SUBLIMAZE®

fentanyl citrate

DATA SHEET

1. PRODUCT NAME

SUBLIMAZE® fentanyl 50 micrograms/mL injection

2. QUALITATIVE AND QUANTITATTIVE COMPOSITION

Each 1 mL of solution contains 78.5 micrograms fentanyl citrate equivalent to 50 micrograms fentanyl base.

Excipient(s) with known effect:

Sodium 3.5 mg/mL

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Dose and method of administration

Dose

Dosage should be individualised. Some of the factors to be considered in determining the dose are: age, body weight, physical status, underlying pathological condition, use of other medicines, type of anaesthesia to be used, and the surgical procedure involved.

Usual dosage in adults

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

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

surgery.

2. **Adjunct to general anaesthesia**

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

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

3. **Adjunct to regional anaesthesia**

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

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

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

Special Populations

Elderly and debilitated patients

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

Obese Patients

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

Renal Impairment

In patients with renal impairment, reduced dosing of SUBLIMAZE should be considered and these patients should be observed carefully for signs of fentanyl toxicity (see **Pharmacokinetic properties**).

Paediatric Populations

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

Method of administration

Precautions to be taken before handling or administering the medicine:

Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway (see **Special warnings and precautions for use**).

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

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

For instructions on dilution of the medicine before administration, see **Special precautions for disposal and other handling**.

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 **Special warnings and precautions for use – Paediatric use**)
- SUBLIMAZE should not be administered to patients suffering from bronchial asthma.
- 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.
- 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 **Interactions with other medicines and other forms of interaction**).

4.4 Special warnings and precautions for use

Drug dependence and potential for abuse

SUBLIMAZE can produce drug dependence of the morphine type and therefore has the potential for being abused. SUBLIMAZE MAY BE HABIT FORMING.

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

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Therefore, it is possible that a higher dose of SUBLIMAZE may be needed to produce the same result.

Physical dependence may result in acute withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of opioids.

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

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).

Withdrawal syndrome

Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy, which may manifest by the occurrence of the following side effects: nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating.

Neonatal withdrawal syndrome

If women take opioids chronically during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome (see ***Use in Pregnancy***).

Hypoventilation (respiratory depression)

Profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the post-operative period. Hyperventilation during anaesthesia may alter the patient's responses to CO_2, thus affecting respiration post-operatively. Therefore, patients should remain under appropriate surveillance.

SUBLIMAZE should be used with caution in patients with severe impairment of pulmonary function because of the possibility of respiratory depression, e.g. patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, or any patient with potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anaesthesia, this can be managed by assisted or controlled respiration.

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

RESUSCITATIVE EQUIPMENT AND AN OPIOID ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNOEA.

Risk from concomitant use of central nervous system (CNS) depressants, especially benzodiazepines or related drugs

Concomitant use of SUBLIMAZE and CNS depressants especially benzodiazepines or related drugs in spontaneous breathing patients, may increase the risk of profound sedation, respiratory depression, coma and death. If a decision is made to administer SUBLIMAZE concomitantly with a CNS depressant, especially a benzodiazepine or a related drug, the lowest effective dose of both drugs should be administered, for the shortest period of concomitant use. Patients should be carefully monitored for signs and symptoms of respiratory depression and profound sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see **Interactions with other medicines and other forms of interaction**).

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 should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumour. In addition, 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 coadministered 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.

Opioid induced hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid, particularly at high doses or with chronic use, in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalized pain (i.e., less focal), or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioids should be reduced or tapered off, if possible.

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.

Use in the elderly or debilitated patients

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, impaired hepatic or renal 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.

4.5 Interactions with other medicines and other forms of interaction

Effects of other medicines on SUBLIMAZE

Central Nervous System (CNS) depressants

Medicines, such as, CNS depressants, barbiturates, benzodiazepines or related drugs, neuroleptics, opioids, alcohol, general anaestheticsand gabapentinoids (gabapentin and pregabalin), may have additive or potentiating effects with SUBLIMAZE.

When patients have received such CNS depressant medicines, the dose of SUBLIMAZE required may be less than usual. Concomitant use with SUBLIMAZE in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death (See **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 **Mechanism of action**) 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 medicine (particularly with the widely differing durations of actions), the physiological alterations involved and be prepared to manage them in patients selected for these forms of anaesthesia.

Neuroleptics

If 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 countermeasures does not correct hypotension, the administration of pressor agents other than adrenaline should be considered. Because of the alpha-adrenergic blocking action of droperidol, adrenaline may paradoxically decrease the blood pressure in patients treated with droperidol. Pulmonary arterial pressure may also be decreased. This should be considered when interpreting pulmonary arterial pressure measurements as it might determine the final management of the patient.

When droperidol is used with 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 (MAOIs)

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 (CYP3A4) inhibitors

Fentanyl is metabolised mainly via the human cytochrome P450 3A4 enzyme. It is a high clearance medicine, which is rapidly and extensively metabolised. When SUBLIMAZE is used, the concomitant use of a CYP3A4 inhibitor may result in a decrease in fentanyl clearance. With a single-dose SUBLIMAZE administration, the period of risk for 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.

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

Oral administration of itraconazole (another potent inhibitor of CYP 3A4) at 200 mg/day given orally for 4 days did not have a statistically significant effect on the pharmacokinetics of IV fentanyl. Co-administration of other potent or less potent CYP3A inhibitors, such as fluconazole or voriconazole and 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 medicines inhibiting CYP 3A4 (e.g. ketoconazole, erythromycin, diltiazem and cimetidine).

