

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Biomed Fentanyl

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 microgram per mL

Each 100 mL bag contains fentanyl citrate equivalent to 1000 microgram fentanyl base

Each 10 mL syringe contains fentanyl citrate equivalent to 100 microgram fentanyl base

20 microgram per mL

Each 100 mL bag contains fentanyl citrate equivalent to 2000 microgram fentanyl base

Each 50 mL syringe contains fentanyl citrate equivalent to 1000 microgram fentanyl base

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

A clear, colourless isotonic solution for injection or infusion.

It contains no preservative. It is formulated with a pH of 4.0 – 7.5.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Fentanyl is indicated for:

- analgesic action of short duration during pre-medication, induction and maintenance of anaesthesia, and in the immediate post-operative period;
- use as an opioid analgesic supplement in general and regional anaesthesia;
- combination with a neuroleptic as an anaesthetic pre-medication for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia.

4.2. Dose and method of administration

Dosage should be individualised according to age, body weight, physical status, underlying pathological condition, use of other medicines, type of anaesthesia to be used, and the surgical procedure involved (see also Section 4.4). Vital signs should be monitored routinely. Fentanyl contains no antimicrobial agent. It should be used only once and any remaining contents discarded.

Usual Dosage in Adults

Premedication

(To be appropriately modified in the elderly, debilitated and those who receive other depressant medicines): 50 to 100 micrograms may be administered intramuscularly 30 to 60 minutes prior to surgery.

Adjunct to general anaesthesia

Induction: 50 to 100 micrograms intravenously initially, repeat at two to three minute intervals until desired effect is achieved. A reduced dose of 25 to 50 micrograms is recommended in elderly and poor risk patients.

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Maintenance

25 to 50 micrograms may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

Adjunct to regional anaesthesia

50 to 100 micrograms may be administered intramuscularly or slowly intravenously when additional analgesia is required.

Post-operatively (recovery room)

50 to 100 micrograms 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 of 20 to 30 micrograms per 10 kg is recommended.

Impaired Renal Function

Fentanyl should be used with caution.

Impaired Hepatic Function

Fentanyl should be used with caution.

4.3. Contraindications

- Fentanyl is contraindicated in patients with known hypersensitivity or intolerance to fentanyl, other opioid analgesics, or to any of the excipients.
- Fentanyl should not be administered to patients suffering from bronchial asthma (see Section 4.4).
- As for any opioid analgesic, fentanyl 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 Section 4.4). Fentanyl may obscure the clinical course of patients with head injury.
- Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. There is no evidence that fentanyl is potentiated by MAO inhibitors, but since such potentiation is found with other opioid analgesics, the use of Fentanyl in patients who have received MAO inhibitors within 14 days is not recommended (See Section 4.5).
- 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.
- Fentanyl should not be administered to children two years of age or younger, because safe conditions for use have not been established. (See Section 4.4).
- Use in patients after operative interventions in the biliary tract.

4.4. Special warnings and precautions for use

Adequate facilities should be available for post-operative monitoring and ventilation. Resuscitative equipment, oxygen and an opioid antagonist should be readily available to manage apnoea. Fentanyl should only be used by experienced doctors and in patients who are under constant supervision.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of fentanyl with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine

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sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see Section 4.5).

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when fentanyl is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see Section 4.5).

Concomitant Neuroleptics

If fentanyl is used with neuroleptics, the user should be familiar with the special properties of each medicine, particularly with regard to durations of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available.

Total Opioid Use

As with other potent opioids, the respiratory depressant effect of fentanyl persists longer than the measured analgesic effect. The total dose of all opioid analgesics should be considered before additional opioid analgesics are given during recovery from anaesthesia. It is recommended that post-operative opioids, when required, should be used initially in reduced doses, as low as $\frac{1}{4}$ to $\frac{1}{3}$ of those usually recommended.

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 benzodiazepines 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.

Nonepileptic myoclonic movements can occur.

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 to achieve adequate therapeutic effect.

Respiratory Depression

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Depression of respiration is the most marked and dangerous side effect of Fentanyl. In the post-operative period, patients may exhibit delayed depression of respiration. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary. (See Impaired Respiration below).

Impaired Respiration

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, opioids may additionally decrease respiratory drive and increase airway resistance. During anaesthesia, this can be managed by assisted or controlled respiration.

Use of Opioid Antagonists for Respiratory Depression

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists.

However, 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 opioid antagonist action. Consult individual product information before employing opioid antagonists.

