PRODUCT NAME
SUFENTA[TRADEMARK]
Sufentanil citrate

DOSAGE FORMS AND STRENGTHS
SUFENTA is a sterile, preservative-free, isotonic aqueous solution for intravenous or epidural use.
SUFENTA contains an amount of sufentanil citrate that is equivalent to 5 mcg sufentanil per mL.
For excipients, see List of Excipients.

CLINICAL INFORMATION
Indications
Intravenous SUFENTA is used both as an analgesic adjunct to nitrous oxide/oxygen and as a sole anesthetic 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. SUFENTA is also suited for epidural administration in neuraxial anesthesia.

Intravenous SUFENTA is indicated:
-as an analgesic adjunct during induction and maintenance of balanced general anesthesia
-as an anesthetic agent for induction and maintenance of anesthesia in patients undergoing major surgical procedures.

Epidural SUFENTA is indicated:
-for the postoperative management of pain following general surgery, thoracic or orthopedic procedures and caesarean section.
-as an analgesic adjunct to epidural bupivacaine during labor and vaginal deliveries.

DOSAGE AND ADMINISTRATION
The dosage of SUFENTA should be individualized according to age, body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. 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 (I.V.) dose of an anticholinergic agent just before anesthetic induction.

Use as analgesic adjunct
In patients undergoing general surgery, doses of SUFENTA of 0.5-5 mcg/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 mcg/kg may be expected to last 50 minutes. Supplemental doses of 10-25 mcg should be individually adjusted to the needs of each patient and to the anticipated remaining operation time.

Use as anesthetic agent
When used in doses of ≥ 8 mcg/kg SUFENTA produces sleep and maintains a dose-related profound level of analgesia without the use of additional anesthetic agents. In addition sympathetic and hormonal responses to surgical stimuli are attenuated. Supplementary doses of 25-50 mcg generally suffice to maintain cardiovascular stability during anesthesia.

Epidural Administration
Proper placement of a needle or catheter in the epidural space should be verified before SUFENTA is injected.

Use for postoperative management of pain
An initial dose of 30-50 mcg may be expected to provide adequate pain relief for up 4-6 hours. Additional boluses of 25 mcg may be administered if there is evidence of lightening of analgesia.

Use as analgesic adjunct during labor and vaginal delivery
The addition of SUFENTA 10 mcg to epidural bupivacaine (0.125%-0.25%) provides a longer duration and a better quality of analgesia. If required, two subsequent injections of the combination may be given. It is recommended not to exceed a total dose of 30 mcg sufentanil.

Special populations
Elderly (65 years of age and older)
As with other opioids the dose should be reduced in elderly and in debilitated patients.

Pediatric population
The safety and efficacy of epidural SUFENTA in paediatric patients has been documented in only a limited number of cases.

CONTRAINDICATIONS
SUFENTA is contraindicated in patients with known intolerance to any of its components or to other opioids.

Intravenous use in labor or before clamping of the cord during cesarean section is contraindicated due to the possibility of respiratory depression in the newborn infant. This in contrast to the epidural use in labour, during which sufentanil in doses up to 30 mcg does not influence the condition of the mother or the newborn. (see *Pregnancy and breast-feeding*).

As with other opioids administered epidurally, SUFENTA should not be given in the presence of: severe hemorrhage or shock; septicemia, infection at the injection site; disturbances in hemostasis such as thrombocytopenia and coagulopathy; or in the presence of anticoagulant therapy or of other concomitant drug therapy or medical conditions which could contraindicate the technique of epidural administration.

WARNINGS AND PRECAUTIONS
As with all potent opioids:

Respiratory depression
Respiratory depression is dose related and can be reversed by specific opioid antagonists, 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 opioid antagonists should be readily available. Hyperventilation during anesthesia may alter the patient's responses to CO_2, thus affecting respiration postoperatively.

Risk from concomitant use of central nervous system (CNS) depressants, especially benzodiazepines or related drugs
Concomitant use of SUFENTA and CNS depressants especially benzodiazepines 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 SUFENTA 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 Interactions).

