AUSTRALIAN PRODUCT INFORMATION – SUBLIMAZE (FENTANYL CITRATE) INJECTION

WARNINGS

Limitations of use
Because of the risks associated with the use of opioids, SUBLIMAZE 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
SUBLIMAZE 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 SUBLIMAZE. 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 benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis 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 SUBLIMAZE.

1 NAME OF THE MEDICINE

Fentanyl citrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SUBLIMAZE injection contains fentanyl 50 micrograms per mL (as fentanyl citrate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

SUBLIMAZE solution for injection is a clear colourless solution with a pH 3.8-7.5.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SUBLIMAZE 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 an opioid analgesic supplement in general and regional anaesthesia;
- administration with a neuroleptic such as droperidol injection as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia.

4.2 DOSE AND METHOD OF ADMINISTRATION

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 drugs, type of anaesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual dosage in adults

Premedication (To be appropriately modified in the elderly, debilitated and those who have received other depressant drugs)

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

Adjunct to general anaesthesia

Induction - 50 to 100micrograms (1 to 2mL) 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 50micrograms (0.5 to 1mL) is recommended in elderly and poor-risk patients.

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

Adjunct to regional anaesthesia

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

Post-operatively – (Recovery room)

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

Special Populations

Elderly and debilitated patients

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

Renal Impairment

Refer to Section 4.4 Special Warnings and Precautions for Use – Use in Renal Impairment

Paediatrics

For induction and maintenance in children 2-12 years of age, a reduced dose as low as 20 to 30 micrograms (0.4 to 0.6mL) per 10kg is recommended. (See *Section 4.4 Special Warnings and Precautions for Use of SUBLIMAZE with other CNS depressants and in patients with altered response.*)

Instructions for Use and Handling

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)*).

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

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

SUBLIMAZE should not be administered to children two years of age or younger, because safe conditions for use have not been established. (See *Section 4.4 Special Warnings and Precautions for Use – Paediatric use*).

SUBLIMAZE should not be administered to patients suffering from bronchial asthma. As for any opioid analgesic, it should not be used in patients with severe respiratory disease, acute respiratory disease and who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumour (see *Section 4.4 Special Warnings and Precautions for Use*). Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

There is no evidence that fentanyl is potentiated by MAO inhibitors, but since such potentiation is found with other opioid analgesics, the use of SUBLIMAZE in patients who have received MAO inhibitors within 14 days is not recommended. (See *Section 4.4 Special Warnings and Precautions for Use* and *Section 4.5 Interactions with Other Medicines and Other Forms of Interactions*).

SUBLIMAZE may cause thoracic muscle rigidity upon intravenous administration. Therefore, the need for reversal with muscle relaxants contraindicates its use in patients with a history of myasthenia gravis.

SUBLIMAZE is contraindicated for use in chronic (long-term) non-cancer pain (CNCP).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hazardous and harmful use

SUBLIMAZE contains the opioid fentanyl and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed SUBLIMAZE 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 SUBLIMAZE.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Abuse or intentional misuse of SUBLIMAZE 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* and section *6.6 Special precautions for disposal*). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share SUBLIMAZE with anyone else.

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 CO_2, thus affecting respiration post-operatively. Therefore, patients should remain under appropriate surveillance.

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of SUBLIMAZE 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 renal and hepatic impairment (see also subsections *'Use in renal impairment'* and *'Use in the elderly or debilitated patients'*). 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 risk can 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 (naloxone) before employing opioid 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 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.

Risk from concomitant use of benzodiazepines or other central nervous system (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 SUBLIMAZE with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribed SUBLIMAZE concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking SUBLIMAZE.

Tolerance and Opioid use disorder (abuse and dependence)

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.

Repeated use of opioids may lead to Opioid use disorder (OUD). Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients

with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

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 SUBLIMAZE 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*).

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)*.

Accidental ingestion/exposure

Accidental ingestion or exposure of SUBLIMAZE, 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 SUBLIMAZE (see *Section 6.4 Special precautions for storage* and *Section 6.6 Special precautions for disposal*).

Hyperalgesia

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

Ceasing opioids

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

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

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

Muscle rigidity

SUBLIMAZE may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection and its incidence can be reduced by a slow intravenous injection (ordinarily sufficient for lower doses), premedication with benzodiazepines and the use of muscle relaxants.

Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

Non-epileptic (myo)clonic movements can occur.

