Approved Professional Information for SUFENTA FORTE®

SCHEDULING STATUS S6

1. NAME OF THE MEDICINE

SUFENTA FORTE® solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 50 µg sufentanil as sufentanil citrate.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion. For IV or epidural use.

A clear colourless solution, free from visible foreign material.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUFENTA FORTE administered intravenously in adults is indicated:

- as a primary anaesthetic agent for the induction and maintenance of anaesthesia with 100 % oxygen in patients undergoing cardiac surgery associated with the use of cardiopulmonary bypass apparatus
- as an analgesic adjunct in the maintenance of balanced general anaesthesia in cardiac surgery associated with the use of cardiopulmonary bypass apparatus, as well as surgical procedures requiring endotracheal intubation and ventilation.

SUFENTA FORTE administered by epidural route in adults is indicated:

- for the post-operative management of pain following general surgery, thoracic or orthopaedic procedures and caesarean sections
- as an analgesic adjunct to epidural bupivacaine with or without adrenaline (epinephrine) during labour and vaginal deliveries.

Use in children

Intravenous SUFENTA FORTE is indicated as an analgesic agent for use during induction and/or maintenance of balanced general anaesthesia in children over the age of 1 month.
Epidural SUFENTA FORTE is indicated for use in children aged 1 year and over for the post-operative management of pain following general surgery, thoracic or orthopaedic procedures.

4.2 Posology and method of administration

Posology

The dosage of SUFENTA FORTE should be individualised. Factors to be considered in determining the dose are age, body mass, physical status, underlying pathological condition, use of other medicines, type of anaesthesia to be used and duration of the surgical procedure. The effect of the initial dose should be taken into account in determining the supplemental doses.
In obese patients, the dosage of SUFENTA FORTE should be determined on the basis of standard body mass.

Intravenous administration – Adults

Initial dose: 8 – 30 µg/kg (anaesthetic dose) administered with 100 % oxygen and muscle relaxant. SUFENTA FORTE produces sleep at dosages of 8 µg/kg and maintains a deep level of anaesthesia without the use of additional anaesthetic agents.
Post-operative mechanical ventilation and observation are essential at this dosage level on account of extended post-operative respiratory depression.

Maintenance dose: 0,5 – 0,75 µg/kg as determined by changes in vital signs that indicate surgical stress or lightening of analgesia.

Initial dose: 1 – 8 µg/kg

The duration of action is 1 – 8 hours depending on the dose.

Maintenance dose: 0,1 – 0,5 µg/kg as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

Supplemental dosages should be individualised and adjusted to the remaining operative time anticipated.

Epidural administration:

Proper placement of a needle or catheter in the epidural space should be verified before SUFENTA FORTE is injected to assure that unintentional intravascular or intrathecal administration does not occur. Unintentional intravascular injection of SUFENTA FORTE could result in potentially serious overdose including acute truncal muscular rigidity and apnoea. Unintentional intrathecal injection of the full sufentanil, local anaesthetic epidural doses and volume could produce effects of high spinal anaesthesia including prolonged paralysis and delayed recovery. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to administration of any additional epidural medications. SUFENTA FORTE should be administered by slow injection.

With epidural administration, caution should be exercised in the presence of respiratory depression and in the presence of fetal distress.

Epidural administration requires that the patient should be in a high care environment with continuous supervision. The patient should be closely monitored for at least 2 hours after each dose, as respiratory depression may occur.

Post-operative management of pain – Adults:

An initial dose of 30 – 50 µg may be expected to provide adequate pain relief for up to 4 – 6 hours. Additional boli of 25 µg may be administered if there is evidence of lightening of analgesia. There should be a minimum interval of 1 hour between doses.

Analgesic adjunct during labour and vaginal deliveries:

The recommended dosage is 10 – 15 µg administered with 10 mL bupivacaine 0,125 % with or without epinephrine (adrenaline). SUFENTA FORTE and a local anaesthetic, such as bupivacaine should be mixed together before administration. Doses can be repeated twice (for a total of three doses) at not less than one-hour intervals until delivery.

