NEW ZEALAND DATA SHEET

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, fentanyl should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see section **4.4 Special warnings and precautions for use**).

Hazardous and harmful use

Fentanyl poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see section **4.4 Special warnings and precautions for use**).

Life-threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of fentanyl. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see section **4.4 Special warnings and precautions for use**).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while taking fentanyl (see section **4.4 Special warnings and precautions for use**).

1. PRODUCT NAME

DBL Fentanyl Injection 50 micrograms/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Fentanyl Injection is presented in ampoules and containing 2 mL or 10 mL of a 50 microgram per mL solution of fentanyl present as fentanyl citrate. The pH of the solution is adjusted to between 5.0 to 7.5, if necessary

For the full list of excipients, see section **6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Solution for injection.

DBL Fentanyl Injection is a clear, colourless sterile solution of fentanyl citrate in water for injections.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL Fentanyl Injection is indicated for:

- analgesic action of short duration during anaesthetic periods, premedication, induction and maintenance, and in the immediate post-operative period (recovery room) as the need arises;

- use as a narcotic analgesic supplement in general and regional anaesthesia;

- administration with a neuroleptic such as droperidol injection as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia. The state of neurolept analgesia may be converted to neurolept anaesthesia by the concurrent administration of 65% nitrous oxide in oxygen.

4.2 Dose and method of administration

Dosage

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.

Reduced dosage is generally indicated for high-risk patients, including geriatric or debilitated patients, or those who have received other CNS depressant drugs. When used in conjunction with other CNS depressants as low as 25 to 33% of the usual dose is recommended. Vital signs should be monitored routinely.

Adult Dosage

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.

Children's dosage

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.

Use in Elderly Patients

Elderly patients may require lower doses of fentanyl and a varied dosage regimen as they may be more susceptible to adverse effects, such as respiratory depression and cardiovascular effects.

Dosage adjustment

Renal Impairment

Fentanyl should be used with caution in patients with impaired renal function.

Hepatic Impairment

Fentanyl should be used with caution in patients with impaired hepatic function.

4.3 Contraindications

DBL Fentanyl Injection is contraindicated in patients with known hypersensitivity or intolerance to fentanyl, any of the components of DBL Fentanyl Injection or other opioid analgesics.

DBL Fentanyl Injection should not be administered to patients who fall into the following categories:

- Children two years of age or younger, because the safety of fentanyl in this age group has not been established.
- Severe respiratory disease, acute respiratory disease, respiratory depression, patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury, brain tumour or increased intracranial pressure.
- Patients suffering from bronchial asthma.

- Patients who have received monoamine oxidase (MAO) inhibitors within the previous 14 days (see section **4.5 Interactions with other medicines and other forms of interaction**).

- Patients with myasthenia gravis: Fentanyl may cause thoracic muscle rigidity following intravenous administration. It should not be used in patients with a history of myasthenia gravis, as reversal of thoracic muscle rigidity with muscle relaxants is inappropriate in these patients.

- Use in chronic non-cancer pain.

4.4 Special warnings and precautions for use

Hazardous and harmful use

DBL Fentanyl Injection contains the opioid fentanyl and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed 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 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 sections **6.4 Special precautions for storage** and **6.6 Special precautions for disposal and other handling**). 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 with anyone else.

Accidental ingestion/exposure

Accidental ingestion or exposure of 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 fentanyl (see sections **6.4 Special precautions for storage** and **6.6 Special precautions for disposal and other handling**).

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, 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, in patients with existing impairment of respiratory function (e.g., chronic obstructive pulmonary disease, asthma) and in patients with hepatic and renal impairment (see **Conditions which require dose reduction**). Opioids should be used with caution and with close

monitoring in these patients (see section **4.2 Dose and method of administration**). During anaesthesia, this may be managed by assisted or controlled respiration. The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see section **4.3 Contraindications**).

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, together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

Opioids can cause 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.

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.

It has been reported that diminished sensitivity to CO_2 stimulation may persist longer than depression of respiratory rate. This dose related effect of respiratory depression peaks between 5 and 15 minutes after injection, but seldom lasts longer than 30 minutes.

The effect on respiratory depression persists longer than the measured analgesic effect, and care should be taken, with the total opioid dose considered when fentanyl is given post-operatively. The recommended dose may be as low as quarter of that normally prescribed.

Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anaesthesia may be longer than the duration of narcotic antagonist action. Consult individual prescribing information (naloxone) before employing narcotic antagonists. See also discussion of narcotic antagonists in section **4.9 Overdose**.

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

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 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 Dose and method of administration**).

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

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% to 25% 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.

Neonatal opioid withdrawal syndrome

Refer to section **4.6 Fertility, pregnancy and lactation – Use in pregnancy – Category C**.

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.

Non-epileptic myoclonic movements

Non-epileptic myoclonic movements can occur.

Severe cardiovascular depression

DBL Fentanyl Injection may cause severe bradycardia, severe hypotension including orthostatic hypotension, and syncope. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anaesthetics) (see section **4.5 Interactions with other medicines and other forms of interactions**). In patients with circulatory shock, DBL Fentanyl Injection may cause vasodilation that can further reduce cardiac output and blood pressure. Monitor these patients for signs of hypotension after initiating or titrating the dosage of DBL Fentanyl Injection.

Cardiac arrhythmias

Fentanyl should be used with caution in patients with cardiac arrhythmias (due to its weak cholinergic activity). Fentanyl may produce bradycardia, and possibly asystole, if the patient has received an insufficient amount of anticholinergic agent, or when fentanyl is combined with non-vagolytic muscle relaxants.

Hypotension

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

Rate of injection

Intravenous administration of fentanyl may cause muscle rigidity, particularly of the muscles of respiration and alter the rate of respiration especially in patients suffering from myasthenia gravis. The effect appears to be dependent on the rate of injection. The incidence may be lowered by giving the intravenous injection more slowly. Muscle relaxants may be necessary.

Conditions which require dose reduction

Dosage reduction is desirable in patients suffering from hypothyroidism, chronic hepatic disease and alcoholism.

Management of complications

Patients receiving fentanyl should be kept under close medical supervision. Resuscitative facilities and an opioid antagonist compatible with the patient's condition should be available for the management of complications.

Fentanyl as a supplement for anaesthesia

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

Supervision during use

Fentanyl should only be used by experienced physicians and in patients who are under constant supervision.

Risks from concomitant use with drugs that affect the serotonergic neurotransmitter systems

Caution is advised when fentanyl is co-administered with drugs that affect the serotonergic neurotransmitter systems. The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-uptake Inhibitors (SSRIs), 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.

Cytochrome P450 3A4 interactions

Concomitant use of DBL Fentanyl Injection with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may exacerbate respiratory depression (see section **4.4 Special warnings and precautions for use**), particularly when an inhibitor is added after a stable dose of DBL Fentanyl Injection is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in DBL Fentanyl Injection-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using DBL Fentanyl Injection with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in DBL Fentanyl Injection-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of DBL Fentanyl Injection (see sections **4.2 Dose and method of administration** and **4.5 Interactions with other medicines and other forms of interactions**).

Concomitant use of DBL Fentanyl Injection with CYP3A4 inducers, or discontinuation of a CYP3A4 inhibitor, could result in lower than expected fentanyl plasma concentrations and decrease efficacy. When using DBL Fentanyl Injection with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor, monitor patients closely at frequent intervals and consider adjusting the fentanyl dosage (see sections **4.2 Dose and method of administration** and **4.5 Interactions with other medicines and other forms of interactions**).

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 fentanyl with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general

anaesthetics, tranquilisers, or other CNS depressants, including alcohol, should be reserved for patients for whom other treatment options are not possible.

If a decision is made to prescribe 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. 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.

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 taking fentanyl.

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 interactions**).

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 interactions**).

Combination with neuroleptics

When fentanyl is used in conjunction with neuroleptics such as droperidol, the differing duration of action should be taken into account. Hypotension can occur which may be due to hypovolaemia so appropriate parenteral therapy should be readily available.

Others

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

Use in hepatic impairment

Fentanyl should be administered with caution to patients with liver dysfunction.

Use in renal impairment

Fentanyl should be administered with caution to patients with kidney dysfunction.

Use in the elderly

Elderly patients may require lower doses of fentanyl and a varied dosage regimen as they may be more susceptible to adverse effects, such as respiratory depression and cardiovascular

effects. They may also have age-related kidney function impairment, resulting in lower clearance rates of fentanyl.

