Rapifen™

NAME OF THE MEDICINAL PRODUCT
Trade Name
RAPIFEN

Nonproprietary Names
Alfentanil Hydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION
RAPIFEN is a sterile preservative-free, isotonic, aqueous solution containing alfentanil hydrochloride equivalent to 0.5 mg alfentanil per ml. The other ingredients are sodium chloride and water for injection. RAPIFEN (alfentanil) is supplied in 2 ml and 10 ml ampoules.

PHARMACEUTICAL FORM
RAPIFEN is a very short-acting potent narcotic analgesic for intravenous (I.V.) use.

CLINICAL PARTICULARS
Therapeutic Indications
RAPIFEN is indicated for use as:
- an anaesthetic induction agent.
- a narcotic analgesic in general as well as adjuvant to regional anaesthesia and for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures.

Because of its rapid and short-lasting action, RAPIFEN is particularly suited as a narcotic analgesic for short procedures and outpatient surgery, but also as an analgesic supplement for procedures of medium and long duration, since periods of very painful stimuli can easily be overcome by small increments of RAPIFEN or by adapting its infusion rate.

Posology and Method of Administration
The dosage of RAPIFEN should be individualized according to age, body weight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.
The initial dose should be reduced in the elderly and in debilitated patients. In children it should be increased. 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 agent just before induction. Droperidol may be given to prevent nausea and vomiting.

1. For use as an induction agent
An intravenous bolus dose of ≥120 µg/kg (17 ml/70 kg) RAPIFEN will induce hypnosis and analgesia while maintaining good cardiovascular stability in patients with adequate muscle relaxation.

2. For short procedures and use in outpatients
Small doses of RAPIFEN are most useful for minor, short but painful surgical procedures and for outpatients, provided good monitoring equipment is available.
An intravenous bolus dose of 7 to 15 µg/kg (1 to 2 ml/70 kg) will suffice for procedures lasting less than 10 minutes. Should the duration of the procedure exceed 10 minutes, further increments of 7 to 15 µg/kg (1 to 2 ml/70 kg) should be given every 10 to 15 minutes or as required.
Spontaneous respiration may be maintained in most instances with a dose of 7 µg/kg (1 ml/70 kg) or less, slowly injected; suggested increments with this technique are 3.5 µg/kg (0.5 ml/70 kg).
It is preferable not to administer droperidol or benzodiazepines to outpatients as these drugs may lengthen the recovery period. In outpatients, a preferred technique consists of an anticholinergic agent, a short-acting induction hypnotic, RAPIFEN and N_2O/O_2.
When postoperative nausea occurs, it is of relatively short duration and easily controlled by conventional measures.

3. For procedures of medium duration
The dose of initial intravenous bolus should be adapted to the expected duration of the surgical procedure as follows:

Duration of the procedure (min.)	RAPIFEN I.V. bolus dose	
	µg/kg	ml/70 kg
10-30	20-40	3-6
30-60	40-80	6-12
>60	80-150	12-20

When surgery is more prolonged or more aggressive, analgesia can be maintained by:
- either increments of 15 µg/kg (2 ml/70 kg) RAPIFEN when required (to avoid postoperative respiratory depression, no RAPIFEN should be administered during the last 10 minutes of surgery);
- or a RAPIFEN infusion at a rate of 1 µg/kg/min (0.14 ml/70 kg/min) until 5 to 10 minutes before the completion of surgery.

Periods of very painful stimuli can easily be overcome by small dose increments or by temporarily increasing the infusion rate.
When RAPIFEN is used without N_2O/O_2 or another inhalation anaesthetic, a higher maintenance dose of RAPIFEN is required.

4. For long procedures
RAPIFEN may be used as the analgesic component of anaesthesia for long lasting surgical procedures especially when rapid extubation is indicated. Optimum analgesia and stable autonomic condition are maintained through an individually adapted initial intravenous dose and by adjusting the infusion rate to the severity of the surgical stimuli and the reactions of the patients.

Contraindications
Known intolerance to the drug or to other morphinomimetics.

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 additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist. Profound analgesia is accompanied by marked respiratory depression and loss of consciousness, which can persist or recur in the postoperative period. 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 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 agents, or when RAPIFEN 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.

Interaction with Other Medicinal Products and Other Forms of Interaction
Drugs Modifying the Effect of Alfentanil
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 RAPIFEN required will be less than usual. Likewise, following the administration of RAPIFEN, the dose of other CNS-depressant drugs should be reduced.
Alfentanil is metabolized mainly via the human cytochrome P450 3A4 enzyme. In vitro data suggest that potent cytochrome P450 3A4 enzyme inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may inhibit the metabolism of alfentanil. Available human pharmacokinetic data indicate that the metabolism of alfentanil is inhibited by fluconazole, voriconazole, erythromycin, diltiazem and cimetidine (known cytochrome P450 3A4 enzyme inhibitors). 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 RAPIFEN.
It is usually recommended to discontinue MAO-inhibitors 2 weeks prior to any surgical or anaesthetic procedure.