Special populations for intravenous administration

Elderly (65 years of age and older)

The dose should be reduced in elderly and in debilitated patients.

Patients with severe renal impairment and end stage renal failure

The dosage of SUFENTA FORTE should be reduced in patients with severe renal impairment and end stage renal failure.

SUFENTA FORTE should be titrated with caution in these patients.

Such patients also require prolonged post-operative monitoring.

Paediatric population

Children ≤ 1 month (neonates)

Due to the large variability of pharmacokinetic parameters in neonates, no dosing recommendations can be made (see sections 4.4 and 5.2).

Children > 1 month

Premedication with an anticholinergic such as atropine is recommended for all doses (unless an anticholinergic is contraindicated).

Induction of anaesthesia

SUFENTA FORTE can be administered as a slow bolus injection of 0,2 – 0,5 µg/kg over 30 seconds or longer in combination with an anaesthetic induction agent. For major surgery (e.g. cardiac surgery) doses up to 1 µg/kg can be administered.

Maintenance of anaesthesia in ventilated patients

SUFENTA FORTE can be administered as part of balanced anaesthesia. Dosage depends on the dose of concomitant anaesthetic agents, type and duration of surgery. An initial dose of 0,3 – 2 µg/kg administered by slow bolus injection over at least 30 seconds may be followed by additional boluses of 0,1 – 1 µg/kg as required, up to a total maximum of 5 µg/kg in cardiac surgery.

Special populations for epidural administration

Elderly (65 years and older)

The dose should be reduced in elderly and in debilitated patients.

Paediatric population

SUFENTA FORTE must be administered to children epidurally only by anaesthesiologists

specifically trained in paediatric epidural anaesthesia and in management of respiratory depressant effects of opioids. Appropriate resuscitation equipment, including airway securing devices and an opioid antagonist must be readily available.
Paediatric patients must be monitored for signs of respiratory depression for at least 2 hours after epidural administration of SUFENTA FORTE.

Limited data are available for the use of epidural SUFENTA FORTE in paediatric patients.

Children < 1 year
No data are available for epidural administration of SUFENTA FORTE to newborns and infants younger than 3 months, and limited data are available for children between 3 months and 1 year (see section 5.1).
Safety and efficacy of SUFENTA FORTE in children younger than 1 year have not been established, (see sections 4.4 and 5.1). Therefore, no dosing recommendations can be made for children in this age group.

Children ≥ 1 year
A single bolus dose of 0,25 – 0,75 µg/kg SUFENTA FORTE given intra-operatively provided pain relief for a period, which ranged from 1 to 12 hours in clinical trials. The duration of effective analgesia is influenced by the surgical procedure and concomitant use of epidural amide local anaesthetic.

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

4.3 Contraindications

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

Intravenous use in labour or before clamping of the cord during caesarean section is contraindicated due to the possibility of respiratory depression in the newborn infant. This is in contrast to the epidural use in labour, during which sufentanil in doses up to 30 µg does not influence the condition of the mother or the newborn (see section 4.6).

Epidural SUFENTA FORTE should not be given in the presence of:

- severe haemorrhage or shock
- septicaemia
- infection at the injection site
- disturbances in haemostasis such as thrombocytopenia and coagulopathy and/or anticoagulant therapy
- other concomitant therapy or medical conditions which could contraindicate the technique of epidural administration
- patients on monoamine oxidase inhibitors (MAOIs) within the previous 2 weeks (see section 4.4).

4.4 Special warnings and precautions for use

Respiratory depression is dose related and can be reversed by a specific opioid antagonist, e.g. naloxone, but a repeated dose of the antagonist 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.
The respiratory depression can persist in the post-operative period, and if SUFENTA FORTE has been given intravenously this can recur. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and opioid antagonists should be readily available.

Hyperventilation during anaesthesia may alter the patient's response to CO_2 thus affecting respiration post-operatively.

