

# Data Sheet

## FENTANYL INJECTION

*Fentanyl Citrate Injection 50 micrograms/mL*

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### Presentation

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FENTANYL injection contains fentanyl 50 micrograms/mL as the citrate. It is a clear, colourless solution and is available in 2 mL and 10 mL clear glass ampoules.

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### Uses

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#### **Actions**

Fentanyl is a potent narcotic analgesic with a rapid onset and short duration of action. The principal actions of therapeutic value are analgesia and sedation. At a dose of 100 micrograms (2 mL), the analgesic activity of fentanyl is approximately equivalent to 10 mg of morphine or 75 mg of pethidine. Fentanyl differs from morphine by its short duration of analgesic activity, lack of emetic activity, and minimal hypotensive activity.

The action of fentanyl is qualitatively similar to those of morphine and pethidine, i.e. analgesia, euphoria, miosis, bradycardia, respiratory depression, bronchoconstriction, muscle rigidity and suppression of cough reflexes. These effects can be reversed by specific narcotic antagonists, e.g. naloxone. As with morphine, fentanyl-induced bradycardia from vagal stimulation is blocked or reversed by atropine. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics may last longer than the analgesic effect. As the dose of the narcotic is increased, the decrease in pulmonary exchange becomes greater. Larger doses may produce apnoea. The behavioural effects in mice of fentanyl and morphine are similar, and with toxic doses death is due to respiratory depression. The respiratory depressant properties of fentanyl appear to be due to a central effect by decreasing the sensitivity of the respiratory centre to carbon dioxide. In an experiment in cats, no effect on neuromuscular transmission was observed in the presence of severe respiratory depression.

Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that histamine release rarely occurs with fentanyl. Experiments in dogs, have shown that intravenously administered fentanyl at doses 2-4 times the recommended human dose, had minimal effect on blood pressure and heart rate. Much higher doses of fentanyl citrate, ranging from 100-400 micrograms/kg, produce an immediate fall in blood pressure, followed by partial recovery, and a sustained hypotensive effect lasting up to 30 minutes.

#### **Pharmacokinetics**

The onset of action of fentanyl is almost immediate when the medicine is given intravenously. However, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of analgesic effect is 30 to 60

minutes after a single I.V. dose of up to 100 micrograms. Following intramuscular administration, the onset of action is from 7 to 8 minutes and the duration of action is 1 to 2 hours.

As with longer acting narcotic analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO<sub>2</sub> stimulation following administration of fentanyl to man:

1. DIMINISHED SENSITIVITY TO CO<sub>2</sub> STIMULATION MAY PERSIST LONGER THAN DEPRESSION OF RESPIRATORY RATE.

Fentanyl frequently slows the respiratory rate, but this effect is seldom noted for longer than 30 minutes regardless of the dose administered.

2. Altered sensitivity to CO<sub>2</sub> stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 micrograms (12 mL) fentanyl to healthy volunteers.
3. Duration and degree of respiratory depression is dose-related.
4. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection.

(See also **Warnings and Precautions** concerning respiratory depression.)

Fentanyl produces a minimum of cortical depression, and it is suggested that it exerts its action by filling receptor sites located in the thalamus, mid-brain, and spinal cord. A specific narcotic antagonist, e.g. naloxone, produces reversal of respiratory, cardiovascular, miotic, and motor incoordination effects, as well as analgesia, euphoria, and sedation. Rigidity of the diaphragm and intercostal muscles can be eliminated by succinylcholine. Cholinergic effects, e.g. bradycardia, are reversed by atropine.

Fentanyl is metabolised primarily in the liver. In humans, *in vitro* experiments have demonstrated that fentanyl is metabolised mainly by cytochrome P450 3A4 (CYP 3A4) to norfentanyl *via* oxidative N-dealkylation.

### **Indications**

FENTANYL is indicated for:

- analgesic action of short duration during anaesthetic periods, premedication, induction and maintenance, and in the immediate post-operative period (recovery room) as the need arises;
- use as a narcotic analgesic supplement in general and regional anaesthesia;
- administration with a neuroleptic such as droperidol injection as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia.

