NAME OF THE MEDICINE
Alfentanil Hydrochloride (equivalent to 0.5mg/mL alfentanil)

Chemical Structure

![Chemical Structure Image]

Alfentanil hydrochloride

CAS Number
71195-58-9

DESCRIPTION
RAPIFEN (alfentanil hydrochloride) is a potent short-acting narcotic analgesic for intravenous use by anaesthetists.

It is available as a sterile solution of alfentanil hydrochloride equivalent to 0.5mg/mL alfentanil with 9.0mg sodium chloride in water for Injection to 1mL.

PHARMACOLOGY
Pharmacodynamics
Alfentanil is a potent, short-acting opioid analgesic chemically related to fentanyl.

The onset of action of alfentanil is more rapid than that of an equianalgesic dose of fentanyl, and the maximal analgesic and respiratory depressant effect occurs within 1 to 2 minutes. The time to onset of analgesia was 55.7 (range 15 -120) seconds for alfentanil, compared to 103.8 (range 30 -120) seconds for fentanyl. Depth of analgesia can be adjusted to the pain level of the surgical procedure.

The duration of action of alfentanil is shorter than that of an equianalgesic dose of fentanyl, and is dose-related. Durations of action for short, medium and long procedures are discussed under "DOSAGE AND ADMINISTRATION". For analgesia lasting longer than 60 minutes, an infusion is preferable.

The duration of the analgesic effect may be shorter than that of the respiratory depression, in some patients. The duration and degree of apnoea, respiratory...
depression and increased airway resistance usually increase with dose but have also been observed at lower doses (see "PRECAUTIONS"). The time course of respiratory depression is not related to the pharmacokinetics described below.

At higher doses (>120 micrograms/kg) alfentanil can be used as an anaesthetic induction agent. Induction is smooth, pain-free and devoid of cardiovascular and hormonal stress response to intubation.

At induction, alfentanil may produce increased muscular tone, including thoracic muscular rigidity and limb movements. These and other typical signs and symptoms of narcotic analgesics, such as euphoria, miosis and bradycardia, may also be observed if alfentanil is given too rapidly or at too high a dosage.

All actions of alfentanil are rapidly and completely reversed by a specific narcotic antagonist, such as naloxone. A single dose of one of these agents may not be sufficient in prolonged respiratory depression. Repeat doses may be needed.

**Pharmacokinetics**

Alfentanil is a synthetic opioid with μ-opioid receptor agonist activity.

After intravenous administration of RAPIFEN, maximal analgesia, at the recommended dose, occurs after one minute. The low degree of ionisation (11% at pH 7.4) contributes significantly to a rapid distribution. The total volume of distribution varies from 0.4 to 1.0 L/kg, which is approximately one quarter to one tenth that of fentanyl, indicating a limited distribution to the tissues. The small volume of distribution is also attributable to the limited liposolubility and strong plasma protein binding of the drug mainly to alpha1-acid-glycoprotein.

Alfentanil is metabolised mainly by the liver with only 1% of the active substance found unaltered in the urine. It is metabolised by N-and O-dealkylation. 70-80% of the metabolites are eliminated in the urine. The plasma clearance averages 356 mL/min. Clearance is decreased in obese patients. As with fentanyl, "secondary peaks" in plasma concentrations have been reported.

The sequential distribution half lives are 1 and 14 minutes. Alfentanil elimination is rapid: The terminal elimination half life is 90 - 111 minutes (range 50 - 150 minutes), which is significantly faster than for fentanyl.

During average to long-lasting surgical procedures, analgesia can be maintained by repeated injection of RAPIFEN or by a continuous infusion, subsequent to a bolus dose. Repeated or prolonged administration of RAPIFEN produces increased plasma concentrations and accumulation of the drug.

Once steady-state has been reached after infusion, the elimination half-life remains unaltered, providing there has been no drug interaction with drugs such as erythromycin, and hepatic function is not unexpectedly impaired.

Patient recovery (i.e. return to consciousness) generally occurs rapidly on discontinuation of RAPIFEN.

