Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sublimaze 50 micrograms/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 78.5 micrograms fentanyl citrate equivalent to 50 micrograms fentanyl base.
Ampoule of 2 ml contains 100 micrograms of fentanyl.
Ampoule of 10 ml contains 500 micrograms of fentanyl.

Excipient(s) with known effect:

Each 2 ml ampoule contains 7.08 mg of sodium.
Each 10 ml ampoule contains 35.4 mg sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection. (Injection)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an adjunct in the maintenance of general anaesthesia and analgesia.

In conjunction with a neuroleptic agent in the technique of neuroleptanalgesia.

As a respiratory depressant/analgesic in patients requiring prolonged assisted ventilation.

As the sole intravenous anaesthetic agent in surgical procedures.

4.2 Posology and method of administration

Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway (see section 4.4 Special warnings and precautions).

The dosage of fentanyl should be individualised according to age, body weight, physical status, underlying pathological condition, use of other drugs, and type of surgery and anaesthesia.

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 (see section 4.4).

It is recommended to wear gloves while opening the ampoule (see section 6.6 Special precautions for disposal and other handling).

Method of administration:
For intravenous administration.

Posology:
<u>As an adjunct in the maintenance of general anaesthesia and analgesia</u>

Adults:
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
0.0005-0.01 mg/kg

Continuous infusion
0.0005-0.005 mg/kg/h

Children:
0.001 mg/kg supplements as necessary.

In conjunction with a neuroleptic agent in the technique of neuroleptanalgesia

Adults:
The usual dose is 0.1 mg initially, with maintenance doses of 0.05 mg as necessary.

In patients requiring prolonged assisted ventilation

Adults:
Up to 0.6 mg initially, with supplemental doses of 0.05 mg to 0.2 mg.

Children:
0.001 mg/kg supplements as necessary.

As sole IV anaesthetic agent in surgical procedures

Adults:
The usual dose is 0.1 mg to 0.8 mg initially, depending on response, with maintenance doses of 0.05 mg as necessary, in conjunction with controlled ventilation.

Children:
The usual dose is 0.01 mg/kg initially, depending on response, with maintenance doses of 0.001 mg/kg as necessary, in conjunction with controlled ventilation.

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 have dosage calculated according to their estimated lean body mass.

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 Pharmacokinetic properties).

4.3 Contraindications

Hypersensitivity (or idiosyncratic response) to the active substance or to any of the excipients listed in section 6.1 or other opioids.

Respiratory depression, cyanosis, excessive bronchial exudation, bronchoconstriction (reversible or irreversible) or chronic pulmonary disease.

After operative interventions in the biliary tract.

Use in patients who are receiving, or have within two weeks received, monoamine oxidase inhibitors.

4.4 Special warnings and precautions for use

Sublimaze is intended for use in hospitals only by those trained in anaesthesia and familiar with the use of potent opioids when given intravenously.

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

Respiratory depression
As with all potent opioids, respiratory depression is dose-related and can be reversed by a specific opioid antagonist, but additional doses may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist. Profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the post-operative period. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's responses to CO_2, thus affecting respiration post-operatively.

Muscle rigidity
Induction of muscle rigidity, which may also involve the thoracic muscles, can occur, but can be avoided by the following measures: slow IV injection (ordinarily sufficient for lower doses), premedication with benzodiazepines and the use of muscle relaxants.

Non-epileptic (myo) clonic movements can occur.

Cardiac disease
Bradycardia and possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic, or when fentanyl is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.

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

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).

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.

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 mean arterial pressure has occasionally been accompanied by a short-lasting reduction of the cerebral perfusion pressure.

This product should only be used with great caution in patients who are dependent on drugs in view of the severe respiratory depression which may ensue. Patients on chronic opioid therapy or with history of opioid abuse may require higher doses.

It is recommended to reduce the dosage 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.