Paediatric use

The safety of fentanyl citrate in children younger than two years of age has not been established. It should not be administered in children younger than 2 years of age.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

CNS depressants: Other drugs with CNS depressant activity, e.g., other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, other CNS depressants, including alcohol; fentanyl may have additive or potentiating effects with these drugs.

Patients who have received other CNS depressant drugs will require a lower dose of fentanyl than usual. Likewise, following the administration of fentanyl, the dose of other CNS depressant drugs should also be reduced. Post-operative opioids, including fentanyl and other CNS depressant drugs should be given initially in reduced doses, as low as 1/4 to 1/3 of doses usually recommended. The total dose of all opioid analgesics should be considered before giving opioid analgesics during recovery from anaesthesia.

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to the additive pharmacologic effect, the concomitant use of other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics, general anaesthetics, tranquilisers, 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 Special warnings and precautions for use**).
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilisers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.

Cytochrome P450 3A4 Inhibitors and Inducers:

Inhibitors of CYP3A4	
Clinical Impact	The concomitant use of DBL Fentanyl Injection and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of DBL Fentanyl Injection is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease (see section **5.2 Pharmacokinetic properties**), resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
Intervention	If concomitant use is necessary, consider dosage reduction of DBL Fentanyl Injection until stable drug effects are achieved (see section **4.2 Dose and method of administration**). Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider adjusting the DBL Fentanyl Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice.
Inducers of CYP3A4	
Clinical Impact	The concomitant use of DBL Fentanyl Injection and CYP3A4 inducers can decrease the plasma concentration of fentanyl (see section **5.2 Pharmacokinetic properties**), resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl (see section **4.4 Special warnings and precautions for use**). After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase (see section **5.2 Pharmacokinetic properties**), which could increase or prolong both the therapeutic effects and adverse reactions and may cause serious respiratory depression.
Intervention	If concomitant use is necessary, consider adjusting the DBL Fentanyl Injection dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider DBL Fentanyl Injection dosage reduction and monitor for signs of respiratory depression.

Examples	Rifampin, carbamazepine, phenytoin.

MAO Inhibitors: Untoward incidents resulting from concurrent administration of opioids and MAO inhibitors have occurred. Nearly all of these reports have involved pethidine, but the safety of fentanyl has not been established in this situation. Therefore, before receiving fentanyl, patients should not have taken a MAO inhibitor within the previous 14 days (see section **4.3 Contraindications**).

Serotonergic Drugs: Co-administration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI), 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.

Neuroleptics: The combination of fentanyl with a neuroleptic such as droperidol, blood pressure may be altered and cause hypotension (see section **4.4 Special warnings and precautions for use**). 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 fluids therapy, together with other countermeasures, does not correct hypotension, it may be necessary to administer a pressor agent other than adrenaline. Because of the alpha-adrenergic blocking action of droperidol, Adrenaline may paradoxically decrease the blood pressure in patients who have received droperidol due to its alpha-adrenergic blocking action. 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. The EEG pattern may return to normal slowly when droperidol is used with fentanyl. This should be taken into account if the EEG pattern is used for post-operative monitoring.

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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Category C

Australian pregnancy categorisation (Category C): Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

Although no teratogenic or acute embryotoxic effects have been observed in animal experiments, insufficient data are available to evaluate any harmful effects in man.

Consequently, the risks and potential benefits should be considered before this medicine is administered to pregnant patients.

Opioid analgesics may cause respiratory depression in the newborn infant. Administration during childbirth (including caesarean section) is not recommended because fentanyl crosses the placenta and because the foetal respiratory centre is particularly sensitive to opioids. If fentanyl is administered during childbirth, an antidote should be available for the baby.

Prolonged use of fentanyl during pregnancy can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Advise pregnant women using opioids of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly.

Use in lactation

Fentanyl may enter breast milk. Therefore, breastfeeding is not recommended for 24 hours following administration of fentanyl.

4.7 Effects on ability to drive and use machines

Fentanyl may cause drowsiness and general impairment of co-ordination and may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. Ambulatory patients should be cautioned against driving or operating machinery.