A table summarising pharmacokinetic parameters for alfentanil and fentanyl is shown below:
PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Physiochemical Parameters</th>
<th>Alfentanil</th>
<th>Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Solubility</td>
<td>2.1</td>
<td>2.9</td>
</tr>
<tr>
<td>pKa</td>
<td>6.5</td>
<td>8.4</td>
</tr>
<tr>
<td>% ionised at pH 7.4</td>
<td>11%</td>
<td>91%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Alfentanil</th>
<th>Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution t½ (min)</td>
<td>1 and 14</td>
<td>1 and 18</td>
</tr>
<tr>
<td>Elimination t½ (min)</td>
<td>90 - 111</td>
<td>475</td>
</tr>
<tr>
<td>(range 50 - 150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of Distribution (L/kg)</td>
<td>0.4-1.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Protein Binding (%)</td>
<td>92%</td>
<td>84%</td>
</tr>
<tr>
<td>Plasma Clearance (mL/min)</td>
<td>356</td>
<td>574</td>
</tr>
<tr>
<td>Hepatic Metabolism</td>
<td>1% unchanged drug in urine</td>
<td>10% unchanged drug in urine</td>
</tr>
</tbody>
</table>

Special populations

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 PRECAUTIONS).

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 PRECAUTIONS).

INDICATIONS

RAPIFEN is indicated for intravenous use by specialist anaesthetists and their trainees as:

- an analgesic supplement given by incremental intravenous boluses or continuous infusion; and

- an anaesthetic induction agent where in patients undergoing in-patient surgery, when endotracheal intubation and controlled ventilation are to be used.

Because of its rapid onset and short duration of action, intravenous RAPIFEN is particularly suited as a narcotic analgesic for short procedures and outpatients, provided that the patients are maintained under appropriate post-operative surveillance. However, intravenous RAPIFEN is also useful as an analgesic supplement for procedures of medium to long duration, since periods of very painful stimuli can be easily overcome by administration of small increments of RAPIFEN or by adapting the infusion rate.
CONTRAINDICATIONS
RAPIFEN is contraindicated in those with a known intolerance to the medicine, components of the formulation or to other opioid analgesics. Contraindicated in post-operative analgesia. Not for use by unapproved routes of administration.

PRECAUTIONS
Alfentanil should be administered only by persons specifically trained in the use of intravenous and general anaesthetic agents and in the management of respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment, and oxygen should be readily available. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery in an approved recovery facility. (See DOSAGE AND ADMINISTRATION).

RAPIFEN, also at doses below 20 micrograms/kg may cause skeletal muscular rigidity, particularly of the truncal muscles. The incidence and severity of muscular rigidity is usually dose-related. Administration of RAPIFEN at anaesthetic induction dosages (above 120 micrograms/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids.

Respiratory Depression
As with other potent opioids, profound analgesia is accompanied by marked respiratory depression and loss of consciousness which may persist or recur in the postoperative period. There is no reliable way of determining, a priori which individuals are at risk. In the case of alfentanil, respiratory depression is dose-related and usually of short duration, *and can be reversed by specific opioid antagonists, 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*. Recovery room staff should be aware that marked respiratory depression has been reported as occurring after periods of up to several hours after the patient has been perceived to be alert, conversing coherently, and with normal respiration. The risk might be greater with patients on other depressant medicines, for example benzodiazepines and thiopental. As with other narcotic analgesics, patients who have received RAPIFEN should remain under appropriate surveillance. Vital signs should be monitored continuously. This should occur during, and must continue well after recovery (for at least two hours). Resuscitation equipment and a specific opioid antagonist, such as naloxone, should be readily available to manage apnoea. Naloxone administration may need to be repeated. Hyperventilation during anaesthesia may alter the patient’s response to carbon dioxide, thus affecting respiration postoperatively.

Opioids should be titrated with caution in patients with pulmonary disease; decreased respiratory reserve; alcoholism and impaired hepatic and renal function. Such patients also require prolonged post-operative monitoring.

*Risk from concomitant use of Central Nervous System (CNS) depressants, especially benzodiazepines or related drugs
Concomitant use of RAPIFEN 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 RAPIFEN 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 with other medicines).

Muscular Rigidity
RAPIFEN may induce muscle rigidity during induction, including thoracic muscular rigidity. Rigidity may be avoided by the following measures:

a) slow intravenous injection, especially when higher doses are indicated;

b) premedication with benzodiazepines;

c) administration of muscle relaxants prior to RAPIFEN administration.

*Non-epileptic (myo)clonic movements can occur.

Cardiovascular Effects
When insufficient anticholinergic is administered, or when RAPIFEN is administered in combination with non-vagolytic muscle relaxants and induction agents, bradycardia, hypotension and sometimes cardiac arrest may occur.

*Effects on ability to drive and use machines
Driving and the operation of machines can only be resumed when sufficient time has elapsed following the administration of RAPIFEN. Individual reactions vary greatly. *It is recommended that patients not drive or use machines for at least 24 hours after administration of RAPIFEN.

