Rapifen®

PRODUCT NAME
RAPIFEN® (alfentanil hydrochloride)

DOSAGE FORMS AND STRENGTHS
Sterile, preservative-free, isotonic aqueous solution containing alfentanil hydrochloride equivalent to 0.5mg alfentanil per mL.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
RAPIFEN is indicated for use as:
- an anesthetic induction agent.
- an opioid analgesic in general as well as an adjuvant to regional anesthesia 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 an opioid 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 usually be overcome by small increments of RAPIFEN or by adapting its infusion rate.

Dosage and 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 anesthesia.

The initial dose should be reduced in the elderly (> 65 years of age) 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, a small intravenous (I.V.) dose of an anti-cholinergic agent just before anesthetic induction may be administered.

Dosage
Adults
For use as an anesthetic induction agent
An I.V. bolus dose of ≥120 mcg/kg (17 mL/70 kg) RAPIFEN will induce unconsciousness and analgesia while maintaining good cardiovascular stability in patients with adequate muscle relaxation.

For short procedures and use in outpatients
Small doses of RAPIFEN are most useful for minor, short surgical procedures and for outpatients, provided cardiopulmonary monitoring equipment is available.

An I.V. bolus dose of 7 to 15 mcg/kg (1 to 2 mL/70 kg) is usually adequate for procedures lasting less than 10 minutes. Should the duration of the procedure exceed 10 minutes, further increments of 7 to 15 mcg/kg (1 to 2 mL/70 kg) should be given every 10 to 15 minutes or as required.

Although ventilatory support must be available, spontaneous breathing is maintained in most instances with a dose of 7 mcg/kg (1 mL/70 kg) or less, slowly injected; suggested increments with this technique are 3.5 mcg/kg (0.5 mL/70 kg). When postoperative nausea occurs, it is of relatively short duration and usually controlled by conventional measures.

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

Table 1. Dosing for Medium Duration Procedures

Duration of the procedure (min.)	RAPIFEN mcg/kg	**I.V. bolus dose** 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 mcg/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 mcg/kg/min (0.14 mL/70 kg/min) until 5 to 10 minutes before the completion of surgery.

Periods of painful stimuli can easily be managed by small dose increments or by temporarily increasing the infusion rate.

When RAPIFEN is used without N_2O/O_2 or another inhalation anesthetic, a higher maintenance dose of RAPIFEN is required.

For long procedures
RAPIFEN may be used as the analgesic component of anesthesia 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 patient.

Administration
RAPIFEN is administered by bolus injection, or bolus supplemented by increments, or by infusion

Contraindications
Known intolerance to either of its components or to other opioids.

Warnings and Precautions
As with all potent opioids:

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

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

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical dependence, and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids.

Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Neonatal Withdrawal Syndrome
If women take opioids chronically during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome. Neonates exposed to opioids chronically may also experience neonatal withdrawal syndrome (see *Pregnancy*).

Muscle rigidity
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.

Cardiac disease
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.
Special dosing conditions
As with other opioids, RAPIFEN may induce hypotension, especially in hypovolemic 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. 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.

Opioid Induced Hyperalgesia
Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid, particularly at high doses or with chronic use, in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalized pain (i.e., less focal), or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioids should be reduced or tapered off, if possible.

Interactions
Drugs modifying the effect of alfentanil
Central Nervous System (CNS) depressants:
Drugs such as barbiturates, benzodiazepines or related drugs, neuroleptics, general anesthetics, and other, non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depression of opioids. When patients have received such CNS depressant drugs, the dose of RAPIFEN required will be less than usual. Concomitant use with RAPIFEN in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death (see *Warnings and Precautions*).

The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Effect of RAPIFEN on other drugs:
Following the administration of RAPIFEN, the dose of other CNS-depressant drugs should be reduced. This is particularly important after surgery, because profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the postoperative period. Administration of a CNS depressant, such as a benzodiazepine or related drugs. During this period may disproportionally increase the risk for respiratory depression (see *Warnings and Precautions*).

Cytochrome P450 3A4 (CYP3A4) inhibitors:
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.

Monoamine Oxidase Inhibitors (MAOI):
It is usually recommended to discontinue MAO-inhibitors 2 weeks prior to any surgical or anesthetic procedure.

Serotonergic drugs:
Coadministration of 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 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 Breast-feeding
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 *Non-clinical Information)*. Consequently, it is necessary to consider possible risks and potential advantages before administering this drug to pregnant patients.

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

I.V. administration during childbirth (including cesarean section) is not recommended, because RAPIFEN crosses the placenta and may suppress spontaneous breathing 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.

Breast-feeding
RAPIFEN may enter the maternal milk. Therefore, breast-feeding or use of expressed breast milk is not recommended for 24 hours following the administration of RAPIFEN.
Effects on Ability to Drive and Use Machines
It is recommended that patients not drive or use machines for at least 24 hours after administration of RAPIFEN.