Head injuries and increased intracranial pressure

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

The use of rapid bolus injections of opioids should be avoided in patients with compromised intracerebral compliance; in such patients the transient decrease in the mean arterial pressure has occasionally been accompanied by a short-lasting reduction of the cerebral perfusion pressure.

Cardiac effects

SUBLIMAZE may produce bradycardia and possibly cardiac arrest if the patient has received an insufficient amount of anticholinergic, or when SUBLIMAZE is combined with non-vagolytic muscle relaxants. Bradycardia may be treated with atropine. However, SUBLIMAZE should be used with caution in patients with cardiac bradyarrhythmias.

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

Serotonin syndrome

Caution is advised when SUBLIMAZE 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)

and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose.

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, rapid discontinuation of SUBLIMAZE should be considered.

General

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

Vital signs should be monitored carefully.

Obese Patients

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

Use in renal impairment

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

Use in the elderly or debilitated patient

It is recommended to reduce the dosage of SUBLIMAZE in the elderly and in debilitated patients. Opioids should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism, or impaired hepatic function. Such patients also require prolonged post-operative monitoring.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicines on SUBLIMAZE

Central Nervous System (CNS) depressants: Drugs, such as, barbiturates, benzodiazepines or related drugs, neuroleptics, opioids, alcohol, antihistamines, cannabis, centrally-active antiemetics, gabapentinoids (gabapentin and pregabalin), general anaesthetics, hypnotics, sedatives, tricyclic antidepressants and other CNS depressants will have additive or potentiating effects with SUBLIMAZE. When patients have received such CNS depressant drugs, the dose of SUBLIMAZE required may be less than usual. Concomitant use with SUBLIMAZE in spontaneous

breathing patients may increase the risk of respiratory depression, profound sedation, coma and death (see Section 4.4 Special Warnings and Precautions for Use). Post-operative opioids including SUBLIMAZE and other depressants should be given initially in reduced doses, as low as 1/4 to 1/3 of those usually recommended. As with other opioids, the respiratory depressant effect of SUBLIMAZE persists longer than the measured analgesic effect. The total dose of all opioid analgesics should be considered before ordering opioid analgesics during recovery from anaesthesia.

Conduction anaesthesia: Certain forms of conduction anaesthesia, such as spinal anaesthesia and some peridural anaesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see *Section 5 Pharmacological Properties*) SUBLIMAZE can also alter respiration. Therefore, when SUBLIMAZE 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.

Neuroleptics: If SUBLIMAZE is administered with a neuroleptic, the user should be familiar with the special properties of each drug, particularly the difference in duration of action. When SUBLIMAZE is used with a neuroleptic such as droperidol, blood pressure may be altered and hypotension can occur. If this occurs, the possibility of hypovolaemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient improves venous return to the heart and should be considered when operative conditions permit. Care should be exercised in moving and positioning patients because of the possibility of orthostatic hypotension. If volume expansion with fluids together with other counter measures do not correct hypotension, the administration of pressor agents other than adrenaline should be considered. Because of the alpha-adrenergic blocking action of droperidol, adrenaline may paradoxically decrease the blood pressure in patients treated with droperidol. Pulmonary arterial pressure may also be decreased. This should be considered when interpreting pulmonary arterial pressure measurements as it might determine the final management of the patient. When droperidol is used with SUBLIMAZE and the EEG is used for post-operative monitoring, it may be found that the EEG pattern returns to normal slowly. Neuroleptics can induce extrapyramidal symptoms that can be controlled with anti-Parkinson agents.

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

Serotonergic Drugs: Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Cytochrome P450 3A4 (CYP 3A4) inhibitors: Fentanyl, a high clearance drug, is rapidly and extensively metabolised in the liver via CYP 3A4 enzyme and has a high hepatic extraction ratio. Therefore, hepatic blood flow rather than enzyme activity is the main determinant of fentanyl clearance. Theoretically, co administration of CYP 3A4 enzyme inhibitors should cause only a small increase in plasma concentrations of fentanyl. When SUBLIMAZE is used, the concomitant

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

Ritonavir is a highly potent inhibitor of CYP 3A4. Oral administration of ritonavir in healthy volunteers, at 200-300mg t.d.s. for 2 days, significantly inhibits the metabolism of fentanyl at a dose of 5 micrograms/kg, given as a single intravenous infusion over 2 minutes. Ritonavir decreased the clearance of fentanyl by 67%, prolonged the half-life of fentanyl by 100% and increased AUC (0 to infinity) by 174%. Ritonavir had no significant effect on the steady state volume of distribution of fentanyl. When fentanyl is given continuously with ritonavir, the dose of fentanyl should be reduced in order to lower the risk for severe and prolonged respiratory depression. When fentanyl is given as a single dose concomitantly with ritonavir, the duration of respiratory monitoring should be increased and the dose of fentanyl may need to be reduced. Oral administration of itraconazole (another potent inhibitor of CYP 3A4) at 200mg/day for 4 days did not have a statistically significant effect on the pharmacokinetics of fentanyl at a dose of 3micrograms/kg given as a single intravenous infusion over 2 minutes. Co-administration of other potent or less potent CYP3A inhibitors, such as voriconazole or fluconazole, and SUBLIMAZE may also result in an increased and/or prolonged exposure to fentanyl.

