

DATA SHEET

NAME OF MEDICINE

SUBLIMAZE® fentanyl 50 micrograms/mL injection

ATC code: N01AH02

PRESENTATION

SUBLIMAZE injection contains fentanyl 50 micrograms/mL (as fentanyl citrate). It is a clear, colourless solution and is available in 2 mL and 10 mL clear glass ampoules.

USES

Actions

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

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

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 narcotic antagonist, e.g. naloxone, produces reversal of respiratory, cardiovascular, miotic, and motor incoordination effects, as well as analgesia, euphoria, and sedation. Rigidity of the diaphragm and intercostal muscles can be eliminated by succinylcholine. Cholinergic effects, e.g. bradycardia, are reversed by atropine.

Pharmacokinetics

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 narcotic analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO₂ stimulation following administration of fentanyl to man:

1. DIMINISHED SENSITIVITY TO CO₂ 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 CO₂ 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 **WARNINGS AND PRECAUTIONS** 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

Pediatrics

The plasma protein binding of Fentanyl in newborns is approximately 62% and 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.

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.

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

DOSAGE AND 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 medicines, type of anaesthesia to be used, and the surgical procedure involved.

The initial dose should be reduced in the elderly and in debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

Vital signs should be monitored routinely.

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.

Usual dosage in children

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 **WARNINGS AND PRECAUTIONS** for use of SUBLIMAZE with other CNS depressants and in patients with altered response.)

Administration

The injectable solution must not be mixed with other products.

CONTRAINDICATIONS

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

SUBLIMAZE should not be administered to children two years of age or younger, because safe conditions for use have not been established. (See **WARNINGS AND PRECAUTIONS – Use in children**) SUBLIMAZE should not be administered to patients suffering from bronchial asthma. As for any narcotic analgesic, it should not be used in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumour. (See **WARNINGS AND PRECAUTIONS**). Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics.

There is no evidence that fentanyl is potentiated by MAO inhibitors, but since such potentiation is found with other narcotic analgesics, the use of SUBLIMAZE in patients who have received MAO inhibitors within 14 days is not recommended. (See **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.

WARNINGS AND PRECAUTIONS

Drug dependence

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.

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 CO₂, 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, narcotics may additionally decrease respiratory drive and increase airway resistance. During anaesthesia, this can be managed by assisted or controlled respiration.

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

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNOEA.

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 benzodiazapines 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.

General

As has been observed with all narcotic 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.

Pregnancy and lactation

Use in pregnancy

Category C.

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.

Administration (I.M. or I.V.) during childbirth (including caesarian section) is not recommended because fentanyl crosses the placenta and because the foetal respiratory centre is particularly sensitive to opiates. If fentanyl is nevertheless administered, an antidote for the child should always be at hand.

Use in lactation

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

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

Effects on 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.

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.

Effects on ability to drive and use machines

Patients should only drive or operate a machine if sufficient time has elapsed after the administration of SUBLIMAZE.

ADVERSE 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 $\geq 1\%$ of SUBLIMAZE-treated subjects in these studies are shown in Table 1.

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

System/Organ Class	SUBLIMAZE
Adverse Reaction	(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

Table 3: Adverse Drug Reactions Identified During Postmarketing Experience with SUBLIMAZE by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders	
<i>Very rare</i>	Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Nervous System Disorders	
<i>Very rare</i>	Convulsions, Loss of consciousness, Myoclonus
Cardiac Disorders	
<i>Very rare</i>	Cardiac arrest (also see PRECAUTIONS)
Respiratory, Thoracic and Mediastinal Disorders	
<i>Very rare</i>	Respiratory depression (also see PRECAUTIONS)
Skin and Subcutaneous Tissue Disorders	
<i>Very Rare</i>	Pruritus

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**).

INTERACTIONS

Effects of other medicines on SUBLIMAZE

Medicines, such as, CNS depressants, barbiturates, benzodiazepines, neuroleptics, narcotics, alcohol and general anaesthetics, will have additive or potentiating effects with SUBLIMAZE.

When patients have received such medicines, the dose of SUBLIMAZE required will be less than usual. Post-operative narcotics 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 narcotics, the respiratory depressant effect of SUBLIMAZE persists longer than the measured analgesic effect. The total dose of all narcotic analgesics should be considered before ordering narcotic analgesics during recovery from 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 **ACTIONS**) 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.

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.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic 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.

Fentanyl is metabolised mainly *via* the human cytochrome P450 3A4 enzyme. It is a high clearance medicine, which is rapidly and extensively metabolised. Oral administration of itraconazole (a 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 fluconazole or voriconazole and SUBLIMAZE may result in an increased exposure to fentanyl.

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

There are no data on the *in vivo* interactions between fentanyl and other medicines inhibiting 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.

The total plasma clearance and volume of distribution of etomidate is decreased by a factor 2 to 3 without a change in half-life 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.

OVERDOSAGE

Signs and Symptoms

The oral LD₅₀ for SUBLIMAZE in rats is 18.0 mg/kg. The intravenous LD₅₀ is 2.3 mg/kg, and the intramuscular LD₅₀ is 1.0 mg/kg in rats. The toxic dose in man is unknown.

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. Cardio-respiratory depression accompanied by cyanosis occurs, followed by a fall in body temperature, circulatory collapse, coma and death.

Treatment

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

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

PHARMACEUTICAL PRECAUTIONS

Shelf Life

5 years when stored below 30°C.

Special Precautions for Storage

Protect from light.

MEDICINE CLASSIFICATION

Controlled Drug (B3)

PACKAGE QUANTITIES

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

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

FURTHER INFORMATION

SUBLIMAZE injection contains sodium chloride and water for injections.

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

NAME AND ADDRESS OF THE SPONSOR

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DATE OF PREPARATION

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