Drug dependence and potential for abuse
Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Therefore, it is possible that a higher dose of SUFENTA may be needed to produce the same result.

Physical dependence may result in acute withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of opioids.

Sufentanil can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of SUFENTA may result in overdose and/or death. Persons at increased risk of opioid abuse may still be appropriately treated with SUFENTA.

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)

Muscle rigidity
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.

Cardiac disease
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.

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.

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.

With epidural administration, caution should be exercised in the presence of respiratory depression or compromised respiratory function and in the presence of foetal distress. The patient should be closely monitored for at least 1 hour after each dose, as early respiratory depression may occur.

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.

INTERACTIONS

Central Nervous System (CNS) depressants

Drugs such as barbiturates, benzodiazepines or related drugs, neuroleptics, general anesthetics, 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 SUFENTA required will be less than usual. Concomitant use with SUFENTA in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death (see Warnings and Precautions).

Effect of SUFENTA on other drugs

Following the administration of SUFENTA, 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 Warnings and Precautions).

Cytochrome P450 3A4 (CYP3A4) inhibitors

Sufentanil is metabolized 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 potents cytochrome P4503A4 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.

Monoamine Oxidase Inhibitors (MAOI)

It is usually recommended to discontinue MAO-inhibitors 2 weeks prior to any surgical or anesthetic procedure.

Serotonergic drugs

Coadministration of sufentanil with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), or Monoamine Oxidase Inhibitors (MAOIs), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Pregnancy and breast-feeding

Pregnancy

Safety of intravenous sufentanil in human pregnancy has not been established although studies in animals have not demonstrated any teratogenic effects. (see *Non-Clinical Information*). Sufenta has been shown to have an embryeidal effects in rats and rabbits when given in doses 2.5 times the upper human IV dose for a period of 10 dogs to over 30 dogs. As with other drugs, risk should be weighed against potential benefit to the patient.

Chronic use of an opioid during pregnancy may cause drug dependence in the neonate, leading to neonatal withdrawal syndrome. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome.

Controlled clinical studies during labor have shown that SUFENTA added to epidural bupivacaine in total doses up to 30 mcg has no detrimental effect on the mother or the newborn, but intravenous use is contraindicated not recommended in labor. Sufenta crosses the placenta. After epidural administration of a total dose not exceeding 30 mcg, average plasma concentrations of 0,016 ng/mL were detected in the umbilical vein.

Assisted ventilation equipment must be immediately available for use if required for the mother and infant. An opioid antagonist for the child must always be available

Breast-feeding
SUFENTA is excreted in breast-milk. Caution should be exercised when SUFENTA is administered to a breast-feeding 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.

ADVERSE REACTIONS
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of sufentanil based on the comprehensive assessment of the available adverse event information. A causal relationship with sufentanil cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data
The safety of SUFENTA 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 anesthetic agent for induction and maintenance of anesthesia 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 labor and vaginal deliveries. These subjects took at least 1 dose of sufentanil and provided safety data. Adverse reactions that were reported for ≥ 1% of sufentanil-treated subjects in these trials are shown in Table 1.

Table 1. Adverse 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 discoloration	3.1
Musculoskeletal and Connective Tissue Disorders	
Muscle twitching	2.0
Renal and Urinary Disorders	
Urinary retention	3.2
Urinary incontinence	1.5

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

General Disorders and Administration Site Conditions	
Pyrexia	1.7

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

Table 2. Adverse 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

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

	Hypothermia
	Body temperature decreased
	Injection site pain*
	Injection site reaction
	Pain
Investigations	
	Body temperature increased

Adverse reactions reported from only the trials of sufentanil administered intravenously as an anesthetic agent.

