Sufenta / Sufenta forte

NAME OF THE MEDICINAL PRODUCT
SUFENTA/SUFENTA *FORTE*

QUALITATIVE AND QUANTITATIVE COMPOSITION
SUFENTA contains an amount of sufentanil citrate that is equivalent to 5 µg sufentanil per ml.
SUFENTA *FORTE* contains an amount of sufentanil citrate that is equivalent to 50 µg sufentanil per ml.

PHARMACEUTICAL FORM
SUFENTA/SUFENTA *FORTE* is a sterile, preservative free, isotonic aqueous solution.

CLINICAL PARTICULARS
Therapeutic Indications
Intravenous SUFENTA is used both as an analgesic adjunct to nitrous oxide/oxygen and as a sole anaesthetic in ventilated patients. It is particularly suitable for longer and more painful interventions where a potent analgesic is required to help maintain good cardiovascular stability.
INTRAVENOUS SUFENTA is indicated:
- as an analgesic adjunct during induction and maintenance of balanced general anaesthesia.
- as an anaesthetic agent for induction and maintenance of anaesthesia in patients undergoing major surgical procedures.

Posology and Method of Administration
The dosage of SUFENTA should be individualised according to age, body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anaesthesia. The effect of the initial dose should be taken into account in determining supplemental doses.
INTRAVENOUS ADMINISTRATION
- To avoid bradycardia, it is recommended to administer a small intravenous dose of an anticholinergic just before induction. Droperidol may be given to prevent nausea and vomiting.
- *Use as analgesic adjunct*
  In patients undergoing general surgery, doses of SUFENTA of 0.5-5 µg/kg provide intense analgesia, reducing the sympathetic response to surgical stimulation and preserving cardiovascular stability. The duration of activity is dose-dependent. A dose of 0.5 µg/kg may be expected to last 50 minutes. Supplemental doses of 10-25 µg should be individually adjusted to the needs of each patient and to the anticipated remaining operation time.
- *Use as anaesthetic agent*
  When used in doses of ≥8 µg/kg SUFENTA produces sleep and maintains a dose-related profound level of analgesia without the use of additional anaesthetic agents. In addition sympathetic and hormonal responses to surgical stimuli are attenuated. Supplementary doses of 25-50 µg generally suffice to maintain cardiovascular stability during anaesthesia.
- *Use in the elderly and special patient groups:*
  As with other opioids the dose should be reduced in elderly and in debilitated patients
- *Use in children:*
  The safety and efficacy of intravenous SUFENTA in children under 2 years of age has been documented in only a limited number of cases.
  For induction and maintenance of anaesthesia in children of 2-12 years of age undergoing major surgery, an anaesthetic dose of 10-20 µg/kg administered with 100% oxygen has been used.

Contraindications
SUFENTA is contraindicated in patients with known intolerance to either of its components or to other morphinomimetics.
Intravenous use in labour or before clamping of the cord during caesarean section is not recommended due to the possibility of respiratory depression in the newborn infant. See Special warnings and special precautions for use and Pregnancy and lactation.

Special Warnings and Special Precautions for Use
As with all potent opioids:
Respiratory depression is dose related and can be reversed by specific narcotic antagonists (naloxone), but a repeated dose of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist. Marked respiratory depression accompanies profound analgesia. It can persist in the postoperative period, and if SUFENTA has been given intravenously it can even recur. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and narcotic antagonists should be readily available.
Hyperventilation during anaesthesia may alter the patient's responses to CO_2, thus affecting respiration postoperatively.
Induction of muscle rigidity, which may also involve the thoracic respiratory muscles, can occur, but can be avoided by the following measures: slow I.V. injection (ordinarily sufficient for lower doses), premedication with benzodiazepines and the use of muscle relaxants.
Non-epileptic (myo)clonic movements can occur.
Bradycardia and possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic or when SUFENTA 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.
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.
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. 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.
Intravenous use in labour or before clamping of the cord during caesarean section is not recommended due to the possibility of respiratory depression in the newborn infant.

Interaction with Other Medicinal Products and Other Forms of Interaction
Drugs such as barbiturates, benzodiazepines, neuroleptics, halogenic gases and other, non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depression of narcotics.
When patients have received such drugs, the dose of SUFENTA required will be less than usual. Likewise, following the administration of SUFENTA, the dose of other CNS-depressant drugs should be reduced.
Sufentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. However, no *in vivo* inhibition by erythromycin (a known cytochrome P450 3A4 enzyme inhibitor) has been observed. Although clinical data are lacking, *in vitro* data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may inhibit the metabolism of sufentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of SUFENTA.
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, a related opioid, during surgical or anaesthetic procedures in patients on MAO-inhibitors.

