NEW ZEALAND DATA SHEET

Biomed Fentanyl 10 mcg/mL, 20 mcg/mL

1. PRODUCT NAME

Biomed Fentanyl 10 mcg/mL 100 mL bag
Biomed Fentanyl 10 mcg/mL 10 mL syringe
Biomed Fentanyl 20 mcg/mL 100 mL bag

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

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

A clear, colourless isotonic solution. It contains no preservative.
It is formulated with a pH of 4.0 – 7.5.

The following product is a solution for IV injection:
Biomed Fentanyl 10 mcg/mL 10 mL syringe

The following products are solutions for IV infusion:
Biomed Fentanyl 10 mcg/mL 100 mL IV bag
Biomed Fentanyl 20 mcg/mL 100 mL IV bag

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Biomed Fentanyl is indicated for:

- analgesic action in the post-operative period as the need arises;
- use as an opioid analgesic supplement in general and regional anaesthesia.

4.2. Dose and method of administration

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.

Biomed Fentanyl contains no antimicrobial agent. It should be used only once and any remaining contents discarded. The injectable solution must not be mixed with other products (see Section 6.2)

Usual Dosage in Adults

1. 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 to recommended in elderly and poor risk patients.

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

2. Adjunct to regional anaesthesia
50 to 100 micrograms may be administered slowly intravenously when additional analgesia is required.

3. Post-operatively (Recovery room)
50 to 100 micrograms may be administered for the control of pain, tachypnoea, and emergence delirium. The dose may be repeated in one or two hours as needed.

Special Populations

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

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

Renal Impairment
In patients with renal impairment, reduced dosing of Biomed Fentanyl should be considered and these patients should be observed carefully for signs of fentanyl toxicity (see Section 5.2).

Paediatric Populations
For induction and maintenance in children 2-12 years of age, a reduced dose as low as 20 to 30 micrograms per 10 kg is recommended. (See Section 4.4 for use of Biomed Fentanyl with other CNS depressants and in patients with altered response).

Method of administration

Precautions to be taken before handling or administering the medicine:
Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway (see Section 4.4).
It is recommended to use gloves while handling Biomed Fentanyl (see Section 6.6).
The injectable solution must not be mixed with other products (see Section 6.2).

4.3. Contraindications

- Biomed Fentanyl is contraindicated in patients with known intolerance to fentanyl, any of the components of Biomed Fentanyl or other opioids.
- Biomed 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 – Paediatric use)
- Biomed Fentanyl should not be administered to patients suffering from bronchial asthma.
- Biomed 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.
- There is no evidence that fentanyl is potentiated by MAO inhibitors, but since such potentiation is found with other opioid analgesics, the use of Biomed Fentanyl in patients who have received MAO inhibitors within 14 days is not recommended. (See Section 4.5).

4.4. Special warnings and precautions for use

Hazardous and harmful use
Biomed Fentanyl contains the opioid fentanyl and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed Biomed Fentanyl at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed Biomed Fentanyl.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see Section 6.4 and Section 6.6). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share Biomed Fentanyl with anyone else.

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_2, thus affecting respiration post-operatively. Therefore, patients should remain under appropriate surveillance.
Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of Biomed Fentanyl but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients and in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma). Opioids should be used with caution and with close monitoring in these patients (see Section 4.2). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see Section 4.3).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, (see Section 4.2).

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

Respiratory depression caused by opioid analgesics is dose related and can be reversed by opioid antagonists, but additional doses may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist. Appropriate surveillance should be maintained. (See discussion of opioid antagonists in Section 4.9.)

Resuscitative equipment and an opioid antagonist should be readily available to manage apnoea.

Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of Biomed Fentanyl with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe Biomed Fentanyl concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while using Biomed Fentanyl.

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced.

Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing Biomed Fentanyl in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see Ceasing opioids and Section 4.2).

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

Accidental ingestion/exposure
Accidental ingestion or exposure of Biomed Fentanyl, especially by children, can result in a fatal overdose of fentanyl. Patients and their caregivers should be given information on safe storage and disposal of unused Biomed Fentanyl (see Section 6.4 and Section 6.6).

Hyperalgesia
Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see Tolerance, dependence and withdrawal). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids
Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see *Tolerance, dependence and withdrawal*). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see Section 4.2). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

Muscle rigidity
Biomed 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.

Non-epileptic (myo)clonic movements can occur.

Head injuries and increased intracranial pressure
Biomed 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.

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
Biomed Fentanyl may produce bradycardia and possibly cardiac arrest if the patient has received an insufficient amount of anticholinergic, or when Biomed Fentanyl is combined with non-vagolytic muscle relaxants. Bradycardia may be treated with atropine. However, Biomed 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.

