SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sufentanil Narcomed®, 50 microgram / ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 75 micrograms of sufentanilcitrate, corresponding to 50 micrograms of sufentanil.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Sufentanil Narcomed® is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anaesthesia during procedures involving endotracheal intubation and artificial respiration.

- As an analgesia component of combination anaesthesia.
- For the induction and maintenance of general anaesthesia in major operations

4.2 Posology and method of administration

The dosage is adjusted according to the individual response and the clinical effect. The following factors should be taken into account: patient's age, bodyweight, general condition, and any concurrently administered medication. The dose also depends on the type and length of operation and the depth of anaesthesia required. The effect of the initial dose should be taken into account for the calculation of further doses.

Droperidol may be added during induction to prevent the occurrence of nausea and vomiting.

The following dosage guidelines should be observed:

Adults

Use as an analgesic component in combination anaesthesia: 0.5-5.0 µg/kg bodyweight as intravenous bolus or as a 2-10 minutes infusion. Maintenance dose for analgesia when clinical signs indicate a decrease in analgesic effect: 0.15-0.7 µg/kg bodyweight (equivalent to 0.2 – 1.0 ml Sufentanil Narcomed® / 70 kg bodyweight).

Intravenous induction dose when used as the sole anaesthetic: 8-30 µg/kg bodyweight. Maintenance dose for anaesthesia when clinical signs indicate a decrease in anaesthetic effect: 0.35-1.4 µg/kg bodyweight (equivalent to 0.5-2.0 ml Sufentanil Narcomed® /70 kg bodyweight).

Children

The efficacy and safety of sufentanil in children under two years old has only been documented in a limited number of cases.

For induction and maintenance of general anaesthesia in children aged 2-12 years a dose of 10- 20 µg/kg bodyweight is recommended, combined with 100% oxygen ventilation. Additional doses of 1-2 µg/kg bodyweight can be administered if clinical signs indicate a decrease in anaesthetic effect.

Additional dosage information

The total dose should be carefully titrated in patients with the following diseases: non-compensated hypothyroidism, pulmonary diseases (especially those with reduced respiratory reserve), liver and/or kidney insufficiency, obese patients and alcoholics. In these patients a longer period of postoperative observation is recommended.

The dose should be reduced in weak and elderly patients and in patients who have already received medication which causes respiratory depression. Higher doses may be required in patients receiving opioid therapy or those with a record of opioid misuse.

Administration routes and methods

Intravenous bolus injection or intravenous infusion. De duration of the administration depends on the length of the operation. Additional dosage may be required when there is a need from the individual patient.

4.3 Contraindications

Known hypersensitivity to sufentanil or to other opioids

Intravenous use in childbirth or prior to cutting the umbilical cord in Caesarean sections, as sufentanil may cause respiratory depression in neonates.

Sufentanil must not be administered to neonates, during pregnancy or to women who are breast-feeding. Breast-feeding may be resumed 24 hours after anaesthesia.

Simultaneous use of MAO inhibitors or treatment with MAO inhibitors within the last 14 days prior to administration of sufentanil

Acute hepatic porphyria

Existing respiratory depression due to other medications

Diseases in which respiratory depression has to be avoided.

Hypovolemia, hypotension

Myasthenia gravis

4.4 Special warnings and precautions for use

Intravenous sufentanil should only be used by a trained anaesthetist in hospitals or other locations with facilities

for intubation and artificial respiration.

After each dose, the patient should be monitored frequently for a sufficiently long period.

Caution is required in patients with cranio-cerebral trauma. Administration of rapid bolus injections of opioids should be avoided in patients with compromised cerebral blood-flow. In such patients a transient reduction in the mean arterial pressure has occasionally been accompanied by a short-term reduction in cerebral perfusion pressure.

Deep anaesthesia is associated with a marked respiratory depression which can continue or recur in the postoperative phase. Patients should therefore be adequately monitored and standard apparatus and medication for reanimation (including antagonists) should always be available. The respiratory depression is dose-dependent and can be completely reversed by specific antagonists (e.g. naloxone). Since the respiratory depression can last longer than the effect of the antagonists, it may be necessary to administer repeated doses of the latter. Hyperventilation during anaesthesia can reduce the reaction of the respiratory centre to CO_2 and thus affect postoperative respiration.

