PROPOSED PACKAGE INSERT: April 2017

SCHEDULING STATUS

Schedule 6.

PROPRIETARY NAME (AND DOSAGE FORM)

SUBLIMAZE® 2 ml injection.

SUBLIMAZE® 10 ml injection.

COMPOSITION

Each ml contains 0,0785 mg (78,5 µg) fentanyl citrate equivalent to 0,050 mg (50 µg) fentanyl base. It is a sterile, preservative-free isotonic aqueous solution also containing sodium chloride and water for injection.

PHARMACOLOGICAL CLASSIFICATION

A.2.7 Narcotic analgesics.

PHARMACOLOGICAL ACTION

Pharmacodynamics

Fentanyl is a narcotic analgesic. Fentanyl obtunds stress related hormonal changes at higher doses. A dose of 100 µg (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 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, meiosis and bradycardia. Histamine release may occur.

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

Pharmacokinetics

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

Distribution:

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

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 %.

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

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 use as a narcotic analgesic supplement in general or regional anaesthesia.

- for administration with a neuroleptic such as droperidol as an anaesthetic premedication; for induction of anaesthesia; and as an adjunct in the maintenance of general and regional anaesthesia.
- for use as an anaesthetic agent with oxygen in selected high-risk patients undergoing major surgery.

CONTRA-INDICATIONS

SUBLIMAZE is contra-indicated in patients with a known intolerance to fentanyl. It should not be administered to children 2 years of age or younger because safety in this age group has not yet been established.

SUBLIMAZE should not be administered to patients suffering from bronchial asthma or in heart failure secondary to chronic lung disease.

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 operation on the biliary tract.

Pregnancy and Lactation

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

Administration (I.M. or I.V.) during childbirth (including caesarean 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.

Fentanyl is excreted into human milk. Therefore, nursing is not recommended for 24 hours following the administration of this drug.

The administration of narcotic analgesics is contra-indicated in patients taking mono-amine oxidase inhibitors or within 10 days of stopping such treatment, and in alcoholism. The risk/benefit of breastfeeding following fentanyl administration should be considered.

WARNINGS

Secondary respiratory depression after the operation has been observed.

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

An opioid antagonist, resuscitative equipment and oxygen should be readily available.

Adequate facilities should be available for postoperative 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.

SUBLIMAZE can produce drug 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.

If SUBLIMAZE is administered with droperidol, 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 and fluids and other countermeasures should be available to manage hypotension. Droperidol can induce extrapyramidal symptoms that can be controlled with anti-Parkinson agents.

INTERACTIONS

Effect of other drugs:

Agents such as barbiturates, benzodiazepines, tricyclic antidepressants, phenothiazines, hypnotics, opioid pre-medication, neuroleptic, halogenic gases and other non-selective central nervous system depressants (e.g. alcohol) may potentiate the respiratory depression of narcotics. When patients have received such agents, the dose of fentanyl required will be less than usual.

Fentanyl, a high clearance drug, is rapidly and extensively metabolised mainly by CYP3A4. Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of IV fentanyl. Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of IV fentanyl by two thirds; however peak plasma concentrations after a single dose of IV fentanyl 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. Co-administration of fluconazole or voriconazole and SUBLIMAZE may result in an increased exposure to fentanyl. With continuous treatment, dose reduction of fentanyl may be required to avoid accumulation of fentanyl, which may increase the risk of prolonged or delayed respiratory depression.

Although clinical data are lacking, *in-vitro* data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. fluconazole, ketoconazole, erythromycin, diltiazem and cimetidine) may inhibit the metabolism of fentanyl.

Effect on other drugs:

Following the administration of SUBLIMAZE, 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 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 drugs are co-administered 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 anti-parkinson agents.

DOSAGE AND DIRECTIONS FOR USE

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

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. To avoid bradycardia, it is recommended to administer a small intravenous dose of an anti-cholinergic just before induction. Droperidol may be given to prevent nausea and vomiting.

USE AS AN ANALGESIC SUPPLEMENT TO GENERAL ANAESTHESIA

Low dose: 2 µg/kg

Fentanyl in small doses is useful for minor, but painful surgery.

Moderate dose: 2 - 20 µg/kg

Where surgery becomes more complicated, a larger dose will be required. The duration of activity is dependent on dosage.

High dose: 20 - 50 µg/kg.

