New Zealand Data Sheet

1 PRODUCT NAME

FENTANYL 50 micrograms/mL Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fentanyl Injection contains fentanyl 50 micrograms/mL as citrate.

Each 2 mL ampoule contains 100 micrograms of fentanyl as fentanyl citrate.

Each 10 mL ampoule contains 500 micrograms of fentanyl as fentanyl citrate.

Excipient(s) with known effect: Sodium 9.0 mg/mL

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Fentanyl Injection 50 mcg/mL is a clear, colourless solution and is available in 2 mL and 10 mL clear glass ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fentanyl Injection is indicated in adults and children aged above two years for:

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

4.2 Dose and method of administration

Dose
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.

Usual dosage in adults

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

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

2. **Adjunct to general anaesthesia**

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

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

3. **Adjunct to regional anaesthesia**

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

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

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

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 Fentanyl Injection should be considered and these patients should be observed carefully for signs of fentanyl toxicity (see Section 5.2 – Pharmacokinetics properties).

Paediatric population
For induction and maintenance in children 2-12 years of age, a reduced dose as low as 20 to 30 micrograms (0.4 to 0.6 mL) per 10 kg is recommended (see Section 4.4 - Special warnings and Precautions for use, for use of Fentanyl Injection with other central nervous system (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 – Special warnings and precautions for use).

It is recommended to wear gloves while opening the ampoule (see Section 6.6 – Special precautions for disposal and other handling).

The injectable solution must not be mixed with other products. (see Section 6.2 Incompatibilities)

For instructions on dilution of the medicine before administration (see Section 6.6 – Special precautions for disposal and other handling).

4.3 Contraindications

Fentanyl Injection is contraindicated in patients with known intolerance to fentanyl, any of the components of Fentanyl Injection or other opioids.

Fentanyl Injection 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 Special warnings and precautions for use – Paediatric use).

Fentanyl Injection should not be administered to patients suffering from bronchial asthma, severe respiratory disease, acute respiratory disease and respiratory depression.

There is no evidence that fentanyl is potentiated by MAOIs but since such potentiation is found with other opioid analgesics, the use of Fentanyl Injection in patients who have received MAOIs within 14 days is not recommended (see Section 4.5 - Interaction with other medicines and other forms of interaction).

Fentanyl Injection 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.

4.4 Special warnings and precautions for use

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

Addiction can occur in patients appropriately prescribed Fentanyl Injection at recommended doses.

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

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Therefore, it is possible that a higher dose of Fentanyl Injection may be needed to produce the same result. The risk (addiction) 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 Fentanyl Injection.

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 Special precautions for storage and section 6.6 Special precautions for disposal). 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 Fentanyl Injection with anyone else.

Physical dependence which can occur after several days to weeks of continued opioid usage may result in acute withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of opioids.

Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of Fentanyl Injection may result in overdose and/or death. Persons at increased risk of opioid abuse may still be appropriately treated with Fentanyl Injection.

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.

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 Fentanyl Injection 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 Dose and Method of Administration).

Hypoventilation (respiratory depression)
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 Fentanyl Injection 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.

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.

Fentanyl Injection should be used with caution in elderly, frail, or debilitated patients and 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, asthma or any patient with potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. Opioids should be used with caution and with close monitoring in these patients (see section 4.2 Dose and method of administration). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section 4.3 Contraindications). During anaesthesia, this can be managed by assisted or controlled respiration.

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 - Overdose).

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 Dose and method of administration).

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.

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

Risk from concomitant use of central nervous system (CNS) depressants, especially benzodiazepines or related drugs
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Fentanyl Injection with benzodiazepines or other CNS depressants in spontaneous breathing patients (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, gabapentinoids, tranquilizers, muscle relaxants, tricyclic antidepressants,

centrally-active anti-emetics, 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 Interactions with other medicines and other forms of interaction].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages of both drugs 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 Injection 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 Interactions with other medicines and other forms of interaction].