Concomitant use of SUFENTA FORTE and CNS depressants, especially benzodiazepines or related medicines, in spontaneous breathing patients, may increase the risk of profound sedation, respiratory depression, coma and death. If a decision is made to administer SUFENTA FORTE 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).

Respiratory depression may follow intravenous or epidural use of SUFENTA FORTE.
Vital signs should be monitored routinely.
Induction of muscle rigidity, which may also involve the thoracic respiratory muscles, can occur but the risk may be reduced if intravenous injections are administered slowly. A neuromuscular blocking agent compatible with the patient’s condition may be administered prophylactically to prevent muscle rigidity or to induce muscle relaxation after rigidity occurs.
Non-epileptic (myo)clonic movements can occur.
Because of its weak cholinergic activity, SUFENTA FORTE should be used with caution in patients with cardiac dysrhythmias.
Bradycardia and possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic or when SUFENTA FORTE is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.
SUFENTA FORTE 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 SUFENTA FORTE should be avoided in patients with compromised intracerebral compliance; in such patients the transient decrease in the mean arterial pressure has been accompanied by a 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 elderly and in debilitated patients. SUFENTA FORTE 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
- increased intracranial pressure.

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 fetal distress.

The patient should be closely monitored for at least 2 hours after each dose, as late respiratory depression may occur.

Paediatric population

Due to the large variability of pharmacokinetic parameters in neonates there is a risk of over- or underdosing of SUFENTA FORTE in the neonatal period (see sections 4.2 and 5.2).

Safety and efficacy of intravenous or epidural SUFENTA FORTE in children younger than 1 year have not been established (see sections 4.2 and 5.2).

4.5 Interaction with other medicines and other forms of interaction

Central nervous system (CNS) depressants

Barbiturates, benzodiazepines or related medicines, neuroleptics, inhalational anaesthetics and other non-selective CNS depressants (e.g. alcohol), may potentiate the respiratory depressive effects of SUFENTA FORTE.

When patients have also received central nervous system depressants, the dose of SUFENTA FORTE required will be less than usual. Concomitant use with SUFENTA FORTE in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death (see section 4.4).

Effect of SUFENTA FORTE on other medicine

Following the administration of SUFENTA FORTE, the dose of other CNS depressants 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).

Cytochrome P450 3A4 (CYP3A4) inhibitors

Sufentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. However, no *in vivo* inhibition by erythromycin (a known CYP3A4 inhibitor) has been observed. Although clinical data are lacking, *in vitro* data suggest that other potent CYP3A4 inhibitors (e.g. fluconazole, ketoconazole, itraconazole, ritonavir, diltiazem and cimetidine) may inhibit the metabolism of sufentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such medicines requires special patient care and observation; in particular, it may be necessary to lower the dose of SUFENTA FORTE.

Monoamine oxidase inhibitors (MAOIs)

Monoamine oxidase inhibitors (MAOIs) must be discontinued 2 weeks prior to the administration of SUFENTA FORTE.

Serotonergic medicines

Coadministration of SUFENTA FORTE with a serotonergic medicine, 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of SUFENTA FORTE in pregnancy and lactation has not been established, although studies in animals have not demonstrated any teratogenic effects.

SUFENTA FORTE added to epidural bupivacaine in total doses up to 30 µg has no detrimental effect on the mother or the newborn, but intravenous use is contraindicated in labour (see section 4.3).

SUFENTA FORTE crosses the placenta. After epidural administration of a total dose not exceeding 30 µg, average plasma concentrations of 0,016 ng/mL were detected in the umbilical vein. An antidote for the child should always be at hand.

Breastfeeding

SUFENTA FORTE is excreted in breast milk. Caution should be exercised when SUFENTA FORTE is administered to a breastfeeding woman. A woman should not breastfeed her infant for 10 hours after receiving SUFENTA FORTE.

4.7 Effects on ability to drive and use machines

Patients should not drive, operate a machine or make legally binding decisions until 24 hours after administration of SUFENTA FORTE, nor should alcohol be consumed during that time period.

