

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fentanyl 50 micrograms/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution for injection contains 78.5 micrograms fentanyl citrate equivalent to 50 micrograms fentanyl.

- 2 ml ampoule contains fentanyl citrate equivalent to 100 micrograms fentanyl.
- 10 ml ampoule contains fentanyl citrate equivalent to 500 micrograms fentanyl.

Excipient(s) with known effect:

Sodium 3.5 mg/ml.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection

Clear, colourless solution

The solution has a pH in between the range of 4.0 – 6.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fentanyl is an opioid analgesic used for adults and children:

- In low doses to provide analgesia during short surgical procedures.
- In high doses as an analgesic/respiratory depressant in patients requiring assisted ventilation.
- In the treatment of severe pain.

4.2 Posology and method of administration

Fentanyl Injection must only be given where the airway can be controlled and only by professionals who can control the airways (see section 4.4).

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

Posology

Use as an analgesic

Adults

The usual dosage regime is as follows:

	Initial	Supplemental
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Spontaneous respiration	50-200 micrograms	50 micrograms
Assisted ventilation	300-3500 Micrograms	100-200 micrograms

Fentanyl Injection 50 micrograms/ml may also be given as an intravenous infusion. In ventilated patients, a loading dose of Fentanyl Injection 50 micrograms/ml may be given as a fast infusion of approximately 1 mcg/kg/min for the first 10 minutes followed by an infusion of approximately 0.1 mcg/kg/min. Alternatively the loading dose of Fentanyl Injection 50 micrograms/ml 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 mcg/kg/minute are necessary if spontaneous ventilation is to be maintained. Higher infusion rates (up to 3 mcg/kg/minute) have been used in cardiac surgery.

Short surgical procedures

Following intravenous administration in unpremedicated adult patients, 2 ml (100 mcg) of Fentanyl Injection may be expected to provide sufficient analgesia for 10 - 20 minutes in surgical procedures with low pain intensity.

Moderate / Prolonged surgical procedure

10 ml (500 mcg) of Fentanyl Injection as a bolus gives an analgesia effect lasting about one hour. The analgesia produced is sufficient for surgery involving moderately painful procedures. Giving a dose of 50micrograms/kg Fentanyl Injection will provide intense analgesia for some four to six hours for intensely stimulating surgery.

Doses in excess of 200 micrograms are for use in anaesthesia only.

Use in elderly and debilitated patients: It is recommended to reduce the dosage in the elderly and debilitated patients. The effect of 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 ideal body mass.

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 mcg/kg	1-1.25 mcg/kg

Assisted Ventilation	2-11 years	1-3 mcg/kg	1-1.25 mcg/kg
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Children under 2 years old:

The safety and efficacy of fentanyl Injection in children under 2 years of age has not been established.

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 4.4).

It is important when estimating the required dose to assess the likely degree of surgical stimulation, the effect of premedicant drugs, and the duration of the procedure.

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 section 5.2 Pharmacokinetic properties).

Method of administration

Intravenous administration, either as a bolus or by infusion, can be administered to both adults and children.

4.3 Contraindications

- Hypersensitivity to the Fentanyl citrate or to any of the excipients listed in section 6.1.
- Respiratory depression without mechanical ventilation
- Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of their discontinuation.
- Known intolerance to fentanyl citrate or other morphinomimetics.

4.4 Special warnings and precautions for use

Fentanyl must only be given where the airway can be controlled and only by professionals who can control the airways.

Warnings:

Tolerance and dependence may occur. 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 disorder (abuse and dependence)

Tolerance, physical dependence, and psychological dependence may develop

upon repeated administration of opioids.

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).

Withdrawal syndrome

Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy, which may manifest by the occurrence of the following side effects: nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating.

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 mcg. This, and the other pharmacological effects of fentanyl, can be reversed by specific narcotic antagonists (e.g. naloxone). Additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.

Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patients response to CO₂, thus affecting respiration postoperatively.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of fentanyl and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe fentanyl concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Cardiac disease

Bradycardia and possibly asystole can occur if the patient has received an insufficient amount of anticholinergic, or when fentanyl is combined with non-vagolytic muscle relaxant. 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 following measures:

- slow I.V. injection (usually sufficient for lower doses)
- premedication with benzodiazepines
- use of muscle relaxants.

Non-epileptic (myo)clonic movement can occur

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 wise to reduce dosage in the elderly and debilitated patients.

In uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism and liver or renal impairment the dosage should be titrated with care and prolonged post-operative monitoring may be 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.

Precautions:

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

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.

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 Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake 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, diarrhoea).

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

Paediatric population

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.

Fentanyl Injection contains 3.5 mg sodium per ml of solution, equivalent to 0.18% of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs on fentanyl

Other Central Nervous System (CNS) depressants

The use of opioid premedication, barbiturates, benzodiazepines, neuroleptics, halogenic gases, gabapentinoids (gabapentin and pregabalin), and other non-selective CNS depressants (e.g. alcohol) may enhance or prolong the respiratory depression of fentanyl.

When the patients have received CNS-depressants, the dose of fentanyl required will be less than usual.

Concomitant use with Fentanyl in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death.

Cytochrome P450 3A4 (CYP3A4) inhibitors

Fentanyl, a high clearance drug, is rapidly and extensively metabolised mainly by CYP3A4.

Itraconazole (a potent CYP3A4 inhibitor) at 200mg/day given orally for 4 days had no 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, peak plasma concentrations after a single dose of IV fentanyl 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.

Co-administration of fluconazole or voriconazole (moderate CYP3A4 inhibitors) and fentanyl may result in an increased exposure to fentanyl.

With continuous treatment of fentanyl and concomitant administration of CYP3A4 inhibitors, a dose reduction of fentanyl may be required to avoid accumulation, which may increase the risk of prolonged or delayed respiratory depression.

Bradycardia and possibly cardiac arrest can occur when fentanyl is combined with non-vagolytic muscle relaxants.

The concomitant use of droperidol can result in a higher incidence of hypotension.

Serotonergic Drugs

Co-administration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (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, during this period may disproportionately increase the risk for respiratory depression.

Plasma concentration of etomidate increased considerably (by a factor of 2 to 3) when combined with fentanyl

The total plasma clearance and volume of distribution of etomidate is decreased by a factor 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.

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 (see section 4.4).

4.6 Fertility, pregnancy and lactation

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 Section 5.3, Preclinical safety data). The potential risk for humans is unknown.

Administration during childbirth (including Caesarean section) is not

recommended because fentanyl crosses the placenta and the foetal respiratory centre is particularly sensitive to opioids. If fentanyl is nevertheless administered, assisted ventilation equipment must be immediately available for the mother and infant if required. An antidote for the child should always be at hand.

Breast-feeding

Fentanyl is excreted into human milk. It is therefore recommended that breast feeding is not initiated within 24 hours of treatment. The risk/benefit of breast feeding following fentanyl administration should be considered.

Fertility

There are no human data on fertility available. In animal studies, male fertility was impaired (see section 5.3 Preclinical safety data).

4.7 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 24 hours following administration.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

4.8 Undesirable effects

The safety of fentanyl IV was evaluated in 376 subjects who participated in 20 clinical trials evaluating fentanyl IV as an anaesthetic. These subjects took at least 1 dose of fentanyl IV and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported ($\geq 5\%$ incidence) Adverse Drug Reactions (ADRs) were (with % incidence): nausea (26.1); vomiting (18.6); muscle rigidity (10.4); hypotension (8.8); hypertension (8.8); bradycardia (6.1) and sedation (5.3).

Including the above-mentioned ADRs, Table 1 displays ADRs that have been reported with the use of fentanyl IV from either clinical trials or postmarketing experience.

The displayed frequency categories use the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); and not known (cannot be estimated from the available clinical trial data).