Instructions for Use and Handling
Wear gloves while opening ampoule.

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.

Special dosing conditions
As with other opioids, RAPIFEN may induce hypotension, especially in hypovolaemic patients. Appropriate measures should be taken to maintain a stable arterial pressure.

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.

*It is recommended to reduce the dosage in the elderly and in debilitated patients. As with other opioids, RAPIFEN 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.

Head Injury
RAPIFEN may obscure the clinical course of patients with head injuries.
Use in Hypothyroidism
It is recommended that the dose of RAPIFEN is reduced in those patients with hypothyroidism, because of reduced clearance. The dosage should be titrated individually and adjusted according to the clinical response.

Use in Obese Patients
It is recommended that the dosage of RAPIFEN is reduced in obese patients because of reduced clearance. The dosage should be titrated individually and adjusted according to the clinical response.

Use in the Elderly
It is recommended that the dose of RAPIFEN is reduced in the elderly, because of reduced clearance. A dosage reduced by about a third has been effective, but in general, the dosage should be individualised, and based on the clinical response.

Use in Hepatic Impairment
It is recommended that the dose of RAPIFEN is reduced in those patients with chronic liver disease, because of decreased plasma protein concentrations and reduced clearance possibly resulting in more prolonged and pronounced clinical effects. Because of the variable pharmacokinetics and pharmacodynamics, the dosage should be titrated individually and adjusted on the basis of the clinical response.

Use in Renal Impairment
Due to an increased plasma free fraction of alfentanil in patients with renal failure, the clinical effects of RAPIFEN may be prolonged and more pronounced. Therefore, the dose of RAPIFEN should be titrated with caution in these patients.

Use in Pregnancy - Category C
A concern with narcotic analgesics in pregnancy is with their use during labour when they may cause respiratory depression in the newborn infant. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus. "I.V. administration during childbirth (including caesarean section) is not recommended, because RAPIFEN crosses the placenta and may suppress spontaneous respiration in the newborn period. If RAPIFEN is administered nevertheless, 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. The half-life of the opioid antagonist may be shorter than the half-life of alfentanil, therefore, repeated administration of the opioid antagonist may be necessary. Respiratory depression and hypotension are basic pharmacological actions of alfentanil. Careful monitoring by trained personnel is routinely required.

RAPIFEN has been shown to have an embryocidal effect on rats and rabbits when given in doses of 1.25mg/kg for a period of 10 days to over 30 days. These effects may have been due to maternal toxicity following prolonged administration of the medicine. No teratogenic effect has been observed after the administration of RAPIFEN to rats and rabbits at doses up to 1.25mg/kg IV. It should be noted, however, that alfentanil crosses the placenta and may suppress spontaneous respiration in the newborn period.

The foetal respiratory centre is known to be more sensitive to opiates.
Withdrawal symptoms in newborn infants have been reported with prolonged use of opioids.
Consequently, it is necessary to consider potential risks and potential advantages before administering alfentanil to pregnant patients.

**Use in Lactation**

RAPIFEN may be excreted in human milk. Therefore, breast-feeding or use of expressed breast milk is not recommended during the 24 hours following its administration.

**Paediatric Use**

Adequate data to support the use of alfentanil in children under 12 years of age are presently not available.

**Carcinogenicity**

No long term animal studies of RAPIFEN have been performed to evaluate carcinogenic potential.

**Genotoxicity**

Mutagenicity studies showed no evidence of mutagenic activity (Ames Salmonella assay) and chromosomal damage (micronucleus and dominant lethal tests).

**INTERACTIONS WITH OTHER MEDICINES**

**Anaesthetic Agents**

As with other opioids, the respiratory depressant and cardiovascular depressant effects of RAPIFEN may be potentiated by halogenated inhalation agents, and particularly propofol. Propofol also appears to alter the disposition of RAPIFEN pharmacokinetics, resulting in elevated plasma levels of alfentanil.

**Central Nervous System (CNS) depressants**

RAPIFEN may potentiate the respiratory and cardiovascular depressant effects of medicines such as barbiturates, benzodiazepines, phenothiazine derivatives, other non-selective hypnotics. Medicines such as barbiturates, benzodiazepines *or related drugs, neuroleptics, *general anaesthetics and other non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depression of narcotics. When patients have received such medicines, the dose of RAPIFEN required will be less than usual.

Likewise, following the administration of RAPIFEN, the dose of other CNS-depressant medicines 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 of respiratory depression (see PRECAUTIONS).