Serotonin syndrome
Caution is advised when Biomed Fentanyl is co-administered with drugs that affect the serotonergic neurotransmitter systems. This is mainly applicable to the use of fentanyl at higher doses such as during anaesthesia and post-operative recovery.

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, confusion), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia, diaphoresis), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity, tremor, myoclonus), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, a dose reduction or discontinuation of at least one of the serotonergic medicines being taken should be considered depending on the severity of symptoms.

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

Vital signs should be monitored carefully.

Due to the sodium content of Biomed Fentanyl, precaution should be taken on (repeated) dosing in patients who require sodium restriction such as patients with heart failure. (Concentration in the product formulation is 3.5 mg/mL).

Obese patients
Biomed Fentanyl should be administered with additional caution in obese patients. Obese patients should be observed carefully for signs of fentanyl toxicity.

Use in renal impairment
Opioids should be titrated with caution. It is recommended to reduce the dosage of Biomed Fentanyl in patients with renal impairment. They should be observed carefully for signs of fentanyl toxicity. Such patients also require prolonged post-operative monitoring.

Use in the elderly or debilitated patients
It is recommended to reduce the dosage of Biomed 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.

Paediatric use
The safety of Biomed Fentanyl in children younger than two years of age has not been established.

4.5. Interaction with other medicines and other forms of interaction

Effects of other medicines on Biomed Fentanyl

Central Nervous System (CNS) depressants
Medicines, such as, CNS depressants, barbiturates, benzodiazepines or related drugs, neuroleptics, opioids, alcohol and general anaesthetics, may have additive or potentiating effects with Biomed Fentanyl.

When patients have received such CNS depressant medicines, the dose of Biomed Fentanyl required may be less than usual. Concomitant use with Biomed Fentanyl in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death (See Section 4.4). Post-operative opioids including Biomed 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 opioids, the respiratory depressant effect of Biomed Fentanyl persists longer than the measured analgesic effect. The total dose of all opioid analgesics should be considered before ordering opioid analgesics during recovery from anaesthesia.

Conduction 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 Section 5.1 – Mechanism of action) Biomed Fentanyl can also alter respiration. Therefore, when Biomed 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.

Neuroleptics
If Biomed 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 Biomed 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 does 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 Biomed Fentanyl and the EEG is used for post-operative monitoring, it may be found that the EEG pattern returns to normal slowly.

Neuroleptics can induce extrapyramidal symptoms that can be controlled with anti-Parkinson agents.

Monoamine oxidase inhibitors (MAOI)
Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. Since the safety of fentanyl in this regard has not been established, the use of Biomed Fentanyl in patients who have received MAO inhibitors within 14 days is not recommended.

Serotonergic drugs
Coadministration 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 (see Section 4.4).

Cytochrome P450 3A4 (CYP3A4) inhibitors
Fentanyl is metabolised mainly via the human cytochrome P450 3A4 enzyme. It is a high clearance medicine, which is rapidly and extensively metabolised. When Biomed Fentanyl is used, the concomitant use of a CYP3A4 inhibitor may result in a decrease in fentanyl clearance. With a single-dose Biomed Fentanyl administration, the period of risk for respiratory depression may be prolonged, which may require special patient care and longer observation. With multiple-dose Biomed Fentanyl administration, the risk for acute and/or delayed respiratory depression may be increased, and a dose reduction of Biomed Fentanyl may be required to avoid accumulation of fentanyl.

Oral ritonavir (a potent CYP3A4 inhibitor) reduced the clearance of a single intravenous Biomed Fentanyl dose by two thirds, although peak plasma concentrations were not affected.

Oral administration of itraconazole (another 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. Co-administration of other potent or less potent CYP3A inhibitors, such as fluconazole or voriconazole and Biomed Fentanyl may also result in an increased and/or prolonged exposure to fentanyl.

There are no data on the in vivo interactions between fentanyl and other medicines inhibiting CYP3A4 (e.g. ketoconazole, erythromycin, diltiazem and cimetidine).

Effects of Biomed Fentanyl on other medicines
Following the administration of Biomed Fentanyl, the dose of other CNS-depressant drugs should be reduced. This is particularly important after surgery, because profound analgesic is accompanied by marked respiratory depression, which can persist or recur in postoperative period. Administration of a CNS depressant, such as a benzodiazepine or related drugs, during this period may disproportionally increase the risk for respiratory depression (see Section 4.4).

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 Biomed 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 medicines are co-administered with Biomed Fentanyl their dose may need to be reduced.