Muscle rigidity
Fentanyl Injection 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
Fentanyl Injection 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
Fentanyl Injection may produce bradycardia and possibly cardiac arrest if the patient has received an insufficient amount of anticholinergic, or when Fentanyl Injection is combined with non-vagolytic muscle relaxants. Bradycardia may be treated with atropine. However, Fentanyl Injection 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 Fentanyl Injection is co-administered with medicines that affect the serotonergic neurotransmitter systems. This is mainly applicable to the use of fentanyl used 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 medicines such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with medicines which impair metabolism of serotonin (including 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 Fentanyl Injection.

Vital signs should be monitored carefully.

Use of opioids in chronic (long-term) non-cancer pain (CNCP)
Opioid analgesics have an established role in the treatment of acute pain, cancer pain and palliative and end-of-life care. Current evidence does not generally support opioid analgesics in improving pain and function for most patients with chronic non-cancer pain. The development of tolerance and physical dependence and risks of adverse effects, including hazardous and harmful use, increase with the length of time a patient takes an opioid. The use of opioids for long-term treatment of CNCP is not recommended.

The use of an opioid to treat CNCP should only be considered after maximised non-pharmacological and non-opioid treatments have been tried and found ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain. Opioids should only be prescribed as a component of comprehensive multidisciplinary and multimodal pain management.

Opioid therapy for CNCP should be initiated as a trial in accordance with clinical guidelines and after a comprehensive biopsychosocial assessment has established a cause for the pain and the appropriateness of opioid therapy for the patient (see Hazardous and harmful use, above). The expected outcome of therapy (pain reduction rather than complete abolition of pain, improved function and quality of life) should be discussed with the patient before commencing opioid treatment, with agreement to discontinue treatment if these objectives are not met.

Owing to the varied response to opioids between individuals, it is recommended that all patients be started at the lowest appropriate dose and titrated to achieve an adequate level of analgesia and functional improvement with minimum adverse reactions. Immediate-release products should not be used to treat chronic pain, but may be used for a short period in opioid-naïve patients to develop a level of tolerance before switching to a modified-release formulation. Careful and regular assessment and monitoring is required to establish the clinical need for ongoing treatment. Discontinue opioid therapy if there is no improvement of pain and/or function during the trial period or if there is any evidence of misuse or abuse. Treatment should only continue if the trial has demonstrated that the pain is opioid responsive and there has been functional improvement. The patient's condition should be reviewed regularly and the dose tapered off slowly if opioid treatment is no longer appropriate (see Ceasing Opioids).

Accidental ingestion/exposure
Accidental ingestion or exposure of Fentanyl Injection, 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 Fentanyl Injection (see section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal).

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 Dose and Method of Administration). 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.

Use in the elderly or debilitated patients
It is recommended to reduce the dosage of Fentanyl Injection 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 population
The safety of Fentanyl Injection 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 Fentanyl Injection

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 Fentanyl Injection.

When patients have received such CNS depressant medicines, the dose of Fentanyl Injection required may be less than usual. Concomitant use with Fentanyl Injection in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death (see Section 4.4 Special warnings and precautions for use**)**. Post-operative opioids including Fentanyl Injection 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 Fentanyl Injection 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.

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	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.
Intervention	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 Warnings and Precautions].
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

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) Fentanyl Injection can also alter respiration. Therefore, when Fentanyl Injection 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 Fentanyl Injection 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 Fentanyl Injection 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 Fentanyl Injection and the electroencephalogram (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 MAOIs has been reported with opioids analgesics. Since the safety of fentanyl in this regard has not been established, the use of Fentanyl Injection in patients who have received MAOIs within 14 days is not recommended (see Section 4.3 - Contraindications).

Serotonergic drugs
Co-administration of fentanyl with serotonergic agents, such as SSRIs or SNRIs or

MAOIs, 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 Fentanyl Injection is used, the concomitant use of a CYP3A4 inhibitor may result in a decrease in fentanyl clearance. With a single-dose Fentanyl Injection administration, the period of risk for respiratory depression may be prolonged, which may require special patient care and longer observation. With multiple-dose Fentanyl Injection administration, the risk for acute and/ or delayed respiratory depression may be increased, and a dose reduction of Fentanyl Injection may be required to avoid accumulation of fentanyl.