Concomitant use with RAPIFEN in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death (see PRECAUTIONS).

**Cytochrome P450 3A4 (CYP3A4) inhibitors**

Alfentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. Available human pharmacokinetic data indicate that the metabolism of alfentanil may be inhibited by fluconazole, voriconazole, erythromycin, diltiazem and cimetidine (known cytochrome P450 3A4 enzyme inhibitors). In-vitro data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. ketoconazole,itraconazole, ritonavir) may also inhibit the
metabolism of alfentanil. 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 RAPIFEN.

**Monoamine Oxidase Inhibitors (MAOI)**

Monoamine oxidase inhibitors have been reported to potentiate the effects of opioid analgesics, the use of RAPIFEN in patients who have received irreversible MAO inhibitors within two weeks should be avoided.

**Serotonergic drugs**

Co-administration of alfentanil 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.

**Effect of alfentanil on the metabolism of other medicines**

In combination with RAPIFEN, the blood concentrations of propofol are 17% higher than in the absence of RAPIFEN. The concomitant use of RAPIFEN and propofol may require a lower dose of RAPIFEN.

**ADVERSE EFFECTS**

The adverse reactions are those associated with the intravenous opioids, e.g. respiratory depression, apnoea, muscular rigidity (which may also involve the thoracic muscles), myoclonic movements, bradycardia, (transient) hypotension, nausea, vomiting and dizziness.

Other less frequently reported adverse reactions are:

- Laryngospasm.
- Allergic reactions (such as anaphylaxis, bronchospasm, urticaria) and asystole have been reported; since several medicines were co-administered during anaesthesia, it is uncertain whether there is a causal relationship to alfentanil.
- Recurrence of respiratory depression after the operation has been observed in rare instances.

See also “PRECAUTIONS”.

Although it is unlikely, alfentanil could cause opioid-dependence, and has a potential for being abused.

**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

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

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

<table>
<thead>
<tr>
<th>System / Organ Class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td>Agitation</td>
</tr>
<tr>
<td></td>
<td>Crying</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
</tr>
<tr>
<td></td>
<td>Unresponsive to stimuli</td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td>Arrhythmia</td>
</tr>
</tbody>
</table>

CCDS180818v008 9  RAPIFEN(190123)API
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 Administration Site Conditions**
- Pain

**Injury, Poisoning and Procedural Complications**
- Confusion postoperative
- Agitation postoperative
- Airway complication of anaesthesia
- Anaesthetic complication neurological
- Procedural complication
- Endotracheal intubation complication

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**Postmarketing Data**

Adverse drug reactions first identified during postmarketing experience with RAPIFEN are included in Table 3. The frequencies are provided according to the following convention:

- Very common \( \geq \frac{1}{10} \)
- Common \( \geq \frac{1}{100} \) and \( < \frac{1}{10} \)
- Uncommon \( \geq \frac{1}{1,000} \) and \( < \frac{1}{100} \)
- Rare \( \geq \frac{1}{10,000} \), \( < \frac{1}{1,000} \)
- Very rare \( < \frac{1}{10,000} \), including isolated reports

<table>
<thead>
<tr>
<th>Immune System Disorders</th>
<th>( \text{Very rare} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity (including anaphylactic reaction, anaphylactoid reaction, and urticaria)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric Disorders</th>
<th>( \text{Very rare} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorientation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous System Disorders</th>
<th>( \text{Very rare} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of consciousness(^a), Convulsion, Myoclonus</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye Disorders</th>
<th>( \text{Very rare} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac Disorders</th>
<th>( \text{Very rare} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, Thoracic and Mediastinal Disorders</th>
<th>( \text{Very rare} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory arrest, Respiratory depression(^b), Cough</td>
<td></td>
</tr>
</tbody>
</table>

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\(^a\) Loss of consciousness

\(^b\) Respiratory depression
**DOSAGE AND ADMINISTRATION**

RAPIFEN should be administered intravenously (other routes of administration have not been evaluated). The dosage should be individualised taking into consideration factors such as age, body weight, physical status, underlying pathological condition (see also PRECAUTIONS), use of other medicines (see *Interaction With Other Medicines*), type of anaesthesia to be used and type and duration of the surgical procedure. As a general principle, the lowest effective dose should be used.

*To avoid bradycardia a small I.V. dose of an anticholinergic (e.g. atropine) just before anesthetic induction may be administered.*

Co-administration of droperidol or benzodiazepines may lengthen recovery from RAPIFEN, of importance in outpatients (a successful outpatient technique has consisted of an anticholinergic, a short-acting induction hypnotic, RAPIFEN and nitrous oxide/oxygen).