Impaired Liver and Kidney Function

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 medicines.

Bradycardia

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.

Sphincter of Oddi Spasm

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

Adjunct to Conduction Anaesthesia; Nitrous Oxide

Certain forms of conduction anaesthesia, such as spinal anaesthesia and some peridural anaesthetics, can alter respiration by blocking intercostals nerves.

Through other mechanisms, fentanyl can also alter respiration. Therefore, when fentanyl is used to supplement these forms of anaesthesia, the anaesthetist should be familiar with the physiological alterations involved and be prepared to manage them in patients selected for these forms of anaesthesia.

Monitoring

Vital signs should be monitored carefully.

Elderly, Debilitated Patients

The initial fentanyl dose should be reduced in elderly and debilitated patients. Elderly patients may be more susceptible to adverse effects, such as respiratory depression and cardiovascular effects. They may also have age related kidney function impairment, resulting lower clearance of rates of fentanyl. 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 postoperative monitoring.

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Hypotension

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

Serotonin Syndrome

Caution is advised when fentanyl is coadministered 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.

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 may obscure the clinical course of patients with a head injury.

Rapid bolus infusion 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.

Use in Children

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

4.5. Interaction with other medicines and other forms of interaction

Coadministration of the following medicines may enhance or prolong the effects of fentanyl: azole antifungals, macrolide antibiotics and protease inhibitors such as Ritonavir.

Coadministration of the following medicines may decrease the plasma concentration of fentanyl: phenytoin.

The concurrent administration of fentanyl and naltrexone precipitates opioid withdrawal symptoms.

Benzodiazepines and other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see Section 4.4). Examples include benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, and alcohol.

Neuroleptics

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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.

Monoamine Oxidase (MAO) inhibitors

Severe and unpredictable potentiation of opiate effects by MAO inhibitors has been reported with opioid 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. (See Section 4.3).

Nitrous Oxide

Nitrous oxide has been reported to produce cardiovascular depression when given with high doses of fentanyl.

Amiodarone

Profound bradycardia, sinus arrest and hypotension have occurred when patients receiving amiodarone have been given fentanyl for anaesthesia.

Adrenergic Blockers and Calcium Channel Blockers

The combination of calcium channel blockers and beta-adrenergic blockers during fentanyl anaesthesia should be used with caution since severe hypotension has been reported to occur.

Serotonin Syndrome

Opioids can interact with antidepressants and migraine medicines to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity.

Coadministration of sibutramine hydrochloride with fentanyl may increase the risk of serotonin syndrome (hypertension, hyperthermia, myoclonus and mental status changes).

4.6. Fertility, pregnancy and lactation

Pregnancy

Category C.

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. The potential risk for humans is unknown.

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.

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Administration (IM or IV) during childbirth (including caesarean 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, 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.

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.

4.7. Effects on ability to drive 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.

4.8. Undesirable effects

More Common

Respiratory depression, apnoea, muscular rigidity, myoclonic movements, bradycardia, tachycardia, vein pain and allergic dermatitis. 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. If respiratory depression occurs during anaesthesia, assisted or controlled respiration will provide adequate ventilation without reversing analgesia. Respiratory depression can be immediately reversed by opioid antagonists (e.g. nalorphine or naloxone) which, it should be noted, will also reverse analgesia. Secondary rebound respiratory depression has been observed after the operation in rare instances.

Muscular rigidity 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 suxamethonium. 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 pre-anaesthetic regimen tends to reduce the occurrence of such effects.

Less Common

Hypotension, hypertension, dizziness, blurred vision, miosis, nausea, emesis, constipation, laryngospasm, diaphoresis, itching, euphoria, seizures, spasm of the sphincter of Oddi, anaphylaxis, headache, loss of consciousness, myoclonus, phlebitis, hyperventilation, hiccups, cough, hypothermia, airway complications of anaesthesia, agitation postoperative. Motor stimulation and bronchospasm may occur with high doses of fentanyl. Less frequently, cardiac arrhythmias, postoperative mental depression, paradoxical CNS excitation or delirium may occur.

Fentanyl/Neuroleptic Combination

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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. When they occur, 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.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Signs and Symptoms

The oral LD50 for fentanyl in rats is 18.0 mg/kg. The intravenous LD50 is 2.3 mg/kg, and the intramuscular LD50 is 1.0 mg/kg in rats. The toxic dose in man is unknown.