There are no data on the *in vivo* interactions between fentanyl and other drugs inhibiting CYP 3A4 (e.g. ketoconazole, erythromycin, diltiazem and cimetidine).

Effects of SUBLIMAZE on other medicines

Following the administration of fentanyl, the dose of other CNS-depressant drugs should be reduced. This is particularly important after surgery, because profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the postoperative period. Administration of a CNS depressant, such as benzodiazepine or related drugs, during this period may disproportionally increase the risk of respiratory depression (see *Section 4.4 Special Warnings and Precautions for Use*).

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy – Pregnancy Category C

There are no adequate data from the use of SUBLIMAZE in pregnant women. The foetal respiratory centre is particularly sensitive to opiates. Intramuscular or intravenous administration during childbirth (including caesarean section) is not recommended because fentanyl crosses the placenta (foetal blood concentrations about 40% of maternal blood concentrations) and may suppress spontaneous respiration in the newborn period. If fentanyl is administered, assisted ventilation equipment must be immediately available for the mother and infant if required. An opioid antagonist for the child must always be available. Prolonged use of an opioid, including fentanyl, during pregnancy may cause drug dependence in the neonate, leading to neonatal withdrawal syndrome. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

In pregnant rats, fentanyl is embryocidal as evidenced by increased resorptions at doses of 30 micrograms/kg/day intravenously or 160micrograms/kg/day or greater subcutaneously. Intravenous administration to rats at 30micrograms/kg/day during organogenesis was associated with prolonged delivery time and increased postnatal mortality of offspring. There was no effect on embryofoetal development when rats received subcutaneous fentanyl at doses up to 500micrograms/kg/day throughout gestation, and no evidence of teratogenicity in rabbits administered fentanyl at intravenous doses up to 400µg/kg/day during organogenesis. The potential risk for humans is unknown.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

CLINICAL TRIAL DATA

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

Table 1. Adverse Drug Reactions Reported by ≥ 1% of SUBLIMAZE-treated Subjects in 20 Clinical Trials of SUBLIMAZE

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

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

Table 2. Adverse Drug Reactions Reported by < 1% of SUBLIMAZE-treated Subjects in 20 Clinical Trials of SUBLIMAZE

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

Post-marketing Data

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

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

Table 3:	Adverse Drug Reactions Identified During Postmarketing Experience with SUBLIMAZE 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
Gastrointestinal Disorders	
Unknown	Dysphagia

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

Signs and symptoms

The manifestations of SUBLIMAZE 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 bradyapnoea to apnoea, may occur. This may be accompanied by cyanosis, followed by a fall in body temperature, circulatory collapse, coma and death. Toxic leukoencephalopathy has been observed with fentanyl overdose.

Treatment

In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained. An oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration.

A specific opioid antagonist, such as 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 over dosage of fentanyl may be longer than the duration of opioid antagonist action. Consult the package insert of the individual opioid antagonists for details about use. The patient should be carefully observed for 24 hours. Body warmth and adequate fluid intake should be maintained. If hypotension occurs, and is severe or persists, the possibility of hypovolaemia should be considered and managed with appropriate parenteral fluid therapy. The use of an opioid antagonist will also reverse analgesia.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

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

Histamine assays and skin wheal testing 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.

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

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

The onset of action of fentanyl is almost immediate when the drug is given intravenously. However, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of analgesic effect is 30 to 60 minutes after a single I.V. dose of up to 100micrograms. Following intramuscular administration, the onset of action is from 7 to 8 minutes and the duration of action is 1 to 2 hours.

As with longer acting opioid analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO_2 stimulation following administration of fentanyl to man:

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. Altered sensitivity to CO_2 stimulation has been demonstrated for up to four hours following a single intravenous dose of 600micrograms (12mL) fentanyl to healthy volunteers. Duration and degree of respiratory depression is dose-related.