Sufentanil can result in muscular rigidity, including rigidity of the thorax muscles, however, this can be prevented by employing the following procedures: slow intravenous injection (at low doses this is normally sufficient prophylaxis), premedication with a benzodiazepine or the use of muscle relaxants.

If the preoperative dose of anticholinergic drug is insufficient or if sufentanil is combined with a non-vagolytic relaxant, bradycardia or even asystole can occur. Bradycardia can be treated with atropine.

Caution is required in cases of hypothyroidism, pulmonary disorders, liver and/or kidney insufficiency, in elderly, obesity, alcoholism, and in patients receiving other substances known to have a depressant effect on the central nervous system. In these patients a longer period of postoperative observation is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration with barbiturates, opioids, tranquillizers, neuroleptics, alcohol, other anaesthetics, or other substances which exert a depressant effect on the central nervous system, can result in a reciprocal enhancement of the depressive effect on respiration and on the central nervous system.

Concurrent use of high doses of sufentanil and N_2O can lead to a drop in blood pressure, heart frequency, and heart minute volume.
It is generally recommended that MAO inhibitors should not be taken for two weeks prior to anaesthetic or surgical procedures.

Sufentanil is mainly metabolised by cytochrome oxydase CYP 3A4. Clinical observations of interactions have not been observed. However, experimental data suggest that CYP 3A4 inhibitors, such as e.g. erythromycin, ketoconazole, itraconazole, and ritonavir may inhibit the metabolism of sufentanil to such an extent that a prolonged respiratory depression could result. In cases of necessary concomitant administration the patient should be monitored particularly carefully. A dose reduction of Sufentanil Narcomed® might possibly become necessary.

4.6 Pregnancy and lactation

Sufentanil crosses the placenta, and in rat foetuses it reaches levels equivalent to 33% of the maximal values measured in maternal plasma. In women, sufentanil rapidly crosses the placenta and transfer increases linearly with the maternal concentration. An umbilical venous: maternal venous ratio of 0.81 was determined. Effects on

reproduction in rats and rabbits (reduced fertility, embryotoxic effects, foetal toxicity, increased deaths among new-born pups) were only observed at dose levels that were toxic for parental animals. Teratogenic effects were not observed.

There are no human studies investigating the use of sufentanil during pregnancy and lactation.

Sufentanil must not be administrered during pregnancy and lactation.

Nursing can be continued 24 hours after anaesthesia.

4.7 Effects on ability to drive and use machines

Following narcosis with sufentanil the patient should not drive or operate machines for as long as it is considered necessary by the supervising physician. The patient should be accompanied home and should not drink alcoholic beverages.

4.8 Undesirable effects

Typical opiate symptoms, such as respiratory depression, apnoea, skeletal muscle rigidity (thorax rigidity), myoclonic movements, hypotension, bradycardia, nausea, vomiting and dizziness. Occasionally pruritus and pain at the site of injection.

Other less commonly reported adverse effects are:

- laryngospasm
- allergic reactions and asystole; due to the fact that in narcosis various drugs are administered concurrently it is especially difficult to assign such reactions to sufentanil.
- reappearance of postoperative respiratory depression bas occasionally been observed.

4.9 Overdose

Overdose can result in augmentation of the pharmacological effect as well as that of undesirable effects of the drug. Clinical symptoms are mainly characterised by respiratory depression, which can vary from bradypnea to apnoea depending on individual sensitivity.

Treatment

Oxygen and assisted or controlled respiration are indicated for the treatment of hypoventilation or apnoea. A specific antagonist, such as naloxone, can be used to control respiratory depression, however, such treatment cannot replace immediate symptomatic measures. Since the duration of respiratory depression can exceed the duration of the effect of the antagonist, repeated doses of the latter may be required. If muscular rigidity occurs, administration of a muscle relaxant can aid assisted or controlled respiration.

