to CO₂, thus affecting respiration postoperatively.

Administration in labour may cause respiratory depression in the new-born infant.

Hyperalgesia: Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

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 antagonised by atropine.

Muscle rigidity: Muscular rigidity (morphine-like effect) may occur. Rigidity, which may also involve the thoracic muscles, can be avoided by the measures like: Slow IV injection (usually sufficient for lower doses); Premedication with benzodiazepines; Use of muscle relaxants. Non-epileptic (myo)clonic movements can occur.

Precautions: Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway.

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 transient reduction of the cerebral perfusion pressure.

It is recommended to reduce dosage in the elderly and debilitated patients. In uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism and hepatic or renal impairment the dosage should be titrated with care and prolonged post-operative monitoring is required.

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

Myasthenia gravis: In patients with myasthenia gravis, careful consideration should be applied in the use of certain anticholinergic agents and neuromuscular-blocking pharmaceutical agents prior to, and during, the administration of a general anaesthetic regimen which includes administering intravenous fentanyl.

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.

Bile duct: As with other opioids, due to the anticholinergic effects administration of fentanyl may lead to increases of bile duct pressure and in isolated cases spasms of the Sphincter of Oddi might be observed.

Intestinal motility: As with other opioids, fentanyl can have an inhibitory effect on intestinal motility. This should be considered in the pain management of intensive care patients with inflammatory or obstructive intestinal diseases.

Serotonin Syndrome: Caution is advised when fentanyl is coadministered with drugs that affect the serotonergic neurotransmitter systems (see section Interactions with other medicinal products). 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, diarrhoea). If serotonin syndrome is suspected, rapid discontinuation of fentanyl should be considered.

Paediatric population

Techniques that involve analgesia in a spontaneously breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation / analgesia technique, with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support.

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS:

Effect of other drugs on fentanyl

Sedative medicines such as benzodiazepines or related drugs

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited.

Other Central Nervous System (CNS) depressants

The use of other CNS depressants such as opioid premedication, barbiturates, neuroleptics, general anaesthetics, gabapentinoids (gabapentin and pregabalin) and other non-selective CNS depressants (e.g. alcohol) may enhance or prolong the respiratory depression of fentanyl. When patients have received other CNS-depressants, 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. The pharmacological effects of fentanyl citrate can be reversed by naloxone.

Antipsychotics - Droperidol: The concomitant use of droperidol can result in a higher incidence of hypotension.

Antihypertensive - Clonidine: Co-administration of clonidine may enhance fentanyl effects and especially prolong fentanyl-induced respiratory depression

Cytochrome P450 3A4 (CYP3A4) inhibitors

Fentanyl, a high clearance drug, is rapidly and extensively metabolised mainly by CYP3A4. When IV fentanyl is used, the concomitant use of a CYP3A4 inhibitor may result in a decrease in fentanyl clearance. With single-dose IV fentanyl administration, the period of risk for respiratory depression may be prolonged, which may require special patient care and longer observation. With multipledose fentanyl administration, the risk for 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 IV fentanyl dose by two thirds, although peak plasma concentrations of IV 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 dose of IV fentanyl. Co-administration of fluconazole or voriconazole (moderate CYP3A4 inhibitors) and fentanyl may result in an increased exposure and/or prolonged exposure to fentanyl.

Bradycardia and possibly cardiac arrest can occur when fentanyl is combined with non-vagolytic muscle relaxants (e.g. vecuronium).

Serotonergic Drugs

Co-administration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Reuptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition (see section Contraindications)

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, during this period may disproportionately increase the risk for respiratory depression (see above). Plasma concentrations of etomidate increased considerably (by a factor 2-3) when combined with fentanyl. 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.

FERTILITY, PREGNANCY AND LACTATION:

Fertility: There are no data on the effects of fentanyl on male or female fertility.

Pregnancy: Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding: Administration to nursing women is not recommended as fentanyl may be secreted in breast milk and may cause respiratory depression in the infant. Therefore breast-feeding or use of expressed breast milk is not recommended within 24 hours of treatment.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Where early discharge is envisaged, patients should be advised not to drive or to operate machinery for at least 24 hours following administration. This medicine can impair cognitive function and can affect a patient's ability to drive safely.