The initial dose of RAPIFEN should be appropriately reduced in the elderly *(>65 years of age)* and in cirrhotic patients. The effect of the initial dose should be considered in determining supplemental doses. Monitoring of the patient should continue well after surgery in a recovery facility that conforms to the current guidelines of the Australian and New Zealand College of Anaesthetics.

**Use as an Analgesic Supplement**

i. *Spontaneous ventilation techniques:*

Doses up to 7 micrograms/kg, administered as a slow intravenous injection, may be used with increments of 2-3 micrograms/kg at 10-15 minute intervals. At this dose with induction of anaesthesia, in particular with propofol (see *Interaction With Other Medicines*), transient apnoea is frequent and the dosage may be adjusted downwards.

ii. *Controlled Ventilation Techniques:*

For attenuation of the hypertensive response to laryngoscopy a dose prior to intubation of 20-50 micrograms/kg is appropriate; such doses may have effect for up to 30-45 minutes.

For short procedures, an initial dose 7-15 micrograms/kg at induction, with intermittent boluses up to 15 micrograms/kg at 10-15 minute intervals are most useful.

For procedures of longer duration, a higher dose may be given at induction (see Table below) and further increments titrated to effect.

<table>
<thead>
<tr>
<th>DURATION OF THE PROCEDURE (min)</th>
<th>RAPIFEN I.V. BOLUS DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 30</td>
<td>Micrograms/kg: 20 - 40</td>
</tr>
<tr>
<td>30 - 60</td>
<td>mL/70kg: 3 - 6</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Micrograms/kg: 40 - 80</td>
</tr>
<tr>
<td></td>
<td>mL/70kg: 6 - 12</td>
</tr>
<tr>
<td></td>
<td>80-150</td>
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<td>12 - 20</td>
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</tbody>
</table>
When surgery is more prolonged or more traumatic, analgesia should be maintained by:

- either increments of up to 15 micrograms/kg (2mL/70kg) RAPIFEN when required (to avoid post-operative respiratory depression, no RAPIFEN should be administered during the last 10 minutes of surgery);
- or a RAPIFEN infusion at a rate of 0.5 to 1 microgram/kg/min (0.14mL/70kg/min) until 5 to 10 minutes before the completion of surgery.

Continuous infusion is preferable for cases greater than 60 minutes duration.

**RAPIFEN SHOULD NOT BE GIVEN IN THE LAST 10 MINUTES PRIOR TO COMPLETION OF SURGERY**

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

RAPIFEN may be administered as an infusion for more prolonged procedures with the following infusion solutions:

- 0.9% sodium chloride injection
- 5.0% glucose injection
- compound sodium lactate intravenous injection (Ringer Lactate Injection)

**WARNING:** The prepared infusion should commence as soon as possible after its preparation and in any case within 24 hours. Any storage of the prepared solution should be at 2 - 8°C.

**Use as an Induction Agent**

An intravenous bolus dose of ≥120 micrograms/kg (17mL/70kg) RAPIFEN will induce hypnosis and analgesia while maintaining good cardiovascular stability in patients with adequate muscle relaxation.

When post-operative nausea occurs it is of relatively short duration and easily controlled by conventional measures.

**OVERDOSAGE**

The manifestations of RAPIFEN overdose are an extension of its pharmacological actions. Depending on the individual sensitivity, the clinical picture will be determined primarily by respiratory depression, varying from bradypnoea to apnoea.

In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated.

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 controlled with appropriate parenteral fluid administration.

A specific narcotic antagonist, naloxone, should be available for use 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.
Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdose.

PRESENTATION AND STORAGE CONDITIONS
1mg alfentanil in 2mL glass ampoules in cartons of 5 ampoules. AUST R 50506
5mg alfentanil in 10mL glass ampoules in cartons of 5 ampoules. AUST R 50508
Store below 25°C. Protect from light. Ampoules should be removed only for immediate use.
The shelf life is 5 years.

POISON SCHEDULE OF THE MEDICINE
Schedule 8 – Controlled Drug

NAME AND ADDRESS OF SPONSOR
JANSSEN-CILAG Pty Ltd
1-5 Khartoum Road
Macquarie Park NSW 2113, Australia
Telephone: 1800 226 334
NZ Office: Auckland New Zealand
Telephone: 0800 800 806

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)
14th October 1994

DATE OF MOST RECENT AMENDMENT
24 January 2019

Please note change(s) presented as *italicised text* in Product Information.