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Rapifen® 0.5mg/ml Injection

Alfentanil hydrochloride

Product Description

Clear, colourless solution. Free from visible foreign matter.

DOSAGE FORMS AND STRENGTHS

Solution for injection or infusion

Sterile, preservative-free, isotonic aqueous solution containing alfentanil hydrochloride equivalent to 0.5 mg alfentanil per mL

For excipients, see *List of Excipients*.

CLINICAL PARTICULARS

Therapeutic Indications

RAPIFEN is indicated for use in adults 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.

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 anesthesia.

To avoid bradycardia, a small intravenous (I.V.) dose of an anticholinergic agent just before anesthetic induction may be administered.

Dosage

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 ventilitory 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 I.V. bolus dose	
	mcg/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 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.

Special populations

Elderly and debilitated patients

The initial dose should be reduced in the elderly (>65 years of age) and in debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

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.

Drug dependence and potential for abuse

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Therefore, it is possible that a higher dose of RAPIFEN may be needed to produce the same result.

Physical dependence may result in acute withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of opioids.

Alfentanil can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of RAPIFEN may result in overdose and/or death. Persons at increased risk of opioid abuse may still be appropriately treated with RAPIFEN.

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.

Risks from concomitant use with benzodiazepines

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of RAPIFEN with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when RAPIFEN is used with benzodiazepines.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (*see Interactions*).

Serotonin syndrome with concomitant use of serotonergic drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of RAPIFEN with serotonergic drugs (*see Interactions with Other Medicaments*). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (see *Interactions with Other Medicaments*). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue RAPIFEN if serotonin syndrome is suspected.

Adrenal insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids.

Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual function/ reproduction

Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see Postmarketing Experience).

Interactions

Drugs modifying the effect of alfentanil

Central Nervous System (CNS) depressants

Drugs such as barbiturates, benzodiazepines, 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 patient may increase the risk of respiratory depression; profound sedation, coma, and death.

Benzodiazepines

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

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, during this period may disproportionally increase the risk for respiratory depression.

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 (MAOIs)

It is usually recommended to discontinue MAO-inhibitors 2 weeks prior to any surgical or anesthetic procedure.

Serotonergic drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue RAPIFEN if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezoid and intravenous methylene blue) (see *Warnings and*Precautions).

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

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.

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.

Undesirable Effects

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 Administration 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 Administration 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	≥1/1,000 and <1/100
Rare	≥1/10,000, <1/1,000
Very rare	<1/10,000, including isolated reports

In Table 4, adverse reactions are presented by frequency category based on incidence in clinical trials or epidemiological studies, when known. The frequency category "not known" is used for adverse reactions for which no valid estimate of the incidence rate can be derived from clinical trials.

Table 4. Adverse Reactions Identified During Postmarkeling Experience with RAPIFEN by Frequency Category Estimated from Clinical Trials or Epidemiologic Studies

Immune System Disorders	
Not known	Hypersensitivity (including anaphylactic reaction, anaphylactoid reaction, and urticaria)
Psychiatric Disorders	
Not known	Disorientation
Nervous System Disorders	
Not known	Loss of consciousnessa, Convulsion, Myoclonus
Eye Disorders	
Not known	Miosis
Cardiac Disorders	
Not known	Cardiac arrest
Respiratory, Thoracic and Mediastinal Disorders	
Not known	Respiratory arrest, Cough
Uncommon	Respiratory depressionb
Skin and Subcutaneous Tissue Disorders	
Not known	Erythema, Rash
General Disorders and Administration Site Conditions	
Not known	Pyrexia

[a] Postoperative period

[b] Including fatal outcome

Serotonin syndrome (see *Warnings and Precautions*)

Adrenal insufficiency (see *Warnings and Precautions*)

Androgen deficiency

Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The casual role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

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 exclude 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 awakens rapidly without opioid after effects.

Special Populations

Pediatrics

The data in children are limited. The values for the pharmacokinetic parameters are shown in the table below.

Table 5. Pharmacokinetic Parameters of Alfentanil in Pediatric Subjects

	t1/2β (hr)	CL (ml/kg /min)	Vdss (L/kg)
Preterm Neonates (0-27 days) Gestational age 25-40 weeks; *n=68*	0.7-8.8	0.9-8.4	0.3-1.2
Term Neonates (0-27 days) Gestational age: 35-41 weeks; *n= 18*	4.1-5.5	1.7-3.2	0.5-0.8
Infants 28 days - 23 months; *n= 34*	0.9-1.2	7.7-13.1	0.4-1.1
Children 2-11 years; *n= 32*	0.7-1.3	4.7-10.2	0.2-1.0
Adolescents 12-14 years; *n= 3*	1.1-1.9	5.5-7.4	0.3-0.6

• Note: Data for neonates, infants, and children are given as range of mean values.

• CL = clearance, Vdss = volume of distribution at steady state, t1/2β = half-life in the elimination phase.

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 halflife 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

36 months

Storage Conditions

Store below 30° C.

Keep out of the sight and reach of children.

Nature and Contents of Container

2 ml x 5 ampules

Instructions for Use/Handling

Wear gloves while opening ampule.

1. Maintain the ampule between thumb and index finger, leaving the tip of the ampule free.
2. With the other hand, hold the tip of ampule putting the index finger against the neck of ampule, and the thumb on the colored point in parallel to the identification colored ring(s).
3. Keeping the thumb on the point, sharply break the tip of ampule while holding firmly the other part of the ampule 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.

MANUFACTURER

DEMO S.A Pharmaceuticals
21st km National Road,
Athens - Lamia, Krioneri Attiki, 14568,
Greece

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Piramal Critical Care

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