Effect of Alfentanil on the Metabolism of other Drugs
In combination with RAPIFEN, the blood concentrations of propofol are 17% higher than in the absence of RAPIFEN. The concomitant use of alfentanil and propofol may require a lower dose of RAPIFEN.

Pregnancy and Lactation
Use During Pregnancy
Although no teratogenic or acute embryotoxic effects have been observed in animal experiments, insufficient data are available to evaluate any harmful effects in man. See Preclinical Safety Data. Consequently, it is necessary to consider possible risks and potential advantages before administering this drug to pregnant patients.
Administration (I.V.) during childbirth (including caesarian section) is not recommended, because RAPIFEN crosses the placenta and because the fetal respiratory centre is particularly sensitive to opiates. If RAPIFEN is administered nevertheless, an antidote for the child should always be at hand.

Use During Lactation
RAPIFEN may enter in the maternal milk. Therefore, nursing is not recommended for 24 hours following the administration of RAPIFEN.
Effects on Ability to Drive and Use Machines
Car driving and the operation of machines can only be resumed when sufficient time has elapsed after administration of RAPIFEN.
Individual reactions vary. On average, the patient should wait 3 to 6 hours after doses of 1 to 3 ml and 12 to 24 hours after higher doses and infusions.

Undesirable Effects
Clinical Trial Data
The safety of RAPIFEN was evaluated in 1157 subjects who participated in 18 clinical trials. RAPIFEN was administered as an anaesthetic induction agent or as an analgesic/anaesthesia adjuvant to regional and general anaesthesia, in short, medium, and long surgical procedures. These subjects took at least one dose of RAPIFEN and provided safety data. Adverse Drug Reactions (ADRs) that were reported for ≥1% of RAPIFEN-treated subjects in these trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥1% of RAPIFEN-treated Subjects in 18 Clinical Trials of RAPIFEN

System / Organ Class Adverse Reaction	RAPIFEN (n=1157) %
Psychiatric Disorders	
Euphoric mood	1.8
Nervous System Disorders	
Movement disorder	7.9
Dizziness	2.4
Sedation	1.5
Dyskinesia	1.4
Eye Disorders	
Visual disturbance	1.1
Cardiac Disorders	
Bradycardia	5.4
Tachycardia	1.0
Vascular Disorders	
Hypotension	4.1
Hypertension	2.2
Blood pressure decreased	1.3
Blood pressure increased	1.0
Respiratory, Thoracic and Mediastinal Disorders	
Apnoea	8.6
Gastrointestinal Disorders	
Nausea	17.0
Vomiting	14.0
Musculoskeletal and Connective Tissue Disorders	
Muscle rigidity	3.1
General Disorders and Administrative Site Conditions	
Fatigue	2.0
Chills	1.8
Injection site pain	1.6
Injury, Poisoning, and Procedural Complications	
Procedural pain	1.1

Additional ADRs that occurred in <1% of RAPIFEN-treated subjects in the 18 clinical trials are listed below in Table 2.

Table 2. Adverse Drug Reactions Reported by <1% of RAPIFEN-treated Subjects in 18 Clinical Trials of RAPIFEN

System / Organ Class Adverse Reaction
Psychiatric Disorders
Agitation
Crying
Nervous System Disorders
Headache
Somnolence
Unresponsive to stimuli
Cardiac Disorders
Arrhythmia
Heart rate decreased
Vascular Disorders
Vein pain
Respiratory, Thoracic and Mediastinal Disorders
Bronchospasm
Hiccups
Hypercapnia
Laryngospasm
Epistaxis
Respiratory depression
Skin and Subcutaneous Tissue Disorders
Dermatitis allergic
Hyperhidrosis
Pruritus
General Disorders and Administrative Site Conditions
Pain
Injury, Poisoning and Procedural Complications
Confusion postoperative
Agitation postoperative
Airway complication of anaesthesia
Anaesthetic complication neurological
Procedural complication
Endotracheal intubation complication

Postmarketing Data
Adverse drug reactions first identified during postmarketing experience with RAPIFEN 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.

Table 3. Adverse Drug Reactions Identified During Postmarketing Experience with RAPIFEN by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders	
Very rare	Hypersensitivity (including anaphylactic reaction, anaphylactoid reaction, and urticaria)
Psychiatric Disorders	
Very rare	Disorientation
Nervous System Disorders	
Very rare	Loss of consciousness[a], Convulsion, Myoclonus
Eye Disorders	
Very rare	Miosis
Cardiac Disorders	
Very rare	Cardiac arrest
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Respiratory arrest, Respiratory depression[b], Cough
Skin and Subcutaneous Tissue Disorders	
Very rare	Erythema, Rash
General Disorders and Administration Site Conditions	
Very rare	Pyrexia

[a] Postoperative period.
[b] Including fatal outcome.