Pregnancy and Lactation
Safety of intravenous sufentanil in human pregnancy has not been established although studies in animals have not demonstrated any teratogenic effects. See Preclinical safety data. As with other drugs, risk should be weighed against potential benefit to the patient.
Intravenous use is not recommended in labour.
If Sufenta is nevertheless administered, an antidote for the child should always be at hand.
SUFENTA is excreted in breast milk. Caution should be exercised when SUFENTA is administered to a nursing woman.

Effects on Ability to Drive and Use Machines
Patients should drive or operate a machine only if sufficient time has elapsed after the administration of SUFENTA.

Undesirable Effects
Clinical Trial Data
The safety of SUFENTA/SUFENTA *FORTE* was evaluated in 650 sufentanil-treated subjects who participated in 6 clinical trials. Of these, 78 subjects participated in 2 trials of sufentanil administered intravenously as an anaesthetic agent for induction and maintenance of anaesthesia in subjects undergoing major surgical procedures (coronary artery bypass or open-heart). The remaining 572 subjects participated in 4 trials of epidural sufentanil administered as a postoperative analgesic or as an analgesic adjunct to epidural bupivacaine during labour and vaginal deliveries. These subjects took at least 1 dose of sufentanil and provided safety data. Adverse Drug Reactions (ADRs) that were reported for ≥1% of sufentanil-treated subjects in these trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥1% of Sufentanil-treated Subjects in 6 Clinical Trials of Sufentanil

System / Organ Class Adverse Reaction	Sufentanil (n=650) %
Nervous System Disorders	
Sedation	19.5
Tremor neonatal	4.5
Dizziness	1.4
Headache	1.4
Cardiac Disorders	
Tachycardia	1.8
Vascular Disorders	
Hypertension	4.9
Hypotension	3.2
Pallor	1.4
Respiratory, Thoracic and Mediastinal Disorders	
Cyanosis neonatal	2.0
Gastrointestinal Disorders	
Nausea	9.8
Vomiting	5.7
Skin and Subcutaneous Tissue Disorders	
Pruritus	15.2
Skin discolouration	3.1
Musculoskeletal and Connective Tissue Disorders	
Muscle twitching	2.0
Renal and Urinary Disorders	
Urinary retention	3.2
Urinary incontinence	1.5
General Disorders and Administration Site Conditions	
Pyrexia	1.7

Additional ADRs that occurred in <1% of sufentanil-treated subjects in the 6 clinical trials are listed in Table 2.

Table 2. Adverse Drug Reactions Reported by <1% of Sufentanil-treated Subjects in 6 Clinical Trials of Sufentanil

System / Organ Class Adverse Reaction
Infection and Infestation
Rhinitis
Immune System Disorders
Hypersensitivity
Psychiatric Disorders
Apathy
Nervousness
Nervous System Disorders
Ataxia
Dyskinesia neonatal
Dystonia
Hyperreflexia
Hypertonia
Hypokinesia neonatal
Somnolence
Eye Disorders
Visual disturbance
Cardiac Disorders
Arrhythmia*
Electrocardiogram abnormal
Atrioventricular block
Bradycardia
Cyanosis
Respiratory, Thoracic and Mediastinal Disorders
Bronchospasm
Cough
Dysphonia
Hiccups
Hypoventilation
Respiratory disorder
Skin and Subcutaneous Tissue Disorders
Dermatitis allergic*
Dry skin
Hyperhidrosis
Rash
Rash neonatal
Musculoskeletal and Connective Tissue Disorders
Back pain
Hypotonia neonatal
Muscle rigidity*
General Disorders and Administration Site Conditions
Chills
Hypothermia
Body temperature decreased
Injection site pain*
Injection site reaction
Pain
Investigations
Body temperature increased

* ADRs reported from only the trials of sufentanil administered intravenously as an anaesthetic agent.

Postmarketing Data
Adverse drug reactions first identified during postmarketing experience with sufentanil citrate are included in Table 3. In the table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10000 and <1/1000
Very rare	<1/10000, including isolated reports

In Table 3, ADRs are presented by frequency category based on spontaneous reporting rates. The frequency category "not known" is used for ADRs for which no valid estimate of the incidence rate can be derived from clinical trials.