Oral administration of itraconazole (a potent inhibitor of CYP3A4) at 200 mg/day given 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 Fentanyl Injection may result in an increased exposure to fentanyl.

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

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

Effects of Fentanyl Injection on other medicines
Following the administration of Fentanyl Injection, the dose of other CNS-depressant medicines 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 of respiratory depression (see Section 4.4 Special warnings and precautions for use**)**.

The total plasma clearance and volume of distribution of etomidate is decreased by a factor of 2 to 3 without a change in half-life when administered with fentanyl. Simultaneous administration of Fentanyl Injection 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 Fentanyl Injection their dose may need to be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C.
There are no adequate data from the use of Fentanyl Injection 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 (I.M. or I.V.) 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.

Breastfeeding
Fentanyl is excreted into human milk. Therefore, breast-feeding or use of expressed breast milk is not recommended for 24 hours following the administration of this medicine.

The risk/benefit of breast-feeding following Fentanyl Injection 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 Injection.

4.8 Undesirable effects

Clinical trial data
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 the 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

Post-marketing experience

Adverse drug reactions first identified during post-marketing 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
Not known	Cannot be estimated from the available data

Table 3: Adverse drug reactions identified during post-marketing experience with fentanyl by frequency category estimated from spontaneous reporting rates

Immune system disorders	
Very rare	Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric disorders	
Not known	Delirium
Nervous system disorders	
Very rare	Convulsions, loss of consciousness, myoclonus
Cardiac disorders	
Very rare	Cardiac arrest (also see Section 4.4 – Special warnings and precautions for use)
Respiratory, thoracic and mediastinal disorders	
Very rare	Respiratory depression (also see Section 4.4 – Special warnings and precautions for use)
Skin and subcutaneous tissue disorders	
Very rare	Pruritus
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 – Interaction with other medicines and other forms of interaction).

Reporting of suspected adverse reactions

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 LD_{50} for Fentanyl Injection in rats is 18.0 mg/kg. The intravenous LD_{50} is 2.3 mg/kg, and the intramuscular LD_{50} is 1.0 mg/kg in rats. The toxic dose in man is unknown.

The manifestations of Fentanyl Injection 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 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: Opioid analgesic, 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 (2 mL), the analgesic activity of fentanyl is approximately equivalent to 10 mg of morphine or 75 mg of pethidine. Fentanyl differs from morphine by its short duration of analgesic activity, lack of emetic activity, and minimal hypotensive activity.

The action of fentanyl is qualitatively similar to those of morphine and pethidine, i.e. analgesia, euphoria, miosis, bradycardia, respiratory depression, bronchoconstriction, muscle rigidity and suppression of cough reflexes. These effects can be reversed by

specific 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. Following intramuscular administration, the onset of action is from 7 to 8 minutes and the duration of action is 1 to 2 hours.

As with longer acting 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 (12 mL) fentanyl to healthy volunteers.

3. Duration and degree of respiratory depression is dose-related.

4. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection.

(See also Section 4.4 – Special warnings and precautions for use 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 Vc (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 (CYP3A4) 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

Paediatric population
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 - Dose 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 concentration. 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 tumours at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/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

Fentanyl Injection contains:

Sodium chloride
Sodium hydroxide
Water for injections

6.2 Incompatibilities

The injectable solution must not be mixed with other medicines except those mentioned in Section 6.6 – Special precautions for disposal and other handling.

6.3 Shelf life

3 years
Diluted solution should be used within 24 hours of preparation.

6.4 Special precautions for storage

Store at or below 25°C.
Protect from light.

6.5 Nature and contents of container

Clear glass ampoules

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

If desired, fentanyl may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with plastic infusion sets. These should be used within 24 hours of preparation.

It is recommended to wear gloves when opening the ampoule.

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

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

7 MEDICINE SCHEDULE

Controlled Drug B1

8 SPONSOR

Mercury Pharma (NZ)
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 22 October 2010

10 DATE OF REVISION OF TEXT

07 December 2022

Summary table of changes

Section changes	Summary of new information
4.4 and 4.5	Updated to mention the risk of Serotonin syndrome as per Medsafe letter dated 12 July 2022