4.6 Fertility, pregnancy and lactation

Use in 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. 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.

Administration (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

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

Table 1: Adverse Drug Reactions Reported by ≥1% of Fentanyl Treated Subjects in 20 Clinical Trials of Fentanyl

System/Organ Class Adverse reaction	**Fentanyl (n=376) %**
Nervous System Disorders	
Sedation	5.3
Dizziness	3.7
Dyskinesia	3.2
Eye Disorders	
Visual disturbance	1.9
Cardiac Disorders	
Bradycardia	6.1
Tachycardia	4.0
Arrhythmia	2.9
Vascular Disorders	
Hypotension	8.8
Hypertension	8.8
Vein pain	2.9
Respiratory, Thoracic and Mediastinal Disorders	
Apnoea	3.5
Bronchospasm	1.3
Laryngospasm	1.3
Gastrointestinal Disorders	
Nausea	26.1
Vomiting	18.6
Skin and Subcutaneous Tissue Disorders	
Dermatitis allergic	1.3
Musculoskeletal and Connective Tissue Disorders	
Muscle rigidity (which may also involve the thoracic muscles)	10.4
Injury, Poisoning and Procedural Complications	
Confusion postoperative	1.9
Anaesthetic complication neurological	1.1

Additional ADRs that occurred in <1% of fentanyl treated subjects in 20 clinical trials are listed below in Table 2.

Table 2: Adverse Drug Reactions Reported by <1% of fentanyl treated Subjects in 20 Clinical Trials of fentanyl

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

Postmarketing Data

Adverse drug reactions first identified during postmarketing experience with fentanyl are included in Table 3, based on spontaneous reporting rates. The frequencies are provided according to the following convention:

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

Table 3: Adverse Drug Reactions Identified During Postmarketing Experience with Fentanyl by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders Very rare	Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Nervous System Disorders Very rare	Convulsions, Loss of consciousness, Myoclonus
Cardiac Disorders Very rare	Cardiac arrest (also see Section 4.4)
Respiratory, Thoracic and Mediastinal Disorders Very rare	Respiratory depression (also see Section 4.4)
Skin and Subcutaneous Tissue Disorders Very Rare	Pruritus
Psychiatric disorders Not known	Delirium
General Disorders and Administration Site Conditions Not known	Drug withdrawal syndrome (see Section 4.4)

When a neuroleptic is used with fentanyl, the following adverse reactions may be observed: chills and/or shivering; restlessness, post-operative hallucinatory episodes; and extrapyramidal symptoms (see Section 4.5).

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://pophealth.my.site.com/carmreportnz/s/

4.9. Overdose

Signs and Symptoms
The oral LD_{50} for fentanyl in rats is 18.0 mg/kg. The intravenous LD_{50} is 2.3 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 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 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 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 risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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. 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 opioid antagonists. As with morphine, fentanyl-induced bradycardia from vagal stimulation is blocked or reversed by atropine. Alterations in respiratory rate and alveolar ventilation, associated with opioid analgesics may last longer than the analgesic effect. As the dose of the opioid 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 have indicated 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.

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 opioid 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.

5.2. Pharmacokinetic properties
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.

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 CO_2 stimulation following administration of fentanyl to man:

1. Diminished sensitivity to CO_2 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_2 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 concerning respiratory depression.)

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% (comprised of plasma protein binding about 43% and red blood cell binding about 40%).

Metabolism
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.

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

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 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).

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 Injections

6.2. Incompatibilities

The injectable solution must not be mixed with any other products except those mentioned in Section 4.2.

6.3. Shelf life

Biomed Fentanyl 10 mcg/mL

100 mL IV bag with foil overwrap	24 months
10 mL polypropylene syringe	12 months

Biomed Fentanyl 20 mcg/mL

100 mL IV bag with foil overwrap	17 months

6.4. Special precautions for storage

Store at or below 25ºC. Do not refrigerate or freeze. Protect from light.

6.5. Nature and contents of container

Biomed Fentanyl 10 mcg/mL available in:
100 mL IV bag with foil overwrap
10 mL polypropylene syringe

Biomed Fentanyl 20 mcg/mL available in:
100 mL IV bag with foil overwrap

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

7. MEDICINE SCHEDULE

Controlled Drug B1

8. SPONSOR

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9. DATE OF FIRST APPROVAL

23 September 2010

10. DATE OF REVISION OF THE TEXT

13 October 2025

Summary table of changes:

Section Changed	Summary of new information
Throughout	50 mL syringe pack size removed
2	Excipients with known effects removed
4.8	Website address for reporting of suspected adverse reactions updated to current
4.9 & 6.1	Minor editorial update