Overdose
Signs and Symptoms
The manifestations of RAPIFEN overdosage are 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
Pharmacodynamics
ATC CODE N01AH02
Alfentanil is a potent fast and short acting narcotic analgesic, chemically related to fentanyl. After intravenous administration of alfentanil action sets in almost instantly, the onset of action amounts to only one quarter of that of an equianalgesic dose of fentanyl. The maximum analgesic and respiratory depressant effect occurs within 1-2 minutes (30 minutes with morphine).
The duration of action of alfentanil is only one third of that of an equianalgesic dose of fentanyl and is clearly dose-related. For analgesia lasting longer than 60 minutes, an infusion is preferable. Its depressant effects on respiratory rate and alveolar ventilation last also shorter than those of fentanyl; in most cases the duration of analgesia exceeds that of the respiratory depression. The duration and degree of respiratory depression tend to be dose-related.
High doses (>120 µg/kg) of alfentanil induce sleep and can be used for induction of anaesthesia. The induction is smooth, pain-free and devoid of cardiovascular and hormonal stress responses to intubation.
Alfentanil has a very wide safety margin. In rats the ratio of LD_{50}/ED_{50} for the lowest level of analgesia, for alfentanil is 1080 compared with 4.6, 69.5 and 277 for pethidine, morphine and fentanyl respectively.
In common with other narcotic analgesics, alfentanil can, depending upon the dose and speed of administration, cause muscle rigidity, as well as euphoria, miosis and bradycardia.
At doses up to 200 µg/kg, alfentanil failed to produce a significant increase in histamine levels or clinical evidence of histamine release.
Recovery after alfentanil administration is rapid and smooth with a low incidence of postoperative nausea and vomiting.
All actions of alfentanil are immediately and completely reversed by a specific narcotic antagonist such as naloxone.

Pharmacokinetic Properties
Pharmacokinetics
Alfentanil is a synthetic opioid with µ-agonist pharmacologic effects, used only intravenously.

Distribution.
The sequential distribution half-lives of alfentanil are 0.4-2.2 min and 8-32 min The low degree of ionisation (11% at pH = 7.4) contributes to a rapid but limited tissue distribution. Reported volumes of distribution are 1.27-4.81 L (volume of distribution of the central compartment) and 12.1-98.2 L (volume of distribution at steady-state). Plasma protein binding of alfentanil is about 92%.

Metabolism
Alfentanil is mainly metabolised in the liver. Only 1% of unchanged alfentanil is found in urine. Metabolites are inactive and 70-80% of them are eliminated via the urine.

Elimination
Alfentanil is rapidly eliminated after intravenous administration. Terminal elimination half-lives of 83-223 min have been reported. The plasma clearance in young subjects averages 356 ml/min, and decreases with age. Only 1% of unchanged alfentanil is found in urine. Once steady-state has been reached after infusion, the elimination half-life remains unaltered. When the administration is discontinued, the patient awakes rapidly without narcotic after effects.

Special Populations
Pediatrics
Protein binding in newborns is 75% and increases in children to 85%. The plasma clearance in newborns is approximately 7.2 ± 3.2mL/kg/min and 4.7 ± 1.7 mL/kg/min in children between 4.5 to 7.75 year. The volume of distribution at steady state was 1230 ± 520 mL/kg in newborns and 163.5 ± 110 mL/kg in children. The half-life is 146 ± 57 minutes in newborns and 40.2 ± 8.9 minutes in children.

Hepatic Impairment
After administration of a single intravenous dose of 50 µg/kg, the terminal half-life in cirrhotic patients is significantly longer than in controls. The volume of distribution remains unchanged. The free fraction of alfentanil increases in cirrhotic patients to 18.5% compared with 11.5% in controls. This increase in free fraction together with a reduction in clearance from 3.06 mL/min/kg in controls to 1.60 mL/min/kg in cirrhotic patients will result in a more prolonged and pronounced effect (see Special Warnings and Special Precautions for Use section).

Renal Impairment
The volume of distribution and clearance of the free fraction is similar in renal failure patients and healthy controls. The free fraction of alfentanil in patients with renal failure is increased to 12.4 to 19 % compared with 10.3 to 11% in controls. This may result in an increase in clinical effect of alfentanil (see Special Warnings and Special Precautions for Use section).

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

PHARMACEUTICAL PARTICULARS
List of Excipients
The inactive ingredients of the injectable solution are sodium chloride and water for injection.

Incompatibilities
The injectable solution must not be mixed with other products.
If desired, RAPIFEN 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.

Shelf Life
Observe expiry date on the outer pack

Special Precautions for Storage
Store between 15° and 30°C.
Keep out of reach of children.

Nature and Contents of Container
RAPIFEN is supplied in 2 ml and 10 ml ampoules.

Instructions for Use and 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.

(See figure)

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JANSSEN-CILAG

Manufactured by: see outer pack
for Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse, Belgium