Postmarketing data

Adverse reactions first identified during postmarketing experience with sufentanil citrate are included in Table 3 and Table 4. In each 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, 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 epidemiological 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 Postmarketing Experience with SUFENTA 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 (see *Warnings and Precautions*)
Vascular Disorders	
Very rare	Shock
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Respiratory arrest, Apnea, Respiratory depression, Pulmonary edema, Laryngospasm (see *Contraindications*, and *Warnings and Precautions*)
Skin and Subcutaneous Tissue Disorders	
Very rare	Erythema
Musculoskeletal and Connective Tissue Disorders	
Very rare	Muscle spasms (see *Warnings and Precautions*)

Table 4. Adverse reactions Identified During Postmarketing Experience with SUFENTA by Frequency Category Estimated from Clinical Trials or Epidemiologic Studies

Immune System Disorders	
Not known	Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction

Table 4. Adverse reactions Identified During Postmarketing Experience with SUFENTA by Frequency Category Estimated from Clinical Trials or Epidemiologic Studies

Nervous System Disorders	
Not known	Coma, Convulsion, Muscle contractions involuntary
Eye Disorders	
Not known	Miosis
Cardiac Disorders	
Not known	Cardiac arrest (*Warnings and precautions*)
Vascular Disorders	
Not known	Shock
Respiratory, Thoracic and Mediastinal Disorders	
Not known	Respiratory arrest, Apnea, Respiratory depression, Pulmonary edema, Laryngospasm (*Contraindications*, and *Warnings and precautions*)
Skin and Subcutaneous Tissue Disorders	
Not known	Erythema
Musculoskeletal and Connective Tissue Disorders	
Not known	Muscle spasms (*Warnings and precautions*)

Overdosage

Symptoms and signs

An overdosage of SUFENTA manifests itself as an extension of its pharmacologic actions. Respiratory depression, which can vary in severity from bradypnea to apnea, may occur.

Treatment

In the presence of hypoventilation or apnea, 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 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 hypovolemia should be considered, and if present, it should be controlled with appropriate parenteral fluid administration.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: opioid anesthetics, ATC Code N01AH03

Mechanism of action

Sufentanil is highly potent opioid analgesics, (7-10 times more potent than fentanyl in man) with a high safety ration (LD50/ED50 for the lowest level of analagesia) in rats; at 25,211 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 opioid 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 opioid antagonist.

Epidural administration:
With epidural use, SUFENTA produces spinal analgesia of a rapid onset (5-10 minutes) and moderate duration (generally 4-6 hours).

Pharmacokinetics properties
Sufentanil is a synthetic opiod with μ-agonist pharmacologic effects.

Distribution
In adults, sufentanil 5 mcg/kg given intravenously is metabolized rapidly (elimination half-life 2,7 hours). The apparent volume of distribution is 2,8 L/kg and the clearance is 2,7 L/kg/min. The pharmacokinetics of sufentanil in patients over age of 70 do not differ from those in young adults. In the neonata (0-1 month) the elimination half life is about 12 hours, the volume of distribution is 4,2 L/kg and the clearance is 6,7 ml/kg/min.

Sufentanil pharmacokinetics are linear within the dose range studied.

With epidural use peak plasma concentrations are reached within 10 minutes and are 4-6 times lower than those after intravenous administration. The addition of epinephrine (50-75 mcg) further reduces the initial fast absorption by 25-50%.

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 metabolized mainly via the human cytochrome P450 3A4 enzyme.

Elimination
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 *Warnings and Precautions*).

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.

NON-CLINICAL INFORMATION
Preclinical effects were observed only at exposure considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

PHARMCEUTICAL INFORMATION
List of Excipients
Sodium chloride
Water for injection

Hydrochloric acid solution
Sodium hydroxide solution

Shelf life
36 months

STORAGE CONDITIONS
Store below 30°C, protect from light.
Keep out of the sight and reach of children.

HOW SUPPLIED
SUFENTA 5 mcg/ml injection
Box @ 5 ampoules @ 10 ml
Reg. No.: DNI1439800243A1

HARUS DENGAN RESEP DOKTER

Manufactured by DEMO S.A. Pharmaceutical Industry, Attiki, Greece dirilis oleh Piramal Critical Care B.V., Voorschoten Netherland.
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