Professional Information for SUBLIMAZE

SCHEDULING STATUS: S6

1. NAME OF THE MEDICINE

SUBLIMAZE® 2 mL solution for injection

SUBLIMAZE® 10 mL solution for injection

SUBLIMAZE should only be used in facilities where immediate access to life support is available.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution contains 0,05 mg (50 µg) fentanyl as fentanyl citrate.

It is a sterile, preservative-free isotonic aqueous solution for intravenous injection.

Sugar free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for intravenous injection.

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUBLIMAZE is indicated:

- for use as an opioid analgesic supplement during intravenous, inhalation or regional anaesthesia.
- as a co-induction anaesthetic for intravenous or inhalation anaesthesia.

4.2 Posology and method of administration

The dosage of SUBLIMAZE should be individualised according to age, body mass, physical status, underlying pathological condition, use of other medicines, and type of surgery and anaesthesia.

The effect of the initial dose should be taken into account in determining supplemental doses.
To avoid bradycardia, a small intravenous dose of an anticholinergic just before induction may be administered.

Use as an analgesic supplement to intravenous or inhalation anaesthesia

Analgesia during anaesthetic induction

1 – 10 µg/kg.

Analgesia during maintenance of anaesthesia

For both balanced anaesthesia and total intravenous anaesthesia (TIVA), dose amounts and the intervals between doses should be adjusted to account for the duration and severity of the surgical procedure.

Bolus administration

0,5 – 10 µg/kg.

Continuous infusion

0,5 – 5 µg/kg/h.

Use as an anaesthetic medicine

When attenuation of the response to surgical stress is especially important, doses of 50 – 100 µg/kg may be administered with oxygen and a muscle relaxant. This technique provides anaesthesia without necessitating the use of additional anaesthetic medicines. In certain cases, doses up to 150 µg/kg may be required to produce this anaesthetic effect. SUBLIMAZE has been used in this

fashion for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated.

Special populations

Use in the elderly and debilitated patients

The 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 the body mass. Obese patients should be dosed based on estimated lean body mass rather than on body mass 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 section 5.2).

Use in children

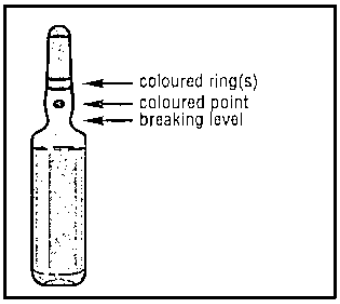
For the induction and maintenance in children aged 2 – 12 years, a reduced dose as low as 1 – 3 µg/kg in divided doses is recommended.

Method of administration

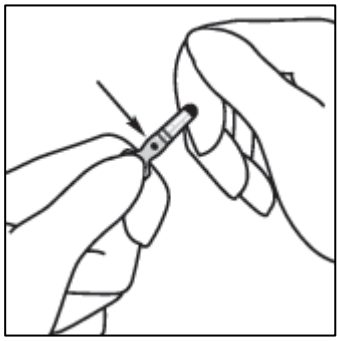
SUBLIMAZE is administered by the intravenous route.

Instructions for use and handling

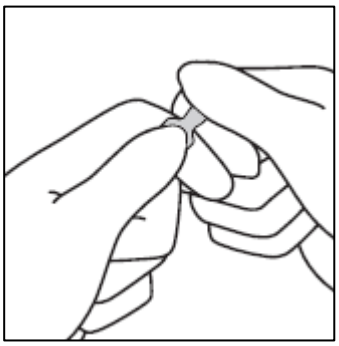
Wear gloves while opening the ampoule.



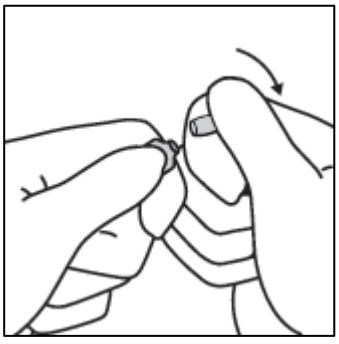
1. Hold the ampoule between thumb and index, leaving the tip of the ampoule free.



2. With the other hand, hold the tip of the ampoule by putting the index finger against the neck of ampoule, and the thumb on the coloured point in parallel to the identification ring(s).



3. Keeping the thumb on the point, sharply break the tip of the ampoule while firmly holding the other part of the ampoule in the hand.