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## **Dosage and Administration**

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Dosage should be individualised. Some of the factors to be considered in determining the dose are: age, body weight, physical status, underlying pathological condition, use of other medicines, type of anaesthesia to be used, and the surgical procedure involved.

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.

Vital signs should be monitored routinely.

### ***Usual Dosage in Adult***

1. **Premedication** (To be appropriately modified in the elderly, debilitated and those who have received other depressant medicines)

50 to 100 micrograms (1 to 2 mL) may be administered intramuscularly 30 to 60 minutes prior to surgery.

2. **Adjunct to general anaesthesia**

**Induction**- 50 to 100 micrograms (1 to 2 mL) may be administered initially intravenously and may be repeated at 2 to 3 minute intervals until the desired effect is achieved. A reduced dose as low as 25 to 50 micrograms (0.5 to 1 mL) is recommended in elderly and poor-risk patients.

**Maintenance** - 25 to 50 micrograms (0.5 to 1 mL) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

3. **Adjunct to regional anaesthesia**

50 to 100 micrograms (1 to 2 mL) may be administered intramuscularly or slowly intravenously when additional analgesia is required.

4. **Post-operatively** - (Recovery room)

50 to 100 micrograms (1 to 2 mL) may be administered intramuscularly for the control of pain, tachypnoea, and emergence delirium. The dose may be repeated in one or two hours as needed.

### ***Usual Dosage in Children***

For induction and maintenance in children 2-12 years of age, a reduced dose as low as 20 to 30 micrograms (0.4 to 0.6 mL) per 10 kg is recommended.

(See **Warnings and Precautions** for use of FENTANYL with other CNS depressants and in patients with altered response.)

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## **Contraindications**

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FENTANYL is contraindicated in patients with known intolerance to fentanyl, any of the components of FENTANYL or other morphinomimetics.

FENTANYL should not be administered to children two years of age or younger, because safe conditions for use have not been established. (See **Warnings and Precautions - Use in children** ) FENTANYL should not be administered to patients suffering from bronchial asthma. As for any narcotic analgesic, it should not be used in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may

have a head injury or brain tumour. (See **Warnings and Precautions** ). Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics.

There is no evidence that fentanyl is potentiated by MAO inhibitors, but since such potentiation is found with other narcotic analgesics, the use of FENTANYL in patients who have received MAO inhibitors within 14 days is not recommended. (See **Interactions** ).

FENTANYL may cause thoracic muscle rigidity upon intravenous administration. Therefore, the need for reversal with muscle relaxants contraindicates its use in patients with a history of myasthenia gravis.

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## Warnings and Precautions

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### ***Drug Dependence***

FENTANYL can produce drug dependence of the morphine type and therefore has the potential for being abused. **Fentanyl may be habit forming.**

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

### ***Hypoventilation (Respiratory Depression)***

Profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the post-operative period. Hyperventilation during anaesthesia may alter the patient's responses to CO<sub>2</sub>, thus affecting respiration post-operatively. Therefore, patients should remain under appropriate surveillance.

FENTANYL should be used with caution in patients with severe impairment of pulmonary function because of the possibility of respiratory depression, e.g. patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, or any patient with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anaesthesia, this can be managed by assisted or controlled respiration.

Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anaesthesia may be longer than the duration of narcotic antagonist action. Consult individual prescribing information (naloxone) before employing narcotic antagonists. See also discussion of narcotic antagonists in **Overdosage.**)

**Resuscitative equipment and a narcotic antagonist should be readily available to manage apnoea.**

### ***Muscle Rigidity***

FENTANYL may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection and its incidence can be reduced by a slow intravenous injection (ordinarily sufficient for lower doses) premedication with benzodiazapines and the use of muscle relaxants.

Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

Non-epileptic (myo)clonic movements can occur.

### ***Head Injuries and Increased Intracranial Pressure***

FENTANYL should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumour. In addition, FENTANYL fentanyl may obscure the clinical course of patients with a head injury.

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.

### ***Cardiac Effects***

FENTANYL may produce bradycardia and possibly asystole if the patient has received an insufficient amount of anticholinergic, or when FENTANYL is combined with non-vagolytic muscle relaxants. Bradycardia may be treated with atropine. However, FENTANYL should be used with caution in patients with cardiac bradyarrhythmias.