Effects of SUBLIMAZE on other medicines

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

The total plasma clearance and volume of distribution of etomidate is decreased by a factor of 2 to 3 without a change in half-life when administered with fentanyl. Simultaneous administration of SUBLIMAZE and intravenous midazolam results in an increase in the terminal plasma half-life and a reduction in the plasma clearance of midazolam. When these medicines are co-administered with SUBLIMAZE their dose may need to be reduced.

4.6 Fertility, pregnancy and lactation

Use in pregnancy

There are no adequate data from the use of SUBLIMAZE in pregnant women. Fentanyl can cross the placenta in early pregnancy. Studies in animals have shown some reproductive toxicity. The potential risk for humans is unknown.

Some tests on female rats showed reduced fertility as well as embryo mortality. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. There was no evidence of teratogenic effects.

Chronic use of an opioid during pregnancy may cause drug dependence in the neonate, leading to neonatal withdrawal syndrome.

Administration (I.M. or I.V.) during childbirth (including caesarean section) is not recommended because fentanyl crosses the placenta and may suppress spontaneous respiration in the newborn period. If fentanyl is administered, assisted ventilation equipment must be immediately available for the mother and infant if required. An opioid antagonist for the child must always be available.

Breast-feeding

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

The risk/benefit of breast-feeding following SUBLIMAZE administration should be considered.

Fertility

Some tests on female rats showed reduced fertility as well as embryo mortality. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. There was no evidence of teratogenic effects.

4.7 Effects on ability to drive and use machines

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

4.8 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

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

Postmarketing Data

Adverse drug reactions first identified during postmarketing 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 and < 1/1,000
Very rare	< 1/10,000, including isolated reports
Not known	cannot be estimated from available data

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)
Psychiatric disorders	
Not known	Delirium
Nervous System Disorders	
Very rare	Convulsions, Loss of consciousness, Myoclonus
Cardiac Disorders	
Very rare	Cardiac arrest (also see **Special warnings and precautions for use**)
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Respiratory depression (also see **Special warnings and**

	precautions for use)
Skin and Subcutaneous Tissue Disorders	
Very rare	Pruritus
General disorders and administration site conditions	
Not known	Drug withdrawal syndrome (see **Special warnings and precautions for use**)

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 (see **Interactions with other medicines and other forms of interaction**).

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Signs and Symptoms

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

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

Treatment

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

A specific opioid antagonist should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdose of fentanyl may be longer than the duration of opioid antagonist action. Consult the package insert of the individual opioid antagonists for details about use. The patient should be carefully observed for 24 hours. Body warmth and adequate fluid intake should be maintained. If hypotension occurs, and is severe or persists, the possibility of hypovolaemia should be considered and managed with appropriate parenteral fluid therapy.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetic general, opioid anaesthetic, ATC code: N01AH01

Mechanism of action

Fentanyl is a potent opioid analgesic with a rapid onset and short duration of action. The principal

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

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

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

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

5.2 Pharmacokinetic properties

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

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

1. DIMINISHED SENSITIVITY TO CO_2 STIMULATION MAY PERSIST LONGER THAN DEPRESSION OF RESPIRATORY RATE.

   Fentanyl frequently slows the respiratory rate, but this effect is seldom noted for longer than 30 minutes regardless of the dose administered.

2. Altered sensitivity to CO_2 stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 micrograms (12 mL) fentanyl to healthy volunteers.

3. Duration and degree of respiratory depression is dose-related.
4. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection.

(See also **Special warnings and precautions for use** concerning respiratory depression.)

Distribution

After intravenous injection, fentanyl plasma concentrations fall rapidly, with sequential distribution

half-lives of about 1 minute and 18 minutes and a terminal elimination half-life of 475 minutes. Fentanyl has a V_c (volume of distribution of the central compartment) of 13 L, and a total V_{dss} (distribution volume at steady-state) of 339 L. The plasma-protein binding of fentanyl is about 84% (comprised of plasma protein binding about 43% and red blood cell binding about 40%).

Metabolism

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

Elimination

Approximately 75% of the administered dose is excreted in the urine within 24 hours and only 10% of the dose eliminated in urine is present as unchanged drug.

Special Populations

Paediatrics

The plasma protein binding of fentanyl in newborns is approximately 62% which is lower than in adults. The clearance and the volume of distribution are higher in infants and children. This may result in an increased dose requirement for fentanyl.

Renal Impairment

Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see **Dose and method of administration**).

Adult Patients with Burns

An increase in clearance up to 44% together with a larger volume of distribution results in lower Fentanyl plasma concentrations. This may require an increased dose of Fentanyl.

Obese Patients

An increase in clearance of fentanyl is observed with increased body weight. In patients with a BMI>30, clearance of fentanyl increases by approximately 10% per 10 kg increase of the fat free mass (lean body mass).

5.3 Preclinical safety data

Carcinogenicity

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

Genotoxicity

In vitro fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in *in vivo* rodent studies and bacterial assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SUBLIMAZE injection contains:

- sodium chloride
- water for injections.

6.2 Incompatibilities

The injectable solution must not be mixed with other products except those mentioned in **Method of administration**.

6.3 Shelf life

3 years

Diluted solution should be used within 24 hours of preparation.

6.4 Special precautions for storage

Store below 30°C.

Protect from light.

6.5 Nature and contents of container

Colourless glass ampoules (PhEur, USP Type I).

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

500 micrograms/10 mL of fentanyl, in cartons of 5 ampoules

6.6 Special precautions for disposal and other handling

If desired, fentanyl may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with plastic infusion sets.

Wear gloves while opening 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.

7. MEDICINE SCHEDULE

Controlled Drug (B3)

8. SPONSOR

Seed Pharma Pty Ltd

9 Wilmay Avenue, Papatoetoe,

Auckland 2025

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

21 June 2022