Accidental dermal exposure should be treated by rinsing the affected area with water. Avoid use of soap, alcohol and other cleaning materials that may cause chemical or physical abrasions to the

4.3 Contraindications

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

SUBLIMAZE should not be administered to patients with uncontrolled bronchial asthma or heart failure secondary to chronic lung disease, due to the potential for histamine release. It should not be used in patients who may be susceptible to respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, or comatose patients who may have a head injury or brain tumour and conditions in which increased intracranial pressure occurs, and after an operation on the biliary tract.

The administration of SUBLIMAZE is contraindicated in patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment, and in alcoholism (see section 4.5).

4.4 Special warnings and precautions for use

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical dependence and psychological dependence may develop upon repeated administration of opioids.

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).

For all patients, prolonged use of SUBLIMAZE may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medicines, including over-the-counter medicines and medicines obtained online, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give SUBLIMAZE to anyone else.

Patients should be closely monitored for signs of misuse, abuse or addiction. The clinical need for analgesic treatment should be reviewed regularly.

Because of the risks, including fatal outcome, associated with accidental ingestion, misuse and abuse, patients and their health care providers must be advised to keep SUBLIMAZE in a safe and secure place, not accessible by others.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with SUBLIMAZE.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women receive SUBLIMAZE during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Opioid-induced hyperalgesia and allodynia

Opioid-induced hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behaviour.

Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biological plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider

appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety).

Secondary respiratory depression after the operation has been observed.

SUBLIMAZE should be administered only by health care providers specifically trained in the use of intravenous anaesthetics and management of the respiratory effects of potent opioids.

Safety has not been demonstrated in children younger than 2 years of age.

Respiratory depression

Respiratory depression may result with intravenous administration of SUBLIMAZE. The risk of respiratory depression is increased if SUBLIMAZE is administered in high dose or too rapidly. Respiratory depression is related to the dose and rate of administration and can be reversed by specific antagonists (naloxone), but additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of the action of the opioid antagonist.

Profound analgesia is accompanied by marked respiratory depression and diminished sensitivity to CO_2 stimulation, which can persist or recur in the post-operative period. Respiratory depression secondary to chest wall rigidity has been reported in the post-operative period. Intraoperative hyperventilation may further alter post-operative response to CO_2. Patients who have received SUBLIMAZE should remain under appropriate surveillance. Resuscitation equipment, oxygen and a narcotic antagonist should be readily available to manage apnoea. Care should be taken after infusion of large doses of SUBLIMAZE to ensure adequate spontaneous breathing has been established and maintained before the patient is released from the recovery area.

Adequate facilities should be available for post-operative monitoring and ventilation of patients administered anaesthetic doses of SUBLIMAZE, in particular where doses above 10 µg/kg are

used. These facilities should be fully equipped to handle all degrees of respiratory depression.

If respiratory depression does occur during anaesthesia, assisted or controlled ventilation will provide adequate respiratory support without reversing analgesia. Respiratory depression can be reversed by administration of the narcotic antagonist, naloxone, which may also reverse analgesia.

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

Concomitant use of SUBLIMAZE and CNS depressants, especially benzodiazepines or related medicines, in spontaneously 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 medicine, the lowest effective dose of both medicines 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 section 4.5).

Muscle rigidity

Induction of muscle rigidity (morphine-like effect) which may also involve the thoracic muscles, can occur, but can be ameliorated by the following measures: slow intravenous injection (ordinarily sufficient for lower doses), premedication with benzodiazepines and the use of muscle relaxants. Non-epileptic (myo)clonic movements can occur.

Precautions

SUBLIMAZE should be given only in an environment where the airway can be controlled and by personnel who can control the airway.

Cardiac disease

SUBLIMAZE has weak cholinergic activity and should be used with caution in patients with cardiac dysrhythmias. Bradycardia and possibly cardiac arrest with asystole can occur if the patient has received an insufficient amount of anticholinergic medicine, or when SUBLIMAZE is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.

Nitrous oxide has been reported to produce cardiovascular depression when given with SUBLIMAZE.

In the supine position, therapeutic doses of opioids such as SUBLIMAZE have minimal effect on blood pressure or cardiac rate and rhythm. SUBLIMAZE may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Special dosing conditions

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.

SUBLIMAZE can produce dependence of the morphine type and therefore has the potential for being abused. Patients on chronic opioid therapy or with a history of opioid abuse, may require higher doses.