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

### ***Others***

As has been observed with all narcotic analgesics, episodes suggestive of sphincter of Oddi spasm may occur with FENTANYL.

Vital signs should be monitored carefully.

### ***Use in the Elderly or Debilitated Patients***

It is recommended to reduce the dosage of FENTANYL 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, impaired hepatic or renal function. Such patients also require prolonged post-operative monitoring.

### ***Use in Children***

The safety of FENTANYL in children younger than two years of age has not been established.

### ***Pregnancy and Lactation***

#### **Use in Pregnancy**

Category C.

There are no adequate data from the use of FENTANYL in pregnant women. Studies in animals have shown some reproductive toxicity. The potential risk for humans is unknown.

*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. There are no long-term animal studies to investigate the tumor-forming potential of fentanyl.

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.

Administration (I.M. or I.V.) during childbirth (including caesarian section) is not recommended because fentanyl crosses the placenta and because the foetal respiratory centre is particularly sensitive to opiates. If fentanyl is nevertheless administered, an antidote for the child should always be at hand.

### **Use in Lactation**

Fentanyl is excreted into human milk. Therefore, breastfeeding is not recommended for 24 hours following the administration of this medicine.

The risk/benefit of breast-feeding following FENTANYL administration should be considered.

### ***Effects on the Ability to Drive and Use Machines***

Patients should only drive or operate a machine if sufficient time has elapsed after the administration of FENTANYL.

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## **Adverse Effects**

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As with other narcotic analgesics, the most common serious adverse reactions reported to occur with FENTANYL are respiratory depression, apnoea, muscular rigidity (which may also involve the thoracic muscles), myoclonic movements, and bradycardia.

If these remain untreated, respiratory arrest, circulatory depression, or cardiac arrest could occur.

Respiratory depression is more likely to occur with intravenous administration if a dose is given too rapidly and it rarely occurs with intramuscular administration. If respiratory depression occurs during anaesthesia, assisted or controlled respiration will provide adequate ventilation without reversing analgesia.

Respiratory depression can be immediately reversed by narcotic antagonists (naloxone) which, it should be noted, will also reverse analgesia.

Muscular rigidity is a common side effect and in some instances may be associated with reduced pulmonary compliance and/or apnoea, laryngospasm and bronchospasm. Prompt reversal of this effect can be achieved with the intravenous administration of an appropriate single dose of a muscle relaxant such as succinylcholine. Assisted or controlled respiration is required to provide ventilation after the use of muscle relaxants. Bradycardia and other cholinergic effects may occur, and can be controlled with an

appropriate dose of atropine. The inclusion of atropine or other anticholinergic agents in the preanaesthetic regimen tends to reduce the occurrence of such effects.

Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, diaphoresis, itching and euphoria.

When a neuroleptic such as droperidol is used with FENTANYL, the following adverse reactions can occur: chills and/or shivering, restlessness, and post-operative hallucinatory episodes sometimes associated with transient periods of mental depression, and extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours post-operatively. Extrapyramidal symptoms can usually be controlled with anti-Parkinson agents. Post-operative drowsiness is also frequently reported following the use of droperidol.

Elevated blood pressure with and without pre-existing hypertension, has been reported following administration of FENTANYL combined with droperidol. This might be due to unexplained alterations in sympathetic activity following large doses. However, it is also frequently attributed to anaesthetic and surgical stimulation during light anaesthesia.

Allergic reactions (such as anaphylaxis, bronchospasm, pruritis, urticaria) and asystole have been reported. Since several medicines were co-administered during anaesthesia, it is uncertain whether there is a causal relationship to FENTANYL.

Secondary rebound respiratory depression after the operation has been observed in rare instances.

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## Interactions

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Medicines, such as, CNS depressants, barbiturates, benzodiazepines, neuroleptics, narcotics, alcohol and general anaesthetics, will have additive or potentiating effects with FENTANYL.