Table 3. Adverse Drug Reactions Identified During Postmarketing Experience with SUFENTA/SUFENTA *FORTE* by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders	
Very rare	Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction
Nervous System Disorders	
Very rare	Coma, Convulsion, Muscle contractions involuntary
Eye Disorders	
Very rare	Miosis
Cardiac Disorders	
Very rare	Cardiac arrest (also see Special warnings and special precautions for use)
Vascular Disorders	
Very rare	Shock
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Respiratory arrest, Apnoea, Respiratory depression, Pulmonary oedema, Laryngospasm (also see Contraindications, and Special warnings and special precautions for use)
Skin and Subcutaneous Tissue Disorders	
Very rare	Erythema
Musculoskeletal and Connective Tissue Disorders	
Very rare	Muscle spasms (also see Special warnings and special precautions for use)

Overdose
Signs and Symptoms
An overdosage of SUFENTA manifests itself as an extension of its pharmacologic actions. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnoea 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 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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
ATC Code N01AH02
Sufentanil is a highly potent opioid analgesic, (7-10 times more potent than fentanyl in man) with a high safety ratio (LD_{50}/ED_{50} for the lowest level of analgesia) in rats; at 25211 this ratio is higher than for fentanyl (277) and for morphine (69.5).
Intravenous sufentanil has a rapid onset of action. Limited accumulation and rapid elimination from tissue storage sites allow a rapid recovery. Depth of analgesia is dose-related and can be adjusted to the pain level of the surgical procedure.
Like other narcotic analgesics, sufentanil, depending on the dose and speed of administration, can cause muscle rigidity, as well as euphoria, miosis and bradycardia.
Histamine assays have not revealed any histamine-releasing potential in patients administered SUFENTA.
All actions of sufentanil are immediately and completely reversed by a specific narcotic antagonist, such as naloxone.

Pharmacokinetic Properties
Sufentanil is a synthetic opioid with µ-agonist pharmacologic effects
Distribution
In studies with intravenous sufentanil doses ranging from 250 to 1500 µg which allow prolonged blood sampling and drug measurements, the following were found: sequential distribution half-lives of 2.3-4.5 min and 35-73 min), a Vc (volume of distribution of the central compartment) of 14.2 L, a Vdss (distribution volume at steady state) of 344 L detection limitations. The sequential distribution half-lives but not the terminal half-life (ranging from 4.1 h after 250 µg to 10-16 h after 500-1500 µg) determine the decline of the sufentanil plasma concentrations from therapeutic to recovery levels. Sufentanil pharmacokinetics are linear within the dose range studied. Plasma protein binding of sufentanil is about 92.5%. Plasma protein binding in children is lower compared to adults and increases with age. In newborns sufentanil is about 80.5% bound to proteins compared to 88.5% in infants and 91.9% in children
Metabolism
The liver and small intestine are the major sites of biotransformation. Sufentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme.
Elimination
The mean (range) terminal elimination half-life of sufentanil is 784 (656-938) min. Because of assay detection limitations, the sufentanil elimination half-life was significantly shorter (240 min) after the 250 µg dose than after 1500 µg. The plasma clearance is 917 mL/min. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug.
Special populations
Hepatic Impairment
The volume of distribution is slightly increased and total clearance slightly decreased in cirrhotic patients compared to controls. This results in a significant prolongation of half-life by about 30% which warrants a longer period of postoperative surveillance (see Special warnings and special precautions for use).
Renal Impairment
The volume of distribution at steady state, total clearance, and terminal elimination half-life in patients on dialysis and undergoing renal transplantation are not different from healthy controls. The free fraction of sufentanil in this population is not different from healthy patients.

Preclinical Safety Data
Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

PHARMACEUTICAL PARTICULARS
List of Excipients
The other ingredients of SUFENTA/SUFENTA *FORTE* are sodium chloride and water for injection.

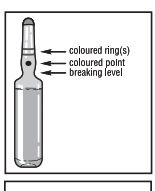
Incompatibilities
The injectable solution must not be mixed with other products.
If desired, SUFENTA/SUFENTA *FORTE* may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with plastic infusion sets, they should be used within 24 hours of preparation.

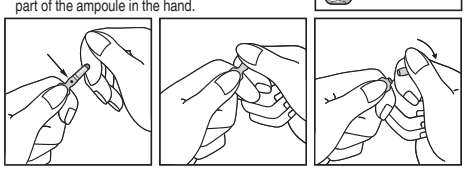
Shelf Life
Observe expiry date on the outer pack

Special Precautions for Storage
Keep ampoule in the outer carton.
Store between 15° and 30° C.
Keep out of reach of children.

Nature and Contents of container
2 and 10 ml ampoules at 5 µg/ml and in 1 and 5 ml ampoules at 50 µg/ml.

Instructions for Use/Handling
1. Maintain the ampoule between thumb and index, leaving the tip of the ampoule free.
2. With the other hand, hold the tip of ampoule putting the index against the neck of ampoule, and the thumb on the coloured point in parallel to the identification coloured ring(s).
3. Keeping the thumb on the point, sharply break the tip of ampoule while holding firmly the other part of the ampoule in the hand.





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JANSSEN-CILAG

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