AUSTRALIAN PRODUCT INFORMATION – RAPIFEN (ALFENTANIL HYDROCHLORIDE) INJECTION

WARNINGS

Limitations of use

Because of the risks associated with the use of opioids, RAPIFEN should only be used in patients for whom other treatment options, including non-opioid analgesics, are ineffective, not tolerated or otherwise inadequate to provide appropriate management of pain (see *section 4.4 Special Warnings and Precautions for Use*).

Hazardous and harmful use

RAPIFEN poses risks of hazardous and harmful use which can lead to overdose and death. Assess the patient's risk of hazardous and harmful use before prescribing and monitor the patient regularly during treatment (see *section 4.4. Special Warnings and Precautions for Use*).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of RAPIFEN. Be aware of situations which increase the risk of respiratory depression, modify dosing in patients at risk and monitor patients closely, especially on initiation or following a dose increase (see *section 4.4 Special Warnings and Precautions for Use*).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required; and monitor patients for signs and symptoms of respiratory depression and sedation. Caution patients not to drink alcohol while on RAPIFEN.

1 NAME OF THE MEDICINE

Alfentanil hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of RAPIFEN contains alfentanil hydrochloride equivalent to 0.5mg alfentanil with 9.0mg sodium chloride in water for injection to 1mL.

3 PHARMACEUTICAL FORM

RAPIFEN solution for injection is a sterile, clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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 *Section 4.4 – Special Warnings and Precautions for use*), use of other medicines (see *Section 4.5 – Interactions With Other Medicines and Other Forms of Interactions*), 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 *Section 4.5 – Interactions With Other Medicines and Other Forms of Interactions*), 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.

DURATION OF THE PROCEDURE (min)	RAPIFEN I.V. BOLUS DOSE	
	Micrograms/kg	mL/70kg
10 - 30	20 - 40	3 - 6
30 - 60	40 - 80	6 - 12
>60	80-150	12 - 20

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.

4.3 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.

Contraindicated for use in patients with severe respiratory disease, acute respiratory disease and respiratory depression.

Contraindicated for use in chronic (long-term) non-cancer pain (CNCP).

Not for use by unapproved routes of administration.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 *Section 4.2 – Dose and Method of 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.

Hazardous and harmful use

RAPIFEN contains the opioid alfentanil and is a potential drug of abuse, misuse and addiction. Addiction can occur in patients appropriately prescribed RAPIFEN at recommended doses.

The risk of addiction is increased in patients with a personal or family history of substance abuse (including alcohol and prescription and illicit drugs) or mental illness. The risk also increases the longer the drug is used and with higher doses. Patients should be assessed for their risks for opioid abuse or addiction prior to being prescribed RAPIFEN.

All patients receiving opioids should be routinely monitored for signs of misuse and abuse. Opioids are sought by people with addiction and may be subject to diversion. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the safe storage and proper disposal of any unused drug (see *section 6.4 Special precautions for storage* and *section 6.6 Special precautions for disposal*). Caution patients that abuse of oral or transdermal forms of opioids by parenteral administration can result in serious adverse events, which may be fatal.

Patients should be advised not to share RAPIFEN with anyone else.

Respiratory Depression

Serious, life-threatening or fatal respiratory depression can occur with the use of opioids even when used as recommended. It can occur at any time during the use of RAPIFEN but the risk is greatest during initiation of therapy or following an increase in dose. Patients should be monitored closely for respiratory depression at these times.

The risk of life-threatening respiratory depression is also higher in elderly, frail, or debilitated patients, in patients with existing impairment of respiratory function (e.g. chronic obstructive pulmonary disease; asthma), and in patients with liver disease (see *Use in hepatic impairment*) and renal failure (see *Use in renal impairment*). Opioids should be used with caution and with close monitoring in these patients (see *section 4.2 Dose and method of administration*). The use of opioids is contraindicated in patients with severe respiratory disease, acute respiratory disease and respiratory depression (see *section 4.3 Contraindications*).

The risk of respiratory depression is greater with the use of high doses of opioids, especially high potency and modified release formulations, and in opioid naïve patients. Initiation of opioid treatment should be at the lower end of the dosage recommendations with careful titration of doses to achieve effective pain relief. Careful calculation of equianalgesic doses is required when changing opioids or switching from immediate release to modified release formulations, together with consideration of pharmacological differences between opioids. Consider starting the new opioid at a reduced dose to account for individual variation in response.

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 benzodiazepines or other CNS depressants, including alcohol

Concomitant use of opioids and benzodiazepines or other CNS depressants, including alcohol, may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of RAPIFEN with CNS depressant medicines, such as other opioid analgesics, benzodiazepines, gabapentinoids, cannabis, sedatives, hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, centrally-active anti-emetics and other CNS depressants, should be reserved for patients for whom other treatment options are not possible. If a decision is made to prescribe RAPIFEN concomitantly with any of the medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible. Patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers should be made aware of these symptoms. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking RAPIFEN.