When patients have received such medicines, the dose of FENTANYL required will be less than usual. Likewise, following the administration of FENTANYL the dose of other CNS depressant medicines should be reduced. Post-operative narcotics including FENTANYL and other depressants should be given initially in reduced doses, as low as 1/4 to 1/3 of those usually recommended. As with other narcotics, the respiratory depressant effect of FENTANYL persists longer than the measured analgesic effect. The total dose of all narcotic analgesics should be considered before ordering narcotic analgesics during recovery from anaesthesia.

Certain forms of conduction anaesthesia, such as spinal anaesthesia and some peridural anaesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see **Actions**) FENTANYL can also alter respiration. Therefore, when FENTANYL is used to supplement these forms of anaesthesia, the anaesthetist should be familiar with the special properties of each medicine (particularly with the widely differing durations of actions), the physiological alterations involved and be prepared to manage them in patients selected for these forms of anaesthesia.

When FENTANYL is used with a neuroleptic such as droperidol, blood pressure may be altered and hypotension can occur. If this occurs, the possibility of hypovolaemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient improves venous return to the heart and should be considered when operative conditions permit. Care should be exercised in moving and positioning patients because of

the possibility of orthostatic hypotension. If volume expansion with fluids together with other countermeasures do not correct hypotension, the administration of pressor agents other than adrenaline should be considered. Because of the alpha-adrenergic blocking action of droperidol, adrenaline may paradoxically decrease the blood pressure in patients treated with droperidol. Pulmonary arterial pressure may also be decreased. This should be considered when interpreting pulmonary arterial pressure measurements as it might determine the final management of the patient.

When droperidol is used with FENTANYL and the EEG is used for post-operative monitoring, it may be found that the EEG pattern returns to normal slowly.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of FENTANYL in patients who have received MAO inhibitors within 14 days is not recommended.

Fentanyl is metabolised mainly *via* the human cytochrome P450 3A4 enzyme. It is a high clearance medicine which is rapidly and extensively metabolised. Oral administration of itraconazole (a potent inhibitor of CYP 3A4) at 200 mg/day given orally for 4 days did not have a statistically significant effect on the pharmacokinetics of IV fentanyl.

Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of IV fentanyl by two thirds. However, after a single dose of IV fentanyl, the peak plasma concentrations were not affected. When fentanyl is used in a single dose, the concomitant use of potent CYP3A4 inhibitors, such as ritonavir, requires special patient care and observation. When fentanyl is given continuously with these medicines, a reduction in the dose of fentanyl may be required. This will avoid the accumulation of fentanyl and hence reduces the risk of prolonged or delayed respiratory depression.

There are no data on the *in vivo* interactions between fentanyl and other medicines inhibiting CYP 3A4 (eg ketoconazole, erythromycin, diltiazem and cimetidine).

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## Overdosage

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### ***Symptoms***

The oral LD<sub>50</sub> for FENTANYL in rats is 18.0 mg/kg. The intravenous LD<sub>50</sub> is 2.3 mg/kg, and the intramuscular LD<sub>50</sub> is 1.0 mg/kg in rats. The toxic dose in man is unknown.

The manifestations of FENTANYL overdosage are an extension of its pharmacological actions. In sufficient overdosage, fentanyl would produce narcosis, which may be preceded by marked skeletal muscle rigidity. Cardio-respiratory depression accompanied by cyanosis occurs, followed by a fall in body temperature, circulatory collapse, coma and death.

### ***Treatment***

In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained. An oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration.

A specific narcotic antagonist, such as naloxone, should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdose of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use. The patient should be carefully observed for 24 hours. Body warmth and adequate fluid intake should be maintained. If hypotension occurs, and is severe or persists, the possibility of hypovolaemia should be considered and managed with appropriate parenteral fluid therapy.

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## **Pharmaceutical Precautions**

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### ***Shelf Life***

3 years when stored below 30°C.

### ***Special Precautions for Storage***

Protect from light.

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## **Medicine Classification**

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Controlled Drug B3

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## **Package Quantities**

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100 micrograms/2 mL of fentanyl, in cartons of 10 ampoules

500 micrograms/10 mL of fentanyl, in cartons of 10 ampoules

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## **Further Information**

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FENTANYL injection contains sodium chloride and water for injections.

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.

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## **Name and Address**

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## **Date of Preparation**

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30 August 2009