

DBL™ Fentanyl Injection

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, tranquillisers, or other 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. NAME OF THE MEDICINE

Fentanyl citrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Fentanyl Injection is a sterile solution of fentanyl citrate and sodium chloride in Water for Injections. It is presented in ampoules and containing 2 mL or 10 mL of a 50 micrograms per mL solution of fentanyl present as fentanyl citrate. The solution does not contain any preservative. The pH of the solution is adjusted with sodium hydroxide or hydrochloric acid to 5.0 to 7.5, if necessary.

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

3. PHARMACEUTICAL FORM

DBL Fentanyl Injection is a clear, colourless solution for injection containing fentanyl citrate equivalent to fentanyl 50 micrograms per mL.

Fentanyl citrate is a white or almost white powder, soluble in water, freely soluble in methanol, sparingly soluble in alcohol.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

DBL Fentanyl Injection is indicated for analgesic action of short duration during premedication, induction and maintenance of anaesthesia and in the immediate post-operative periods. It may be used as an opioid analgesic supplement in general and regional anaesthesia.

Fentanyl may be used in combination with neuroleptic agents such as droperidol 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, bodyweight, physical status, underlying pathological condition, use of other medicines, type of anaesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

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.

Adult dosage

1. Premedication: (To be appropriately modified in the elderly, debilitated and those who have received other CNS depressant drugs). 50 to 100 micrograms (1 to 2 mL) fentanyl administered intramuscularly 30 to 60 minutes prior to surgery (modified for high-risk patients).

2. Adjunct to general anaesthesia:

Induction: 50 to 100 micrograms (1 to 2 mL) administered intravenously and repeated at 2 to 3 minute intervals, until the desired effect is achieved. A reduced dose of 25 to

50 micrograms (0.5 to 1 mL) is recommended for elderly or high-risk patients.

Maintenance: 25 to 50 micrograms (0.5 to 1 mL) should 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) administered intramuscularly or by slow intravenous injection when analgesia is required.
- 4. Post-operatively (Recovery room):** 50 to 100 micrograms (1 to 2 mL) administered intramuscularly repeated in 1 to 2 hours as needed.

Children's dosage

Do not use DBL Fentanyl Injection in children less than 2 years of age. For children aged between 2 to 12 years, fentanyl may be used for induction and maintenance at a reduced level as low as 20 to 30 micrograms (0.4 to 0.6 mL) per 10 kg bodyweight (see section **4.4 Special Warnings and Precautions for Use – Paediatric Use**).

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 Adjustments

Renal/hepatic impairment

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

Instructions for Use

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 – Respiratory Depression (Hypoventilation)**).

DBL Fentanyl Injection is administered by intramuscular or intravenous injection only.

The dosage of fentanyl should be given in the smallest effective dose and as infrequently as possible to minimise the development of tolerance and physical dependence.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Handling Instructions

Wear gloves while 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.

4.3 Contraindications

Fentanyl is contraindicated in patients with a known hypersensitivity or intolerance to fentanyl or other opioid analgesics.

It should not be administered to patients who fall into the following categories:

- Children less than 2 years old, because the safety of fentanyl in this age group has not been established (see section **4.4 Special Warnings and Precautions for Use – Paediatric Use**).
- Patients with severe respiratory disease, acute respiratory disease, respiratory depression, patients who may be particularly susceptible to respiratory depression such as comatose patients who may have head injury, brain tumour or increased intracranial pressure (see section **4.4 Special Warnings and Precautions for Use – Respiratory Depression (Hypoventilation) and Head Injuries and 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 Interactions**).
- 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. Abuse or intentional misuse of fentanyl may result in overdose and/or death. 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**). 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 **4.2 Dose and Method of Administration – Handling Instructions** and **6.4 Special Precautions for Storage**).

Respiratory Depression (Hypoventilation)

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 CO₂, thus affecting respiration post-operatively. Therefore, patients should remain under appropriate surveillance.

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.

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.

Respiratory depression caused by opioid analgesics is dose related and can be reversed by opioid antagonists, such as naloxone, but additional doses of naloxone may be necessary

because the respiratory depression may last longer than the duration of action of the opioid antagonist. Consult individual prescribing information (for naloxone) before employing opioid antagonists. Appropriate surveillance should be maintained for the duration of opioid antagonist action. The use of an opioid antagonist will also reverse analgesia. See also discussion of opioid antagonists in section **4.9 Overdose**.