4.8 Undesirable effects

Adverse reactions

Clinical trial data

The safety of 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 post-operative analgesic or as an analgesic adjunct to epidural bupivacaine during labour and vaginal deliveries. 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
Neonatal tremor	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 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
Neonatal dyskinesia
Dystonia
Hyperreflexia
Hypertonia
Neonatal hypokinesia
Somnolence
Eye disorders
Visual disturbance
Cardiac disorders
Dysrhythmia*
Abnormal electrocardiogram
Atrioventricular block
Bradycardia
Cyanosis
Respiratory, thoracic and mediastinal disorders
Bronchospasm
Cough
Dysphonia
Hiccups
Hypoventilation
Respiratory disorder
Skin and subcutaneous tissue disorders
Allergic dermatitis*
Dry skin
Hyperhidrosis
Rash
Neonatal rash

Musculoskeletal and connective tissue disorders
Back pain
Neonatal hypotonia
Muscle rigidity*
General disorders and administration site conditions
Chills
Hypothermia
Decreased body temperature
Injection site pain*
Injection site reaction
Pain
Investigations
Increased body temperature

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

Post-marketing data

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

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.

Table 3: Adverse drug reactions identified during post-marketing experience with SUFENTA FORTE	
Immune system disorders	
Very rare	Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction
Nervous system disorders	
Very rare	Coma, convulsions, involuntary muscle contractions
Eye disorders	
Very rare	Miosis
Cardiac disorders	
Very rare	Cardiac arrest (see section 4.4)
Vascular disorders	
Very rare	Shock
Respiratory, thoracic and mediastinal disorders	
Very rare	Respiratory arrest, apnoea, respiratory depression, pulmonary oedema, laryngospasm (see sections 4.3 and 4.4)
Skin and subcutaneous tissue disorders	
Very rare	Erythema
Musculoskeletal and connective tissue disorders	
Very rare	Muscle spasms (see section 4.4)

Paediatric populations

Frequency, type and severity of adverse reactions in paediatric patients are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of SUFENTA FORTE is important. It allows continued monitoring of the benefit/risk balance of SUFENTA FORTE. Health care providers are asked to report any suspected adverse reactions via the **"Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

An overdose of SUFENTA FORTE manifests itself as an extension of its pharmacological actions. Respiratory depression, which can vary in severity from bradypnoea to apnoea, may occur.

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, 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 monitored, 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 2.9 Central nervous system depressants. Narcotic analgesics.

Pharmacotherapeutic group: opioid anaesthetics, ATC code: N01AH03.

5.1 Pharmacodynamic properties

Mechanism of action

SUFENTA FORTE injection is an opioid analgesic with hypnotic properties. Intravenous SUFENTA

FORTE produces a dose-related attenuation of catecholamine release, particularly norepinephrine (noradrenaline).

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 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 FORTE.

All actions of sufentanil are immediately and completely reversed by a specific opioid antagonist, e.g. naloxone.

Epidural administration

With epidural use in adults, SUFENTA FORTE produces spinal analgesia with an onset of 5 – 10 minutes and a duration of 4 – 6 hours.

In 15 children aged 4 to 12 years the mean onset and duration of analgesia were 3,0 ± 0,3 and 198 ± 19 minutes, respectively, after epidural administration of 0,75 µg/kg sufentanil.

5.2 Pharmacokinetic properties

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

Distribution

In studies with intravenous sufentanil doses ranging from 250 to 1 500 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 V_c (volume of distribution of the central compartment) of 14,2 L, a V_{dss} (distribution volume at steady state) of 344 L.
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 µg) determines the decline of the sufentanil plasma concentrations from therapeutic to recovery levels. Sufentanil pharmacokinetics are linear within the dose range studied.

Peak plasma concentrations of sufentanil administered epidurally are reached within 10 minutes and are 4 – 6 times lower than those after intravenous administration. The addition of adrenaline (50 – 75 µg) 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 metabolised mainly via the human cytochrome P450 3A4 enzyme.