Repeated use will result in the development of tolerance requiring increases in dosage to achieve the required effects. Generally it is preferable to vary the opioid analgesics at intervals in patients requiring prolonged periods of analgesia.

Interaction with neuroleptics
If fentanyl 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 such a combination is used, there is a higher incidence of hypotension. Neuroleptics can induce extrapyramidal symptoms that can be controlled with anti-Parkinson agents.

Bile duct
As with other opioids, due to the anti-cholinergic effects, administration of fentanyl may lead to increases of bile duct pressure and, in isolated cases, spasms of the Sphincter of Oddi might be observed.

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

Serotonin syndrome
Caution is advised when fentanyl 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., hyper-reflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

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

Paediatric population
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.

Risk from concomitant use of central nervous system (CNS) depressants, especially benzodiazepines or related drugs
Concomitant use of Sublimaze and CNS depressants especiallybenzodiazepines 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 Section 4.5).

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

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.

For SUBLIMAZE 2 ml ampoule: This medicine contains less than 1 mmol sodium (23 mg) per 2 ml ampoule, that is to say essentially 'sodium-free'.

For SUBLIMAZE 10 ml ampoule: This medicinal product 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 medicinal products and other forms of interaction

Effect of other drugs on fentanyl

Central Nervous System (CNS) depressants

Drugs such as barbiturates, benzodiazepines or related drugs, neuroleptics, general anaesthetics, gabapentinoids (gabapentin and pregabalin), and other, non-selective CNS depressants (e.g., alcohol) may potentiate the respiratory depression of opioids.

When patients have received such CNS depressant drugs, the dose of fentanyl 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 Section 4.4).

Cytochrome P450 3A4 (CYP3A4) inhibitors

Fentanyl, a high clearance drug, 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. 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 of fentanyl were not affected. However, itraconazole (another potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of a single intravenous Sublimaze dose. Co-administration of other potent or less potent CYP3A4 inhibitors, such as voriconazole or fluconazole, and Sublimaze may also result in an increased and/or prolonged exposure to fentanyl.

Pretreatment with, or concurrent administration of, cimetidine may increase plasma levels of fentanyl, when repeated doses of both drugs are used.

Bradycardia may be intensified by pretreatment with, or concurrent use of, drugs such as beta-blockers, suxamethonium, halothane, vecuronium, which may themselves cause bradycardia.

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 (see section 4.3 Contraindications).

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

Plasma concentrations of etomidate increased considerably (by a factor of 2-3) when combined with fentanyl. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of fentanyl in pregnant women. Fentanyl can cross the placenta in early pregnancy. Studies in animals have shown some reproductive toxicity (see Section 5.3, Preclinical safety data). The potential risk for humans is unknown.

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

Administration 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 the drug. The risk/benefit of breastfeeding following fentanyl administration should be considered.

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 (see section 5.3 Preclinical data).

4.7 Effects on ability to drive and use machines

Where early discharge is envisaged, patients should be advised not to drive or operate machinery for at least 24 hours following administration.

4.8 Undesirable effects

The safety of fentanyl IV was evaluated in 376 subjects who participated in 20 clinical trials evaluating fentanyl IV as an anaesthetic. These subjects took at least 1 dose of fentanyl IV and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported (≥5% incidence) Adverse Reactions were (with % incidence): nausea (26.1); vomiting (18.6); muscle rigidity (10.4); hypotension (8.8); hypertension (8.8); bradycardia (6.1); and sedation (5.3).

Including the above-mentioned adverse reactions, the following table displays adverse reactions that have been reported with the use of fentanyl IV from either clinical trials or postmarketing experiences.

The displayed frequency categories use the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available clinical trial data).