The patient should be carefully supervised in order to ensure the maintenance of a constant body temperature and balanced levels of body fluids. Serious or prolonged hypotension may be caused by hypovolaemia, which can be treated with adequate volume supplementation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): opioid anesthetics (N01AH03)

Sufentanil is a potent opioid analgesic and is a specific μ-agonist which has a 7-10 fold higher affinity to μ-receptors than fentanyl. The analgesic effect of sufentanil is several fold greater than that of fentanyl, and it maintains good haemodynamic stability whilst simultaneously ensuring a satisfactory myocardial oxygen supply.

Following intravenous administration the maximal effect is reached within a few minutes. Important aspects of the results of pharmacological studies were the cardiovascular stability, EEG responses analogous to fentanyl, and the lack of immunosuppression, haemolysis, or histamine release. The possibility of bradycardia is explained by its effect on the central vagus nucleus, as found with other opioids. Increases in heart frequency caused by pancuronium are either not, or only slightly suppressed by sufentanil.

Sufentanil has a wide safety margin. The LD_{50}/ED_{50} for the lowest grade of anaesthesia in rats is 25,211 and is thus higher than that for fentanyl (277) or morphine (69.5). Limited accumulation and rapid elimination from storage compartments result in a rapid recovery. The depth of analgesia is dose dependent and can be adapted to the level of operative pain.

Depending on the dose and the rapidity of injection, sufentanil can cause muscular rigidity, euphoria, miosis, and bradycardia. All the effects of sufentanil can be immediately and completely reversed by the administration of an antagonist such as naloxone, nalorphine, or levallorphan.

5.2 Pharmacokinetic properties

Monitoring of blood and serum concentrations of sufentanil following intravenous doses of 250-1500 μg revealed the following results:

The half-life of the distribution phases were 2.3- 4.5 min and 35-73 min. The average terminal elimination half-life was 784 min and the range was 656-938 min. The distribution volume in the central compartment was 14.2 l, and the distribution volume in steady state was 344 l. The clearance was 914 ml/min. Due to limitations in the detection method, a significantly shorter elimination half-lire (240 min) was found after administration of a 250 μg dose compared to that found after a dose of 1500 μg.

The drop in plasma concentration from a therapeutic to a subtherapeutic level is determined by the half-lives in the distribution phase and not by the terminal half-lire (4.1 h with 250 μg and up to 10-16 h after 500-1500 μg). Sufentanil showed linear pharmacokinetics in the dose range investigated.

Biotransformation mainly occurred in the liver and intestine. Approximately 80% of the administered dose was excreted within 24 h, only 2% was excreted unchanged. Sufentanil is 92.5% bound to plasma proteins.

5.3 Preclinical safety data

Acute toxicity

Acute toxic effects are described in section 4.9.

Subacute and chronic toxicity

Daily injections of sufentanil for one month revealed effects typical for narcotic analgesics. In dogs, ataxia, hypoxia, mydriasis and sleeping were observed. Rats demonstrated exophthalmia, muscular rigidity and a loss of the righting reflex. In all species there was a reduction in food consumption and a resulting weight loss. The

latter, coupled with a repeated daily reduction in physical activity also explains the unspecific toxic effects.

Mutagenicity /carcinogenicity

The available studies on mutagenicity have not revealed any evidence of a mutagenic potential of sufentanil. No long-term studies in animals are available to assess the carcinogenic potential of sufentanil.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium chloride
Water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

1 ml ampoule (colourless type I glass)
5 ml ampoule (colourless type I glass)
10 ml ampoule (colourless type I glass)

Package sizes:
5 ampoules of 1 ml
5 ampoules of 5 ml
5 ampoules of 10 ml

Hospital packages:
25 (5X5) ampoules of 1 ml
25 (5X5) ampoules of 5 ml
50 (10X5) ampoules of 10 ml

6.6 Special precautions for disposal <and other handling>

Any product content remaining in the container should be discarded.
The container and solution should be inspected visually prior to use. Use only clear, particle free, colourless solution and undamaged container.

7. MARKETING AUTHORISATION HOLDER

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Trapgans 5
1244 RL Ankeveen
Tel: 0031 35 - 52 8 83 77
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8. MARKETING AUTHORISATION NUMBER

Registered under national authorisation number RVG 25565.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Renewal of the Authorisation: 10-08-01

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Date of revision: October 2012.