4.8 Adverse Effects (Undesirable effects)

The major adverse reactions associated with fentanyl are respiratory depression, apnoea, muscle rigidity (which may also involve the thoracic muscles), myoclonic movements and bradycardia, which if untreated, can lead to conditions such as cardiac arrest, circulatory depression and respiratory arrest.

Respiratory depression (usually associated with intravenous use) can be immediately reversed by an opioid antagonist. The respiratory depression is more likely to occur if the intravenous injection is given too rapidly; it rarely occurs with intramuscular injection. Secondary rebound respiratory depression has been observed after the operation in rare instances.

Muscle rigidity is a common side effect, and may be associated with reduced pulmonary compliance and/or apnoea, laryngospasm or bronchospasm. It may be reversed by intravenous administration of a muscle relaxant such as suxamethonium followed by controlled or artificial respiration.

Bradycardia can be controlled by the use of atropine. Bradycardia and other cholinergic effects are less likely if atropine or other anticholinergic agents are included in the pre-anaesthetic regimen.

Other reported adverse effects of fentanyl, when used alone, include elevated blood pressure, hypotension, blurred vision, dizziness, nausea, emesis, laryngospasm, diaphoresis, itching, euphoria and spasm of the sphincter of Oddi.

Less frequently, cardiac arrhythmias, post-operative mental depression, paradoxical CNS excitation or delirium may occur. Motor stimulation and bronchospasm may occur with high doses of fentanyl. Miosis or seizures may occur.

When used in conjunction with a neuroleptic agent such as droperidol, reported adverse effects include chills and/or shivering, restlessness, post-operative hallucinations, drowsiness, mental depression and extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis). These have been observed up to 24 hours post-operatively. Elevated blood pressure, with or 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 following the co-administration of several drugs during anaesthesia. However, it is uncertain whether these reactions have a causal relationship with fentanyl.

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

Symptoms

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

Treatment

In the presence of hypoventilation or apnoea, oxygen should be administered, and respiration should be assisted or controlled as indicated. A patent airway must be maintained. An oropharyngeal airway or endotracheal tube might be indicated.

If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration.

A specific narcotic antagonist, such as naloxone, should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate

countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use. The patient should be carefully observed for 24 hours. Body warmth and adequate fluid intake should be maintained.

If hypotension occurs, and is severe or persists, the possibility of hypovolaemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning of the patient to improve venous return to the heart should be considered and if necessary, a vasopressor and/or naloxone (post-operatively only) may be administered.

Bradycardia may be treated by administering atropine or a neuromuscular blocking agent with vagolytic activity such as pancuronium.

Other supportive measures should also be employed as needed.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Mechanism of action

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

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

5.2 Pharmacokinetic properties

Absorption

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

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

As with longer acting narcotic analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO_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 DBL Fentanyl Injection is noted 5 to 15 minutes following injection.

(See also section **4.4 Special warnings and precautions for use - Respiratory depression**.)

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

Distribution

After intravenous injection, serum concentrations of fentanyl have been shown to decrease rapidly to about 20% of peak concentrations within 5 minutes of injection, followed by a slower decrease over the next 10 to 20 minutes to stabilise at a low concentration for 2 hours after injection. The short duration of action is probably due to the redistribution with up to 70% being bound to plasma proteins.

Metabolism

Fentanyl is metabolised primarily in the liver, to inactive metabolites norfentanyl, 4-N-anilinopiperidine and propionic acid. In humans, *in vitro* experiments have demonstrated that fentanyl is metabolised mainly by cytochrome P450 3A4 (CYP 3A4) to norfentanyl via oxidative N-dealkylation.

Excretion

About 20% of the drug is excreted in the urine within 8 hours with up to 90% as the metabolites and 10% as unchanged fentanyl.

5.3 Preclinical safety data

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

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Sodium chloride
Sodium hydroxide
Water for injection
The solution does not contain any preservative.