Respiratory depression is more likely to occur with intravenous administration if a dose is given too rapidly and it rarely occurs with intramuscular administration.

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

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.

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.

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

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**).

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.

Head Injuries and Increased Intracranial Pressure

Fentanyl is contraindicated in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumour (see section **4.3 Contraindications**). 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.

Neonatal Withdrawal Syndrome

There is a risk that newborn infants will experience neonatal withdrawal syndrome following prolonged use of opioids, including fentanyl, during pregnancy (see section **4.6 Fertility, Pregnancy and Lactation – Use in Pregnancy**).

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.

Severe Cardiovascular Depression

Fentanyl 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, fentanyl 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 fentanyl.

Cardiac Effects

Fentanyl should be used with caution in patients with cardiac arrhythmias, including bradyarrhythmias (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.

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

Muscle Rigidity

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. 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) and the use of muscle relaxants.

Non-epileptic (myo)clonic movements can occur.

Conditions which Require Dose Reduction

Dosage reduction is desirable in patients suffering from hypothyroidism, chronic hepatic disease, pulmonary disease, decreased respiratory reserve and alcoholism. Such patients also require prolonged post-operative monitoring.

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.

Serotonin Syndrome

Caution is advised when fentanyl is co-administered with drugs that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake 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, diaphoresis), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity, tremor, myoclonus), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

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

Cytochrome P450 3A4 Interactions

Concomitant use of fentanyl 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 **Respiratory Depression (Hypoventilation)**), particularly when an inhibitor is added after a stable dose of fentanyl is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in fentanyl-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using fentanyl with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in fentanyl-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of fentanyl (see sections **4.2 Dose and Method of Administration** and **4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Concomitant use of fentanyl with CYP3A4 inducers, or discontinuation of a CYP3A4 inhibitor, could result in lower than expected fentanyl plasma concentrations and decrease efficacy. When using fentanyl 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, tranquillisers, 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.

General

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

Vital signs should be monitored carefully.

Obese Patients

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

Use in Hepatic/Renal Impairment

Fentanyl should be administered with caution to patients with liver or kidney dysfunction. Patients with kidney dysfunction should be observed carefully for signs of fentanyl toxicity. Such patients also require prolonged post-operative monitoring.

Use in the Elderly or Debilitated Patient

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

Safe use of DBL Fentanyl Injection in children younger than 2 years 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, tranquillisers, 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. This is particularly important after surgery, because profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the post-operative period. Administration of a CNS depressant, such as benzodiazepine or related drugs, during this period may disproportionately increase the risk of respiratory depression (see section **4.4 Special Warnings and Precautions for Use**). Post-operative opioids, including fentanyl and other CNS depressant drugs should be given initially in reduced doses, as low as $\frac{1}{4}$ to $\frac{1}{3}$ of doses usually recommended. As with other opioids, the respiratory depressant effect of fentanyl persists longer than the measured analgesic effect. The total dose of all opioid analgesics should be taken into account before giving opioid analgesics during recovery from anaesthesia.

For etomidate, the total plasma clearance is decreased by 2.7-fold and volume of distribution is decreased by a factor 2.4 while half-life increased by 1.2 times when administered with fentanyl. Simultaneous administration of fentanyl and intravenous midazolam results in an increase in the terminal plasma half-life and a reduction in the plasma clearance of midazolam. When these drugs are co-administered with fentanyl their dose may need to be reduced.

Benzodiazepines and other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to the additive pharmacologic effect, the concomitant use of fentanyl with CNS depressant medicines 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	CNS depressant medicines such as benzodiazepines and other sedatives/hypnotics, gabapentinoids, cannabis, anxiolytics, tricyclic antidepressants, muscle relaxants, centrally-active anti-emetics, general anaesthetics, tranquillisers, beta-blockers, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, or alcohol.

Cytochrome P450 3A4 Inhibitors and Inducers:

CYP3A4 Inhibitors	
Clinical Impact	<p>The concomitant use of fentanyl 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 fentanyl is achieved.</p> <p>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.</p>
Intervention	<p>If concomitant use is necessary, consider dosage reduction of fentanyl until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals.</p> <p>If a CYP3A4 inhibitor is discontinued, consider adjusting the fentanyl dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.</p>
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice.