During major surgical procedures, in which surgery is longer and during which the stress response would be detrimental to the well-being of the patient, dosages of 20 - 50 µg/kg of fentanyl with nitrous oxide/oxygen have been shown to have an attenuating effect. When dosages in this range have

been used during surgery, post-operative ventilation and observation are essential in view of the possibility of extended post-operative respiratory depression. Supplemental doses of 25 - 250 µg (0,5 - 5 ml) should be tailored to the needs of the patient and to the anticipated time till completion of the operation.

USE AS AN ANAESTHETIC AGENT

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 agents. In certain cases, doses of up to 150 µg/kg may be required to produce this anaesthetic effect. Fentanyl has been used in this fashion for open heart surgery and certain other major surgical procedures for which protection of the myocardium from excess oxygen demand is particularly indicated.

USE AS AN ADJUNCT TO LOCAL ANAESTHESIA

Intravenous: 0,07 - 1,4 µg/kg.

USE AS A PRE-SURGICAL MEDICATION

Intramuscular: 0,07 - 1,4 µg/kg, 30 to 60 minutes prior to surgery.

POST-OPERATIVE USE

For use in the recovery room period. 0,07 - 1,4 µg/kg intramuscularly. May be repeated in one to two hours as needed.

Use in the elderly

The dose should be reduced in the elderly or debilitated patients.

Use in children

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

Compatibility

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.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Clinical Trial Data:

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

Table 1: Adverse Drug Reactions Reported by >1 % of SUBLIMAZE –treated Subjects in 20 Clinical Trials of SUBLIMAZE.

System/ Organ Class Adverse Reaction	**Fentanyl IV** (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
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	1.3
Dermatitis allergic	
Musculoskeletal and Connective Tissue Disorders	10.4
Muscle rigidity (which may also involve the thoracic muscles)	
Injury, Poisoning and Procedural Complications	1.9
Confusion postoperative	1.1
Anaesthetic complication neurological	

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.

Table 3: Adverse Drug Reactions Identified During Postmarketing Experience with SUBLIMAZE from Spontaneous Reporting.

Immune System Disorders
Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Nervous System Disorders
Convulsions, Loss of consciousness, Myoclonus
Cardiac Disorders
Cardiac arrest

Respiratory, Thoracic and Mediastinal Disorders
Respiratory depression
Skin and Subcutaneous Tissue Disorders
Pruritus

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 anti-parkinson agents (Refer to Interactions).

Vital signs should be monitored routinely.

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 postoperative period. Respiratory depression secondary to chest wall rigidity has been reported in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Patients who have received SUBLIMAZE should remain under appropriate surveillance. Resuscitation equipment 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.

If respiratory depression does occur during anaesthesia, assisted or controlled respiration will provide adequate ventilation without reversing analgesia. Respiratory depression can be reversed

by administration of the narcotic antagonist, naloxone, which, it should be noted, may also reverse analgesia.

Respiratory depression may result with intravenous administration of SUBLIMAZE if it is administered too rapidly.

SUBLIMAZE has weak cholinergic activity and should be used with caution in patients with cardiac arrhythmias. Bradycardia and possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic, 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 higher doses of SUBLIMAZE.

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.

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 agents (other than adrenaline) should be considered. Because of the alpha -adrenergic blocking action of droperidol, adrenaline may paradoxically decrease the blood pressure in patient treated with droperidol.

In the supine position, therapeutic doses of opioids have no major 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.

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

Induction of muscle rigidity which may also involve the thoracic muscles, can occur, but can be avoided 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.

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, or shock. Such patients also require prolonged post operative monitoring.

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 gastro-intestinal 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.

Care should be taken when SUBLIMAZE is given to patients with myasthenia gravis.

It is usually recommended to discontinue MAO-inhibitors 2 weeks prior to any surgical or anaesthetic procedure. However, several reports describe the uneventful use of fentanyl during surgical or anaesthetic procedures in patients on MAO-inhibitors.

Effects on driving ability and use of machinery:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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 bradyapnoea to apnoea.

Treatment

In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific narcotic 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 depressed respiration 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.

IDENTIFICATION

A clear, colourless solution.

PRESENTATION

2 ml ampoules packed in cartons of 5 and 30 ampoules.

10 ml ampoules packed in cartons of 5 ampoules.

STORAGE DIRECTIONS

Store below 25 ^{o}C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

2 ml: B/2.7/1014

10 ml: Q/2.7/34

NAME AND BUSINESS ADDRESS OF THE APPLICANT

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