6.2 Incompatibilities

Fentanyl is incompatible with thiopentone sodium and methohexitone sodium.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Package quantities

Strength	Packs
100 micrograms per 2 mL	5 x 2 mL glass ampoules
500 micrograms per 10 mL	5 x 10 mL glass ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Class B3 Controlled Drug

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

18th October 1990

10. DATE OF REVISION OF THE TEXT

10th August 2020

Summary table of changes

Section changed	Summary of new information
Boxed warnings	Update according to Australian PI (opioid reforms process undertaken by TGA): Include the required boxed warning that applies to all opioids.
3	a) Addition of "solution for injection" as dosage form. b) Alignment of product description (colour) with Australian PI.
4.1	Inclusion of the following information from Australian PI: - The state of neurolept analgesia may be converted to neurolept anaesthesia by the concurrent administration of 65% nitrous oxide in oxygen.
4.2	Inclusion of the following information from Australian PI: - When used in conjunction with other CNS depressants, as low as 25 to 33% of the usual dose is recommended. - Use in elderly patients. - Use in renal impairment and hepatic impairment patients.

Section changed	Summary of new information
4.3	a) Update according to Australian PI (opioid reforms process undertaken by TGA): - Include a contraindication for use in patients with severe respiratory disease, acute respiratory disease and respiratory depression - include a contraindication for use in chronic non-cancer pain. b) Addition of “increased intracranial” as contraindication for alignment with Australian PI. c) Deletion of “severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics” for alignment with Australian PI. d) Wordings and format have been revised for alignment with Australian PI.
4.4	a) Update according to Australian PI (opioid reforms process undertaken by TGA): Inclusion of the required precautions and warning statement that apply to all opioids. b) Inclusion of the following sections for alignment with opioid labels: - Neonatal opioid withdrawal syndrome - Cytochrome P450 3A4 Interactions - Severe cardiovascular depression c) Rearrangement of Section 4.4 in descending order (from most important to least important). d) Inclusion of the following statement for alignment with DBL Pethidine HCl Injection and DBL Morphine Sulfate Injection New Zealand Datasheet. - Therapy should only be initiated by a specialist with experience in chronic pain management and in accordance with guidelines approved by the New Zealand Medical Association. e) Deletion of precautionary statement for “Head Injuries and Increased Intracranial Pressure” for alignment with Australian PI. f) Inclusion of the following information in “Life-threatening respiratory depression” from Australian PI: - It has been reported that diminished sensitivity to CO2 stimulation may persist longer than depression of respiratory rate. This dose related effect of respiratory depression peaks between 5 and 15 minutes after injection, but seldom lasts longer than 30 minutes. - The effect on respiratory depression persists longer than the measured analgesic effect, and care should be taken, with the total opioid dose considered when fentanyl is given post-operatively. The recommended dose may be as low as quarter of that normally prescribed.

Section changed	Summary of new information
	g) Addition of following sub-sections for alignment with Australian PI: - Conditions which require dose reduction - Management of complications - Supervision during use - Combination with neuroleptics - Fentanyl as a supplement for anaesthesia - Effects on laboratory tests h) Deletion of the following information for alignment with Australian PI: - 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. - Sub-section of "Use in the Elderly or Debilitated Patients". i) Cardiac arrhythmias: Alignment with Australian PI. j): Replacement of "Muscle Rigidity" with "Rate of injection" for alignment with Australian PI.
4.5	a) Addition of DDI for Cytochrome P450 3A4 Inhibitors and Inducers. b) Other revisions are made for alignment with Australian PI, updates in boxed warnings and sections 4.4.
4.6	a) Addition neonatal opioid withdrawal syndrome information. b) Inclusion of definition of Australian pregnancy category C. c) Inclusion of "Effects on fertility" sub-section.
4.7	Revision is made for alignment with Australian PI.
4.8	a) Addition of "elevated blood pressure" and "spasm of the sphincter of Oddi" from Australian PI. b) Addition of the following AE from Australian PI: - Less frequently, cardiac arrhythmias, post-operative mental depression, paradoxical CNS excitation or delirium may occur. Motor stimulation and bronchospasm may occur with high doses of fentanyl. Miosis or seizures may occur. c) Other editorial revisions are made for alignment with Australian PI.
4.9	a) Addition of information for treatment of hypotension and bradycardia from Australian PI. b) Addition of contact for advice on the management of overdose.
5.2	a) Metabolism: Addition of "to inactive metabolites norfentanyl, 4-N-anilinopiperidine and propionic acid" in the first sentence from Australian PI.

Section changed	Summary of new information
	b) Addition of information for “Distribution” and “Excretion” from Australian PI.
5.3	Addition of “Genotoxicity” and “Carcinogenicity”.
All	Minor editorial changes.