UNDESIRABLE EFFECTS:

Immune system disorder: Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)

Psychiatric Disorders: Agitation, Euphoric mood, Delirium drug dependence

Nervous system disorder: Muscle rigidity (which may also involve the thoracic muscles), Dyskinesia, Sedation, Dizziness, Headache, Convulsions, Loss of consciousness, Myoclonus.

Eye Disorders: Visual disturbance

Cardiac Disorders: Bradycardia, Tachycardia, Arrhythmia, Cardiac arrest

Vascular Disorders: Hypotension; Hypertension, Venous pain, Phlebitis, Blood pressure fluctuation

Respiratory, Thoracic and Mediastinal Disorders: Laryngospasm; Bronchospasm, Apnoea, Hyperventilation, Hiccups, Respiratory depression.

Gastrointestinal Disorders: Nausea, Vomiting, Dysphagia

Skin and Subcutaneous Tissue Disorders: Allergic dermatitis, Pruritus

General Disorders and Administration Site Conditions: Chills, Hypothermia, Drug withdrawal syndrome, Drug withdrawal syndrome

Injury, Poisoning and Procedural Complications: Postoperative confusion, Airway complication of anaesthesia

When a neuroleptic is used with fentanyl, the following adverse reactions may be observed:

Chills and/or shivering, restlessness, postoperative hallucinatory episodes and extrapyramidal symptoms

OVERDOSE:

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms and signs: The manifestations of fentanyl overdosage are generally an extension of its pharmacological action. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression which varies from bradypnoea to apnoea. Toxic leukoencephalopathy has been observed with fentanyl overdose.

Treatment: Hypoventilation or apnoea: O2 administration, assisted or controlled respiration.

Respiratory depression: Specific opioid antagonist. This does not preclude the use of immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.

Muscular rigidity: Intravenous neuromuscular blocking agent 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 hypovolaemia should be considered and, if present, it should be controlled with appropriate parenteral fluid administration.

PHARMACOLOGICAL PROPERTIES:

Pharmacotherapeutic group: Anaesthetic general, opioid anaesthetic.

ATC code: N01AH01.

Pharmacodynamic properties:

Fentanyl is a synthetic opiate with a clinical potency of 50 to 100 times that of morphine. Its onset of action is rapid and its duration of action is short. In man, a single IV dose of 0.5-1 mg/70 kg body weight immediately produces a pronounced state of surgical analgesia, respiratory depression, bradycardia and other typical morphine-like effects. The duration of action of the peak effects is about 30 minutes. All potent morphine-like drugs provide relief from pain, ventilatory depression, emesis, constipation, physical dependence, certain vagal effects and varying degrees of sedation. Fentanyl, however, differs from morphine not only by its short duration of action but also by its lack of emetic effect and minimal hypotensive activity.

Pharmacokinetic properties:

Some pharmacokinetic parameters for fentanyl are as follows:

Urinary excretion = 8%

Bound in plasma = 80%

Clearance (ml/min/kg) = 13±2

Volume of distribution (litres/kg) = 4.0±0.4

Estimates of terminal half-life range from 141 to 853 minutes.

Renal impairment: If patients with renal impairment receive fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section Posology and method of 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).

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Use finger protection when opening an ampoule.

The injection (both ampoules and vials) is for single patient use and should be used immediately after opening. The injection should not be used if particles are present. Any unused portion should be discarded.

The product can be used either undiluted or diluted. Dilution ranges tested with 0.9 % sodium chloride and 5 % glucose solutions are 1:1 and 1:25. Hence the maximal dilution must not exceed 1 part fentanyl with 25 parts 0.9 % sodium chloride or 5 % glucose solutions.

STORAGE: Store in cool and dry place below 25°C. Protect from light.

PRESENTATION:

OPIFENT 100:

Primary packing: 2 ml clear glass Ampoules.

Secondary packing: Such 5 ampoules are kept in transparent PVC tray and packed in monocardon along with package insert.

OPIFENT 500:

Primary packing: 10 ml clear glass Ampoules.

Secondary packing: Such 5 ampoules are kept in transparent PVC tray and packed in monocardon along with package insert.

Marketed By:



VARENYAM

Varenyam Healthcare Pvt. Ltd.

FF/SF, Sun Welkin Tower-H, Harni-Halol Road,

Vadodra-390022, Gujarat, India

Mfd. By:

Bharat Parenterals Limited

Survey No. 144-A, Jarod-Samlaya Road,

Vill.: Hariपुरa, Tal. Savli, Dist. Vadodra - 391520,

Gujarat, India.