The manifestations of fentanyl overdose are an extension of its pharmacological actions. In sufficient overdose, fentanyl would produce narcosis, which may be preceded by marked skeletal muscle rigidity. Cardio-respiratory depression, which can vary in severity from bradypnoea to apnoea may occur accompanied by cyanosis, followed by a fall in body temperature, circulatory collapse, coma and possibly 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 opioid antagonist, such as nalorphine or 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 overdosage of fentanyl may be longer than the duration of opioid antagonist action. Consult the package insert of the individual opioid 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetic general, opioid anaesthetic, ATC code: N01AH01

Mechanism of Action

Fentanyl is a potent opioid 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, the analgesic activity of fentanyl is approximately equivalent to 10 mg of morphine or 75 mg of pethidine. Alterations in respiratory rate and alveolar ventilation associated with opioid analgesics may last longer than the analgesic effect. As the dose of opioid is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnoea. Fentanyl appears to have less emetic activity than either morphine or pethidine. Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl. Recent assays in man show no clinically significant histamine release at doses up to 50 mcg/kg (0.05 mg/kg or 1 mL/kg). Fentanyl preserves cardiac stability and blunts stress-related hormonal changes at higher doses.

Fentanyl produces minimal cortical depression and may act by filling receptor sites located in the thalamus, midbrain and spinal cord. A specific morphine antagonist (e.g. nalorphine or naloxone) produces reversal of respiratory, cardiovascular, miotic and motor incoordination effects and also produces reversal of analgesia, euphoria and sedation. Rigidity of the diaphragm and intercostals muscles can be eliminated by suxamethonium. Cholinergic effects such as bradycardia are reversed by atropine.

As with longer acting opioid 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 CO₂ stimulation following administration of fentanyl to man:

1. Diminished sensitivity to CO₂ stimulation may persist longer than depression of respiratory rate. Fentanyl frequently slows the respiratory rate (see section 4.4).
2. Altered sensitivity to CO₂ stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 micrograms 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 section 4.4)

5.2. Pharmacokinetic properties

The pharmacokinetics of fentanyl can be described by a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution of fentanyl is 4 L/kg.

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.

Fentanyl plasma protein binding capacity increases with increasing ionisation of the drug.

Alterations in pH may affect its distribution between plasma and the central nervous system. It accumulates in skeletal muscle and fat, and is released slowly into the blood.

Fentanyl is primarily transformed in the liver and demonstrates a high first pass clearance with approximately 75% of an intravenous dose excreted in urine, primarily as metabolites

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with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the faeces, primarily as metabolites.

Special Populations

Paediatrics

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 increase 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).

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

Carcinogenicity

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.

Genotoxicity

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium Chloride
Water for Injection

6.2. Incompatibilities

Fentanyl solution must not be mixed with other products except those mentioned in section 6.6.

6.3. Shelf life

Fentanyl 10 mcg/mL 100 mL bag has a shelf-life of 24 months from the date of manufacture
Fentanyl 20 mcg/mL 100 mL bag has a shelf-life of 17 months from the date of manufacture
Fentanyl 10 mcg/mL 10 mL syringe has a shelf-life of 12 months from the date of manufacture

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Fentanyl 20 mcg/mL 50 mL syringe has a shelf-life of 12 months from the date of manufacture

6.4. Special precautions for storage

Store at or below 25°C. Do not refrigerate or freeze.

6.5. Nature and contents of container

Fentanyl 10 mcg/mL and Fentanyl 20 mcg/mL are available in 100 mL IV bags with overwrap

Fentanyl 10 mcg/mL is available in 10 mL polypropylene syringe

Fentanyl 20 mcg/mL is available in 50 mL polypropylene syringe

6.6. Special precautions for disposal and other handling

For single use only. Discard any unused product.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Controlled Drug B3

8. SPONSOR

Biomed Limited
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Point Chevalier
Auckland

Phone: 0800 833 133

9. DATE OF FIRST APPROVAL

23 September 2010

10. DATE OF REVISION OF THE TEXT

22 November 2019

Summary table of changes:

DATE	CHANGE
22/11/19	Product name change-Biomed Fentanyl. Update to section 6.4 to include Do not refrigerate or freeze.
18/03/19	1, 2, 6 - Removal of references to the fentanyl 10 mcg/mL 50 ml syringe. 4.4 & 4.5-Information added regarding the risks of serious side effects from the concomitant use of opioids, benzodiazepines and other central nervous system depressants. All- Format update.