It is recommended to reduce the dosage in the elderly and in debilitated patients. SUBLIMAZE should be titrated with caution in patients with the following conditions:

- uncontrolled hypothyroidism
- pulmonary disease
- decreased respiratory reserve
- alcoholism
- adrenocortical insufficiency

- impaired renal or hepatic function
- prostatic hypertrophy
- shock.

Such patients also require prolonged post-operative monitoring.

Interaction with neuroleptics

If SUBLIMAZE is administered with a neuroleptic medicine, such as droperidol, the user should be familiar with the special properties of each medicine, particularly the difference in duration of action. When such a combination is used, there is a higher incidence of hypotension, and fluids and other countermeasures should be available to manage hypotension. Neuroleptic medicines, such as droperidol, can induce extrapyramidal symptoms that can be controlled with antiparkinson medicines.

Vital signs should be monitored routinely.
When SUBLIMAZE is used with a tranquilliser such as droperidol, hypotension may occur. If it occurs, the possibility of hypovolaemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor medicines other than epinephrine (adrenaline) should be considered. Because of the alpha-adrenergic blocking action of droperidol, epinephrine (adrenaline) may paradoxically decrease the blood pressure in patients treated with droperidol.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of SUBLIMAZE combined with droperidol. This might be due to alterations in sympathetic activity following large doses of droperidol; however, it is also frequently attributed to anaesthetic and surgical stimulation during light anaesthesia.

It is imperative to discontinue MAO inhibitors 2 weeks prior to any surgical or anaesthetic procedure.

Bile duct

Due to the anticholinergic effects, administration of SUBLIMAZE may lead to increases of bile duct pressure, and spasms of the sphincter of Oddi might be observed.

Serotonin syndrome

Caution is advised when SUBLIMAZE is coadministered with medicines that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic medicines, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), and with medicines which impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]). This may occur within the recommended dose (see sections 4.3 and 4.5).

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 (see sections 4.3 and 4.5).

When a tranquilliser is used with SUBLIMAZE, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anaesthetic doses of SUBLIMAZE are used, even relatively small

dosages of diazepam may cause cardiovascular depression.

The use of SUBLIMAZE should be avoided in patients with raised intracranial pressure. An antidiuretic effect and hypothermia may occur.

SUBLIMAZE increases tone in smooth muscle, especially the sphincters of the gastrointestinal tract. Contact dermatitis has been reported, and pain and irritation may occur on injection. It should be used with caution in patients with inflammatory or obstructive bowel disease.

Myasthenia gravis

In patients with myasthenia gravis, careful consideration should be applied in the use of certain anticholinergics and neuromuscular-blocking pharmaceutical medicines prior to, and during, the administration of a general anaesthetic regimen, which includes administering intravenous fentanyl, such as SUBLIMAZE.

Paediatric patients

Techniques that involve analgesia in a spontaneously breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/analgesia technique, with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support.

Sodium content

SUBLIMAZE 2 mL:

This medicine contains less than 1 mmol sodium (23 mg) per 2 mL ampoule, that is to say it is essentially sodium free.

SUBLIMAZE 10 mL:

This medicine contains 35,4 mg sodium per 10 mL ampoule, equivalent to 1,8 % of the WHO

recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on SUBLIMAZE

Central nervous system (CNS) depressants

Medicines such as barbiturates, benzodiazepines, tricyclic antidepressants, phenothiazines, hypnotics, opioid premedication, neuroleptics, general anaesthetics, gabapentinoids (gabapentin and pregabalin), halogenic gases and other non-selective central nervous system depressants (e.g. alcohol) may potentiate the respiratory depression of opioids. When patients have received such medicines, the dose of SUBLIMAZE required will 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 section 4.4).

Cytochrome P450 3A4 (CYP3A4) inhibitors

SUBLIMAZE, a high clearance medicine, is rapidly and extensively metabolised mainly by CYP3A4. 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 risk for respiratory depression may be prolonged, which may require special patient care and longer observation.

Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of a single IV SUBLIMAZE by two thirds; however, peak plasma concentrations after a single dose of IV SUBLIMAZE were not affected.

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.

When SUBLIMAZE is used in a single dose, the concomitant use of potent CYP3A4 inhibitors such as ritonavir requires special patient care and observation.

Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of a single IV SUBLIMAZE dose. Coadministration of fluconazole or voriconazole and SUBLIMAZE may result in an increased exposure to fentanyl. With continuous treatment, dose reduction of SUBLIMAZE may be required to avoid accumulation of SUBLIMAZE, which may increase the risk of prolonged or delayed respiratory depression.

Although clinical data are lacking, *in vitro* data suggest that other potent CYP3A4 enzyme inhibitors (e.g. fluconazole, ketoconazole, erythromycin, diltiazem and cimetidine) may inhibit the metabolism of fentanyl.

Serotonergic medicines

Coadministration of fentanyl with a serotonergic agent, such as a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI), or a monoamine oxidase inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition (see section 4.3).

Effect of SUBLIMAZE on other medicines

Following the administration of SUBLIMAZE, the dose of other CNS-depressant medicines 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 post-operative period. Administration of a CNS depressant, such as a benzodiazepine or related medicines, during this period may disproportionally increase the risk for respiratory depression (see section 4.4).

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 SUBLIMAZE.

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 coadministered with SUBLIMAZE their dose may need to be reduced.

When SUBLIMAZE is used with a neuroleptic such as droperidol, chills and/or shivering, restlessness, post-operative hallucinatory episodes and extrapyramidal symptoms may be observed. Extrapyramidal symptoms may be controlled with antiparkinson medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Administration during childbirth (including caesarean section) is not recommended prior to delivery because SUBLIMAZE crosses the placenta and because the neonatal respiratory centre is particularly sensitive to opiates. If SUBLIMAZE is nevertheless administered, assisted ventilation equipment must be immediately available for the mother and infant, if required. An antidote (opioid antagonist) for the newborn should always be at hand.

Regular use during pregnancy may cause drug dependence in the fetus, leading to withdrawal symptoms in the neonate. 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.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breastfeeding

SUBLIMAZE is excreted into human milk. Therefore, breastfeeding is not recommended for 24 hours following the administration of SUBLIMAZE.

Fertility

There are no clinical data on the effects of fentanyl on male or female fertility. In animal studies, some tests on rats showed reduced female fertility at maternal toxic doses.

4.7 Effects on ability to drive and use machines

Patients should only drive or operate a machine if 24 hours have elapsed after 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 reactions reported by > 1 % of SUBLIMAZE-treated subjects

System organ class Adverse reaction	**Fentanyl IV** (n = 376) **%**
Nervous system disorders	

Sedation	5,3
Dizziness	3,7
Dyskinesia	3,2
Eye disorders	
Visual disturbances	1,9
Cardiac disorders	
Bradycardia	6,1
Tachycardia	4,0
Dysrhythmia	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	
Allergic dermatitis	1,3
Musculoskeletal and connective tissue disorders	
Muscle rigidity (which may also involve the thoracic muscles)	10,4
Injury, poisoning and procedural complications	
Post-operative confusion	1,9
Neurological anaesthetic complications	1,1

Additional adverse reactions (ADR) that occurred in < 1 % of SUBLIMAZE-treated subjects in the

20 clinical trials are listed below in Table 2.

Table 2: Adverse reactions reported by < 1 % of SUBLIMAZE-treated subjects

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
Post-operative agitation
Procedural complication
Airway complication of anaesthesia

Post-marketing data

Adverse reactions first identified during post-marketing experience with SUBLIMAZE are included in Table 3.

In each table, 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.

In Table 3, adverse reactions are presented by frequency category based on spontaneous reporting rates, while in Table 4, the same adverse reactions are presented by frequency category based on incidence in clinical trials or epidemiology studies, when known. The frequency category "not known" is used for adverse reactions for which no valid estimate of the incidence rate can be derived from clinical trials.

Table 3: Adverse reactions identified during post-marketing experience with SUBLIMAZE from spontaneous reporting

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 (see section 4.3.)
Respiratory, thoracic and mediastinal disorders

Very rare: Respiratory depression (see section 4.3.)

Skin and subcutaneous tissue disorders

Very rare: Pruritus

Table 4: Adverse reactions identified during post-marketing experience with SUBLIMAZE by frequency category estimated from clinical trials or epidemiologic studies

Immune system disorders

Not known: Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)

Psychiatric disorders

Common: Agitation

Uncommon: Euphoric mood

Not known: Delirium, drug dependence (see section 4.4)

Nervous system disorders

Very common: Muscle rigidity (which may also involve the thoracic muscles)

Common: Dyskinesia, sedation, dizziness

Uncommon: Headache

Not known: Convulsions, loss of consciousness, myoclonus

Eye disorders

Common: Visual disturbance

Cardiac disorders

Common: Bradycardia, tachycardia, arrhythmia

Not known: Cardiac arrest (see section 4.3.)