CYP3A4 Inducers	
Clinical Impact	<p>The concomitant use of fentanyl 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).</p> <p>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.</p>
Intervention	If concomitant use is necessary, consider adjusting the fentanyl dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider fentanyl dosage reduction and monitor for signs of respiratory depression.
Examples	Rifampin, carbamazepine, phenytoin.

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 Pharmacological Properties**) fentanyl can also alter respiration. Therefore, when fentanyl is used to supplement these forms of anaesthesia, the anaesthetist should be familiar with the special properties of each drug (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.

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: The concomitant use of opioids including fentanyl with a serotonergic agent, such as a SSRI, SNRI or a MAOI, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see sections **4.4 Special Warnings and Precautions for Use** and **4.3 Contraindications**).

Neuroleptics: The combination of fentanyl with a neuroleptic such as droperidol may cause hypotension (see section **4.4 Special Warnings and Precautions for Use**). If this occurs, the possibility of hypovolaemia should also be considered. Care should be exercised in moving and positioning patients because of the possibility of orthostatic hypotension. If fluid therapy, together with other countermeasures, does not correct hypotension, it may be necessary to administer a pressor agent other than adrenaline. Adrenaline may paradoxically decrease 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. Neuroleptics can induce extrapyramidal symptoms that can be controlled with anti-Parkinson agents.

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

Impairment of fertility has been observed in female rats given fentanyl 160 micrograms/kg/day subcutaneously (no effect dose not established) or 400 micrograms/kg/day intravenously (no effect dose 100 micrograms/kg/day). Fertility in male rats was unaffected at 400 micrograms/kg/day intravenously.

Use in Pregnancy

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 drug 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 (foetal blood concentrations about 40% of maternal blood concentrations) and the foetal respiratory centre is particularly sensitive to opioids which may suppress spontaneous respiration in the newborn. If fentanyl is administered during childbirth, an assisted ventilation equipment must be immediately available for the mother and infant. An opioid antagonist must always be available for the baby.

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

Neonatal withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhoea, and failure to gain weight. The onset, duration, and severity of neonatal 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 withdrawal syndrome and manage accordingly.

In pregnant rats, fentanyl is embryocidal as evidenced by increased resorptions at doses of 30 micrograms/kg/day intravenously or 160 micrograms/kg/day or greater subcutaneously. Intravenous administration to rats at 30 micrograms/kg/day during organogenesis was

associated with prolonged delivery time and increased postnatal mortality of offspring. There was no effect on embryofetal development when rats received subcutaneous fentanyl at doses up to 500 micrograms/kg/day throughout gestation, and no evidence of teratogenicity in rabbits administered fentanyl at intravenous doses up to 400 micrograms/kg/day during organogenesis. The potential risk for humans is unknown.

Use in Lactation

Fentanyl is excreted into human breast milk and may cause sedation or respiratory depression in the newborn/infant. Therefore, breast-feeding or use of expressed breast milk is not recommended for 24 hours following administration of fentanyl. The risk/benefit of breast-feeding following fentanyl administration should be considered.

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. Patients should only drive or operate a machine if sufficient time has elapsed (at least 24 hours) after the administration of fentanyl.

4.8 Adverse Effects (Undesirable Effects)

Clinical Data

The safety of fentanyl was evaluated in 376 subjects who participated in 20 clinical trials evaluating fentanyl used as an anaesthetic. These subjects were administered at least one dose of fentanyl injection and provided safety data. Adverse drug reactions (ADRs), as identified by the investigator, reported for $\geq 1\%$ of fentanyl injection-treated subjects in these studies are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by $\geq 1\%$ of Fentanyl Injection-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 post-operative	1.9
Anaesthetic complication neurological	1.1

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

Table 2. Adverse Drug Reactions Reported by $< 1\%$ of Fentanyl Injection-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	

<p>Hyperventilation</p> <p>General Disorders and Administration Site Conditions</p> <p>Chills</p> <p>Hypothermia</p> <p>Injury, Poisoning and Procedural Complications</p> <p>Agitation postoperative</p> <p>Procedural complication</p> <p>Airway complication of anaesthesia</p>
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Post-marketing Data

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

- Very common: $\geq 1/10$
- Common: $\geq 1/100$ and $< 1/10$
- Uncommon: $\geq 1/1,000$ and $< 1/100$
- Rare: $\geq 1/10,000$, $< 1/1,000$
- Very rare: $< 1/10,000$, including isolated reports

Table 3: Adverse Drug Reactions Identified During Post-marketing Experience with Fentanyl Injection by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders	
Very rare	Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Nervous System Disorders	
Very rare	Convulsions, Loss of consciousness, Myoclonus
Cardiac Disorders	
Very rare	Cardiac arrest (also see section 4.4 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

The major adverse reactions associated with fentanyl are respiratory depression, apnoea, muscle rigidity, 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.