Elimination

The mean (range) terminal elimination half-life of sufentanil is 13 (11 – 15) h. Because of assay detection limitations, the sufentanil elimination half-life was significantly shorter (240 min) after the 250 µg dose than after 1 500 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 unchanged.

Special populations

Hepatic impairment

The volume of distribution is increased and total clearance 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 post-operative surveillance (see section 4.4).

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.

Paediatric population

Pharmacokinetic information in children is limited.

Intravenous administration

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, 91,9 % in children and 92,5 % in adults.

After administration of an intravenous sufentanil bolus of 10 – 15 µg/kg in paediatric patients undergoing cardiac surgery, the pharmacokinetics of sufentanil can be described by a triexponential curve as in adults (Table 4). Clearance normalised to body mass was shown to be higher in infants and children compared to adolescents, whose clearance rates were comparable to that of adults. In neonates, clearance was significantly reduced and exhibited large variability (range 1,2 to 8,8 mL/min/kg and one outlying value of 21,4 mL/min/kg). Neonates were shown to have a greater distribution volume at steady state and a prolonged elimination half-life. Pharmacodynamic differences due to differences in the pharmacokinetic parameters may be greater if the unbound fraction is taken into account.

Table 4: Mean sufentanil pharmacokinetic parameters in children following administration of 10 – 15 µg/kg sufentanil as a single intravenous bolus (N = 28)				
Age group	**N**	**V_{dss} (L/kg) Mean (± SD)**	**$T_{½β}$ (min) Mean (± SD)**	**Cl (mL/kg/min) Mean (± SD)**
Neonates (1 to 30 d)	9	4,15 (1,01)	737 (346)	6,7 (6,1)
Infants (2 to 23 m)	7	3,09 (0,95)	214 (41)	18,1 (2,8)
Children (3 to 11 y)	7	2,73 (0,50)	140 (30)	16,9 (3,2)
Adolescents (13 to 18 y)	5	2,75 (0,53)	209 (23)	13,1 (3,6)

Cl = clearance, normalised to body mass; N = number of patients included in analysis;

SD = standard deviation; $T_{½β}$ = elimination half-life; V_{dss} = volume of distribution at steady state.

Age ranges stated are those of the children studied.

Epidural administration

After epidural administration of 0,75 µg/kg sufentanil in 15 children aged 4 to 12 years, plasma levels taken 30, 60, 120 and 240 min after injection ranged from 0,08 ± 0,01 to 0,10 ± 0,1 ng/mL.
In 6 children aged between 5 and 12 years receiving a 0,6 µg/kg sufentanil bolus followed by continuous epidural infusion containing 0,08 µg/kg/h sufentanil and bupivacaine 0,2 mg/kg/h for 48 h, maximum concentrations were reached at approximately 20 min after bolus injection and ranged from below the limit of quantification (< 0,02 ng/mL) to 0,074 ng/mL.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid solution (for pH adjustment)

Sodium hydroxide solution (for pH adjustment)

Sodium chloride

Water for injection.

6.2 Incompatibilities

SUFENTA FORTE solution must not be mixed with other products. If desired, SUFENTA FORTE may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with preparation.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

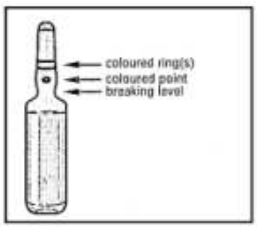
Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

Cartons containing 5 x 5 mL ampoules.

6.6 Special precautions for disposal and other handling

Wear gloves while opening ampoule.



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

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

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 usage of soap, alcohol, and other cleaning materials that may cause chemical or physical abrasions to the skin.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Piramal Critical Care South Africa (Pty) Ltd

Office 2, Ground Floor

Kiepersol House

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300 Acacia Road

Darrenwood 2194

8. REGISTRATION NUMBER

V/2.9/308

9. DATE OF FIRST AUTHORISATION

28 November 1988

10. DATE OF REVISION OF THE TEXT

6 November 2020