The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection. (See *also Section 4.4 Special Warnings and Precautions for Use concerning respiratory depression.*)

Distribution

After intravenous injection, fentanyl plasma concentrations fall rapidly, with sequential distribution half-lives of 1 minute and 18 minutes and a terminal elimination half-life of 475 minutes. Fentanyl has a V_c (volume of distribution of the central compartment) of 13L, and a total V_{dss} (distribution volume at steady-state) of 339L. The total blood binding of fentanyl is about 83% (comprised of plasma protein binding about 43% and red blood cell binding about 40%).

Metabolism

Fentanyl is extensively metabolised by the liver and it has a high hepatic extraction ratio (0.8–1.0). Consequently, the hepatic clearance of fentanyl approaches hepatic blood flow. In humans,

in vitro experiments have demonstrated that fentanyl is metabolised mainly by cytochrome P450 3A4 (CYP 3A4) to norfentanyl via oxidative N-dealkylation.

Elimination

Approximately 75% of the administered dose is excreted in the urine within 72 hours and only 8.4% of the dose recovered in urine is present as unchanged drug.

Special Populations

Paediatrics

Pharmacokinetic information in children is limited and obtained from different sources. CYP3A4 activity is very low at birth but increases after birth to reach 30-40% of adult levels at 1 month of age. The clearance and volume of distribution adjusted for body weight are higher in infants and children than in adults after iv administration of fentanyl. The terminal elimination half-life is longer in newborn infants.

Table 4:

	Cl (mL/kg/min)	V_{ss} (L/kg)	$t_{½}$ beta (hr)
Infants Post-natal age 1-26 days; n= 72	3.4–58.7	1.3–30.3	1.3–15.9
Infants Post-natal age 48-71 days; n= 3	21.9–32.3	6.0–9.5	3.1–15.5
Children 3.17+0.68 years; n= 6	11.5±4.19	3.06±1.02	4.1±1.3
Adolescents 12±1.73 years; n= 3	7.05±1.24	1.92±1.04	3.5±1.2
Data for infants are given as range of individual values, other data as mean ± SD			

After intravenous administration, the plasma protein binding of fentanyl in newborn infants is lower than in adults. It is higher in pre-term neonates (77%) than in those born at term (approximately 62%).

Adult Patients with Burns

An increase in median clearance of 45% together with a larger volume of distribution results in lower fentanyl plasma concentrations. This may require an increased dose of fentanyl.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fentanyl showed no evidence of genotoxic potential in assays for gene mutations (Ames reverse mutation test, mouse lymphoma thymidine kinase assay), chromosomal damage (Chinese hamster ovary cells, mouse micronucleus test) and other genotoxic effects (unscheduled DNA

synthesis in rat hepatocytes, mammalian cell transformation assay). The genotoxic potential of fentanyl is considered to be low.

Carcinogenicity

In a two-year carcinogenicity study in rats, fentanyl was not associated with an increased incidence of tumours at subcutaneous doses up to 33micrograms/kg/day in males or 100micrograms/kg/day in females, which were the respective maximum tolerated doses.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride

Water for injection

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

SUBLIMAZE is supplied in clear glass ampoules which contain:

- 100micrograms/2mL of fentanyl, in cartons of 10 ampoules.
- 500micrograms/10mL of fentanyl, in cartons of 5 ampoules (for HOSPITAL USE ONLY).

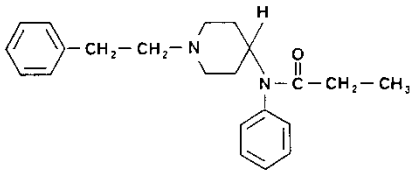
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Fentanyl citrate is a 4-anilinopiperidine derivative.



[dihydro citrate]

N-(1-phenethyl-4-piperidyl) propionanilide dihydrogen citrate

$C_{22}H_{28}N_2O,C_6H_8O_7$ MW: 528.6

CAS number

CAS 438-38-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Controlled Drug (Schedule 8)

8 SPONSOR

PIRAMAL CRITICAL CARE PTY LIMITED
Level 9, Tower A, The Zenith,
821 Pacific Highway,
Chatswood,
NSW, 2067,
Australia
Email: Medical.Information@piramal.com
Toll free number: 1800413707
Website: www.piramalcriticalcare.com

9 DATE OF FIRST APPROVAL

7 March 1994

10 DATE OF REVISION

18-Sep-2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8.	Addition of Dysphagia under Gastrointestinal disorders.
8.	Change in Piramal`s Australian entity address.