4.9 Overdose

Signs and Symptoms

The manifestations of DBL Fentanyl Injection overdosage are an extension of its pharmacological actions. In sufficient overdosage, fentanyl would produce narcosis, which may be preceded by marked skeletal muscle rigidity. Respiratory depression, which can vary in severity from bradypnoea to apnoea, may occur. This may be accompanied by cyanosis, followed by a fall in body temperature, circulatory collapse, coma and death.

Treatment

Respiration may need to be assisted or controlled and an adequate airway be maintained. An opioid antagonist such as naloxone should be available to manage respiratory depression. However, it should be remembered that the duration of respiratory depression may be longer than the duration of action of the opioid antagonist and other more immediate and supportive treatment should be initiated.

If respiratory depression is associated with muscle rigidity, it may be necessary to facilitate assisted or controlled respiration with the use of a neuromuscular blocking agent. If hypotension occurs and is possibly associated with hypovolaemia, appropriate fluid therapy should be used.

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

Hypotension may be treated by administration of 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.

Other supportive measures should also be employed as needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

Fentanyl is a synthetic opioid analgesic related to the phenylpiperidines such as morphine. As an analgesic it is estimated to be about 80 times more potent than morphine. As with morphine and pethidine in equianalgesic doses, fentanyl produces respiratory depression but there is a quicker return to normal respiration in healthy individuals.

Fentanyl unlike other phenylpiperidines rarely produces histamine release and exhibits little hypnotic activity.

Clinical Trials

No data available.

5.2 Pharmacokinetic Properties

Absorption

Following parenteral administration via intravenous or intramuscular injection the action of fentanyl is rapid. Peak analgesic effect occurs within several minutes and has a duration of 30 to 60 minutes following a single dose of up to 100 micrograms given intravenously. Respiratory depressant effects last longer than analgesia.

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, mainly in the liver, to inactive metabolites norfentanyl, 4-N-anilinopiperidine and propionic acid. *In vitro* data show fentanyl is metabolised to norfentanyl mainly by CYP3A4.

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

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Hydrochloric acid

Sodium chloride

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Fentanyl is incompatible with thiopental sodium and methohexitone sodium.

6.3 Shelf Life

Refer to Outer Carton.

6.4 Special Precautions for Storage

Store below 25°C. Protect from light.

6.5 Nature and Contents of Container

DBL Fentanyl Injection is available in the following presentations in 5 ampoule (clear glass) pack sizes:

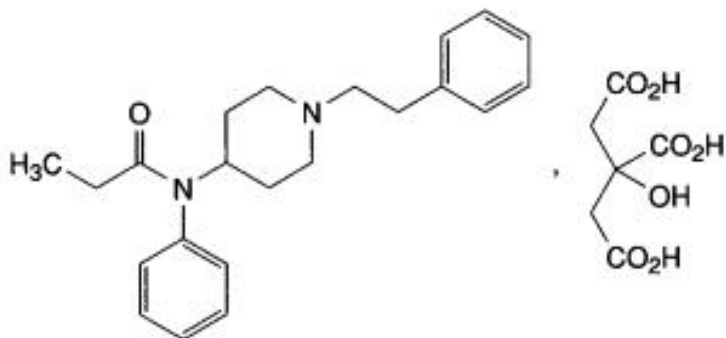
- 100 micrograms per 2 mL
- 500 micrograms per 10 mL

Not all presentations may be available locally.

6.6 Physicochemical Properties

Chemical Structure

The chemical formula of fentanyl citrate is $C_{22}H_{28}N_2O \cdot C_6H_8O_7$ and its molecular weight is 528.6. The chemical structure of fentanyl citrate is shown below:



CAS Number

990-73-8

7. NAME AND ADDRESS OF PRODUCT OWNER

Hospira Australia Pty Ltd
1 Lexia Place
Mulgrave VIC 3170
Australia

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