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

Clinical trial data
The safety of RAPIFEN was evaluated in 1157 subjects who participated in 18 clinical trials. RAPIFEN was administered as an anesthetic induction agent or as an analgesic/anesthesia adjuvant to regional and general anesthesia, in short, medium, and long surgical procedures. These subjects took at least one dose of RAPIFEN and provided safety data. Adverse reactions that were reported for ≥1% of RAPIFEN-treated subjects in these trials are shown in Table 2.

Table 2. Adverse 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	
Apnea	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 adverse reactions that occurred in <1% of RAPIFEN-treated subjects in the 18 clinical trials are listed below in Table 3.

Table 3. Adverse 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 anesthesia
Anesthetic complication neurological
Procedural complication
Endotracheal intubation complication

Postmarketing Data
Adverse reactions first identified during postmarketing experience with RAPIFEN are included in Table 4. 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, <1/1000
Very rare	<1/10000, including isolated reports

In Table 4, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 4. Adverse 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.

Pediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults, with the exception of the following:
Mild to moderate muscle rigidity has been seen more frequently in neonates. Severe rigidity and jerking can occur and may be accompanied by transient impaired ventilation, especially with high doses of RAPIFEN or with a rapid rate of intravenous injection.

Overdose
Signs and Symptoms
The manifestations of RAPIFEN overdose are an extension of its pharmacologic actions. Respiratory depression which can vary in severity from bradypnea to apnea may occur.

Treatment
In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific opioid antagonist should be used as indicated to control respiratory depression. This does not preclude the use of more immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.

If depressed respiration 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 hypovolemia should be considered, and if present, it should be controlled with appropriate parenteral fluid administration.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties
Pharmacotherapeutic group: opioid anesthetics, ATC code: N01AH02.

Mechanism of action
Alfentanil is a potent fast and short-acting opioid analgesic, chemically related to fentanyl.

Pharmacodynamic effects
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 approximately 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. Alfentanil's depressant effects on respiratory rate and alveolar ventilation are of shorter duration 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 mcg/kg) of alfentanil induce sleep and can be used for induction of anesthesia. The induction is smooth, pain-free and devoid of cardiovascular and hormonal stress responses to intubation.

In common with other opioid 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 mcg/kg, alfentanil failed to produce a significant increase in histamine levels or clinical evidence of histamine release.

Recovery after alfentanil administration is typically rapid and smooth with a low incidence of post-operative nausea and vomiting.

All actions of alfentanil are reversed by a specific opioid antagonist.

Pharmacokinetic Properties
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 ionization (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 metabolized 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 subjects below 40 years of age averages 356 mL/min, and decreases approximately 8% per decade increase above 40 years of 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 opioid after effects.

Special Populations
Pediatrics
Protein binding in newborns is 75% and increases in children to 85%. Pharmacokinetic information on the use of alfentanil in children is limited. Alfentanil is metabolized by CYP3A4. CYP3A4 activity is low in neonates and increases after birth to reach 30 to 40% of adult levels at 1 month of age. Activity of CYP3A4 increases further to 45% at 6 months, 80% at 12 months and reaches adult levels at 6 years of age.

Hepatic Impairment
After administration of a single intravenous dose of 50 mcg/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 *Warnings and 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 *Warnings and Precautions*).

NON-CLINICAL INFORMATION

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

Alfentanil has a 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.

PHARMACEUTICAL PARTICULARS

List of Excipients
Sodium chloride
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.

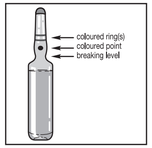
Shelf Life
Refer to Outer Carton

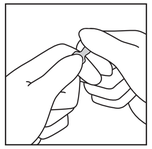
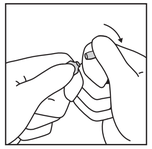
Storage Conditions
Store between 15° and 30°C.
Keep out of sight and reach of children.

Nature and Contents of Container
2 ml ampoules

Instructions for Use And Handling
Wear gloves while opening ampoule.

1. Maintain the ampoule between thumb and index finger, leaving the tip of the ampoule free.
2. With the other hand, hold the tip of ampoule putting the index finger against the neck of ampoule, and the thumb on the coloured point in parallel to the identification colored 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.



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.

PRODUCT OWNER
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LAST DATE OF REVISION OF TEXT
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Parameters	Remarks	Parameters	Remarks
Product name/Generic name	Rapifen 5 x 2 ml PIL Singapore	Market/Country	Singapore
Strength	NA	Barcode (PZN/CIP/EAN/KD/SKUL/VNR)	NA
Component	Pack Insert	Material code	XXXXXXXX
Dimensions	696 x 332 mm	Superseded Material code	NA
Specification	NA	Artwork number	NA
Font size & type	Helvetica World	MAH	PCC PTY UK
Pantone number	As shown	GTIN	NA
Cut margins/Peel off Margins	NA	Special instructions	NA
Unvarnished zone	NA	Anticounterfiet features	NA
Mfg site	NA	Other observation	NA
Reason for revision:	Submission of PRAC update	Pharma Code	NA
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