Vascular disorders

Common: Hypotension, hypertension, venous pain

Uncommon: Phlebitis, blood pressure fluctuation

Respiratory, thoracic and mediastinal disorders

Common: Laryngospasm, bronchospasm, apnoea

Uncommon: Hyperventilation, hiccups

Not known: Respiratory depression (see section 4.3.)

Gastrointestinal disorders

Very common Nausea, vomiting

Uncommon Dysphagia

Skin and subcutaneous tissue disorders

Common: Allergic dermatitis

Not known: Pruritus

General disorders and administration site conditions

Uncommon: Chills, hypothermia, drug withdrawal syndrome

Not known: Drug withdrawal syndrome (see section 4.4)

Injury, poisoning and procedural complications

Common: Post-operative confusion

Uncommon: Airway complication of anaesthesia

When SUBLIMAZE is used with a neuroleptic such as droperidol, chills and/or shivering, restlessness, post-operative hallucinatory episodes, and extrapyramidal symptoms may be observed.

Extrapyramidal symptoms may be controlled with antiparkinson medicines (see section 4.3).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Signs and symptoms

An overdosage of fentanyl manifests itself as an extension of its pharmacological actions. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnoea to apnoea. Toxic leukoencephalopathy has been observed with fentanyl overdose.

Treatment

In the presence of hypoventilation or apnoea, oxygen should be administered, and lung ventilation should be assisted or controlled as indicated.

A specific opioid antagonist, such as naloxone, should be used as indicated to control respiratory depression. This does not preclude the use of more immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.

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

The patient should be carefully observed; body warmth and adequate fluid intake should be

maintained. If hypotension is severe or if it persists, the possibility of hypovolaemia should be considered, and if present, it should be controlled with appropriate parenteral fluid administration.

5 PHARMACOLOGICAL PROPERTIES

Category and class

A. 2.7 Central nervous system depressants. Narcotic analgesics.

Pharmacotherapeutic group: Anaesthetics general, opioid anaesthetics.

ATC code: N01AH01.

5.1 Pharmacodynamic properties

Mechanism of action

Fentanyl is a potent, opioid analgesic.

Pharmacodynamic effects

Fentanyl is a narcotic analgesic. Fentanyl obtunds stress-related hormonal changes at higher doses. The onset of action is within one arm-brain circulation time. However, the maximum analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is approximately 30 minutes after a single intravenous dose of up to 100 µg. Depth of analgesia is dose related and can be adjusted to the pain level of the surgical procedure.

Fentanyl, depending upon the dose and speed of administration, can cause muscle rigidity as well as euphoria, miosis and bradycardia. Histamine release may occur.

All actions of fentanyl are reversible by a specific narcotic antagonist, such as naloxone.

5.2 Pharmacokinetic properties

Fentanyl is a synthetic opioid with µ-agonist pharmacological effects.

Distribution

After intravenous injection in normal volunteers, fentanyl plasma concentrations have sequential distribution half-lives of about 1 minute and 18 minutes and a terminal elimination half-life of approximately 8 hours.

Fentanyl has a Vc (volume of distribution of the central compartment) of 13 L and a total Vdss (distribution volume at steady-state) of 339 L. The plasma-protein binding of fentanyl is about 84 %.

Metabolism

Fentanyl is rapidly metabolised, mainly in the liver by CYP3A4. The major metabolite is norfentanyl. Fentanyl clearance is 574 mL/min.

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 medicine.

Special populations

Paediatric patients

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 SUBLIMAZE.

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 SUBLIMAZE, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.2).

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 mass. 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection.

6.2 Incompatibilities

If desired, SUBLIMAZE 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.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Packed in cartons of 5 ampoules each.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Piramal Critical Care (Pty) Ltd

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8 REGISTRATION NUMBERS

SUBLIMAZE 2 mL: B/2.7/1014

SUBLIMAZE 10 mL: Q/2.7/34

9 DATE OF FIRST AUTHORISATION

SUBLIMAZE 2 mL: 19/04/1984

SUBLIMAZE 10 mL: 21/01/1983

10 DATE OF REVISION OF THE TEXT

24 July 2025