Table 1: Adverse Drug Reactions

System Organ Class	Adverse Drug Reactions			
	Frequency Category			
	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not Known
Immune System Disorders				Hypersensitivity (such as anaphylactic shock,
				anaphylactic reaction, urticaria)
Psychiatric disorders		Agitation	Euphoric mood	Delirium
Nervous System Disorders	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		Pruritis
General Disorders and Administration Site Conditions			Chills; Hypothermia	Drug withdrawal syndrome (see section 4.4)
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 (see Section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via National Regulatory Agents

4.9 Overdose

Symptoms and signs:

The manifestations of fentanyl overdose are generally an extension of its pharmacological action. Depending on the individual sensitivity, the clinical picture is determined by the degree of respiratory depression, which varies from bradypnoea to apnoea, cases of toxic leukoencephalopathy have been reported with fentanyl overdose.

Treatment:

Hypoventilation or apnoea:	O ₂ administration, assisted or controlled respiration.
Respiratory depression:	Specific narcotic antagonist (e.g. naloxone). 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetic general, opioid anaesthetic.

ATC code: N01AH01

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 anaesthesia, respiratory depression, bradycardia and other typical morphine-like effects. The duration of action of the peak effects about 30 minutes. All potent morphine-like drugs produce 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 in animals.

5.2 Pharmacokinetic properties

Fentanyl is a synthetic opioid with μ -agonist pharmacologic effects.

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 V_c (volume of distribution of the central compartment) of 13 L, and a total V_{dss} (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.

Elimination

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

Pediatrics

The plasma protein binding of fentanyl in newborns is approximately 62% which is lower than in adults. The clearance and the volume of distribution are higher in infants and children. This may result in an increased dose requirement for fentanyl.

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 section 4.2 Posology and method of administration).

Adult patients with burns

An increase in clearance up to 44% together with a larger volume of distribution results in lower fentanyl plasma concentrations. This may require an increased dose of fentanyl.

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).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and

carcinogenicity.

Embryo-foetal developmental toxicity studies conducted in rats and rabbits revealed no compound-induced malformations or developmental variations when administered during the period of organogenesis.

In a fertility and early embryonic development study in rats, a male-mediated effect was observed at high doses (300 mcg/kg/day, s.c.) and is considered secondary to the sedative effects of fentanyl in animal studies.

In studies on pre and postnatal development in rats the survival rate of offspring was significantly reduced at doses causing severe maternal toxicity. Further findings at maternally toxic doses in F1 pups were delayed physical development, sensory functions, reflexes and behaviour. These effects could either be indirect effects due to altered maternal care and/or decreased lactation rate or a direct effect of fentanyl on the pups.

Carcinogenicity studies (26-week dermal alternative bioassay in Tg.AC transgenic mice; two-year subcutaneous carcinogenicity study in rats) with fentanyl did not reveal any findings indicative of oncogenic potential. Evaluation of brain slides from the carcinogenicity study in rats revealed brain lesions in animals administered high doses of fentanyl citrate. The relevance of these findings to humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride,
Sodium Hydroxide (for pH-adjustment)
Water for Injections

6.2 Incompatibilities

The product is chemically incompatible with the induction agents thiopentone and methohexitone because of the wide differences in pH.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Protect from light.
Keep container in the outer carton.
Do not store above 25°C.

6.5 Nature and contents of container

2 ml or 10 ml clear glass ampoules, glass type I borosilicate glass, packed in cardboard cartons and contain 10 x 2 ml or 10 x 10 ml ampoules.

Not all pack sizes maybe marketed.

6.6 Special precautions for disposal and other handling

The injection solution should not be used if it contains particles.
If only part used, discard the remaining solution.

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals Ltd
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8 MARKETING AUTHORISATION NUMBER(S)

CTD 13931

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 May 1997
Date of renewal: 02 May 2002

10 DATE OF REVISION OF THE TEXT

22/10/2024