Table 1: Adverse Reactions

System Organ Class	**Adverse Reactions**			
	Frequency Category			
	Very Common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Not Known**
Immune System Disorders				Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric Disorders			Euphoric Mood	Delirium
Nervous System Disorders		Dyskinesia; Sedation; Dizziness	Headache	Convulsions (including clonic convulsions and grand mal convulsion); Stupor; Loss of conciousness/Coma; Myoclonus
Eye Disorders		Visual disturbance		

Cardiac Disorders		Bradycardia; Tachycardia; Arrhythmia		Cardiac arrest
Vascular Disorders		Hypotension; Hypertension; Vein pain	Phlebitis; Blood pressure fluctuation	
Respiratory, Thoracic and Mediastinal Disorders		Laryngospasm; Bronchospasm; Apnoea	Hyperventilation; Hiccups	Respiratory depression
Gastrointestinal Disorders	Nausea; Vomiting		Dysphagia	
Skin and Subcutaneous Tissue Disorders		Dermatitis allergic		Pruritus
Musculoskeletal and Connective Tissue Disorders	Muscle rigidity (which may also involve the thoracic muscles)			
General Disorders and Administration Site Conditions			Chills; Hypothermia	Drug withdrawal syndrome (see section 4.4)
Injury, Poisoning and Procedural Complications		Confusion postoperative; Anaesthetic complication neurological	Airway complication of anaesthesia: Agitation postoperative; Procedural complication	

When a neuroleptic is used with fentanyl, the following adverse reactions may be observed: chills and/or shivering, restlessness, post-operative hallucinatory episodes and extrapyramidal symptoms (see Section 4.4).

Cases of serotonin syndrome have been reported when products containing fentanyl are administered concomitantly with highly serotonergic drugs (see sections 4.4 and 4.5)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms and signs
An overdose of fentanyl manifests itself as an extension of its pharmacologic actions.
Respiratory depression which can vary in severity from bradypnoea to apnoea may occur. Toxic leukoencephalopathy hasbeen observed with fentanyl overdose.

Treatment
In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific opioid antagonist 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 depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking 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

5.1 Pharmacodynamic properties

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

Fentanyl is a well established chemical entity. It is an opioid analgesic with a high affinity for the micro-opioid receptor. Fentanyl can be used as an analgesic supplement to general anaesthesia or as the sole anaesthetic. Fentanyl preserves cardiac stability, and obtunds stress-related hormonal changes at higher doses. A dose of 100 micrograms (2.0 ml) is approximately equivalent in analgesic activity to 10 mg of morphine. The onset of action is rapid. 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 IV dose of up to 100 micrograms. Depth of analgesia is dose-related and can be adjusted to the pain level of the surgical procedure.

Like other opioid analgesics, fentanyl, depending upon the dose and speed of administration, can cause muscle rigidity, as well as euphoria, miosis and bradycardia.

Histamine assays and skin-wheal testing have indicated that clinically significant histamine release is rare with fentanyl.

All actions of fentanyl are reversed by a specific opioid antagonist.

5.2 Pharmacokinetic properties

Fentanyl is a synthetic opioid with micro-agonist pharmacologic effects.

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 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 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 section 4.2 Posology 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

Fentanyl has a broad safety margin. In rats, the ratio LD_{50}/ED_{50} for the lowest level of analgesia is 281.8, as compared with 69.5 and 4.8 for morphine and pethidine respectively.

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 3 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 30°C. Keep ampoules in the outer carton.

6.5 Nature and contents of container

Colourless glass ampoules (Ph. Eur., Type I).

Pack size: packs of 10 x 2 ml ampoules, packs of 5 and 10* x 10 ml ampoules.
**Not all pack sizes maybe marketed.*

6.6 Special precautions for disposal and other handling

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.

For single use only. Discard any unused contents.
See section 4.2.

7 MARKETING AUTHORISATION HOLDER

Piramal Critical Care B.V.
Rouboslaan 32 (ground floor)
2252 TR
Voorschoten
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA22583/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01st April 1978

Date of last renewal: 10th June 2007

10 DATE OF REVISION OF THE TEXT

April 2024