Tolerance, dependence and withdrawal

Neuroadaptation of the opioid receptors to repeated administration of opioids can produce tolerance and physical dependence. Tolerance is the need for increasing doses to maintain analgesia. Tolerance may occur to both the desired and undesired effects of the opioid.

Physical dependence, which can occur after several days to weeks of continued opioid usage, results in withdrawal symptoms if the opioid is ceased abruptly or the dose is significantly reduced. Withdrawal symptoms can also occur following the administration of an opioid antagonist (e.g. naloxone) or partial agonist (e.g. buprenorphine). Withdrawal can result in some or all of the following symptoms: dysphoria, restlessness/agitation, lacrimation, rhinorrhoea, yawning, sweating, chills, myalgia, mydriasis, irritability, anxiety, increasing pain, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhoea, increased blood pressure, increased respiratory rate and increased heart rate.

When discontinuing RAPIFEN in a person who may be physically-dependent, the drug should not be ceased abruptly but withdrawn by tapering the dose gradually (see *Ceasing opioids* and *section 4.2 Dose and Method of Administration*).

Accidental ingestion/exposure

Accidental ingestion or exposure of RAPIFEN, especially by children, can result in a fatal overdose of alfentanil. Patients and their caregivers should be given information on safe storage and disposal of unused RAPIFEN (see *section 6.4 Special precautions for storage and section 6.6 Special precautions for disposal*).

Hyperalgesia

Hyperalgesia may occur with the use of opioids, particularly at high doses. Hyperalgesia may manifest as an unexplained increase in pain, increased levels of pain with increasing opioid dosages or diffuse sensitivity not associated with the original pain. Hyperalgesia should not be confused with tolerance (see *Tolerance, dependence and withdrawal*). If opioid induced hyperalgesia is suspected, the dose should be reduced and tapered off if possible. A change to a different opioid may be required.

Ceasing opioids

Abrupt discontinuation or rapid decreasing of the dose in a person physically dependent on an opioid may result in serious withdrawal symptoms and uncontrolled pain (see *Tolerance, dependence and withdrawal*). Such symptoms may lead the patient to seek other sources of licit or illicit opioids. Opioids should not be ceased abruptly in a patient who is physically dependent but withdrawn by tapering the dose slowly. Factors to take into account when deciding how to discontinue or decrease therapy include the dose and duration of the opioid the patient has been taking, the type of pain being treated and the physical and psychological attributes of the patient. A multimodal approach to pain management should be in place before initiating an opioid analgesic taper. During tapering, patients require regular review and support to manage any increase in pain, psychological distress and withdrawal symptoms.

There are no standard tapering schedules suitable for all patients and an individualised plan is necessary. In general, tapering should involve a dose reduction of no more than 10 percent to 25 percent every 2 to 4 weeks (see *section 4.2 Dose and Method of Administration*). If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to go back to the previous dose until stable before proceeding with a more gradual taper.

When ceasing opioids in a patient who has a suspected opioid use disorder, the need for medication assisted treatment and/or referral to a specialist should be considered.

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.

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 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 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.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 other opioid analgesics, barbiturates, benzodiazepines or related drugs, antihistamines, antipsychotics, neuroleptics, tricyclic antidepressants, centrally-active anti-emetics, gabapentinoids, general anaesthetics, cannabis 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 (*see Section 4.4 – Special Warnings and Precautions for Use*).

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 *Section 4.4 – Special Warnings and Precautions for Use*).

Concomitant use with RAPIFEN in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death (see *Section 4.4 – Special Warnings and Precautions for Use*).

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – 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.

4.7 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 *Section 4.4 – Special Warning and Precautions for Use*.

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

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 Administration 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

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

System / Organ Class Adverse Reaction
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 anaesthesia
Anaesthetic complication neurological
Procedural complication
Endotracheal intubation complication

Post-marketing Data

Adverse drug reactions first identified during post-marketing experience with RAPIFEN are included in Table 3. 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

Table 3. Adverse Drug Reactions Identified During Post-marketing 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 *Section 4.2 – Dose and Method of 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 *Section 4.4 – Special Warning and Precautions for Use*). The time course of respiratory depression is not related to the pharmacokinetics described below.

At higher doses (>120micrograms/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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Alfetanil 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 1.0L/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 356mL/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

	Alfentanil	Fentanyl
Physiochemical Parameters		
Lipid Solubility	2.1	2.9
pKa	6.5	8.4
% ionised at pH 7.4	11%	91%
Pharmacokinetic Parameters		
Distribution t½ (min)	1 and 14	1 and 18
Elimination t½ (min)	90 - 111 (range 50 - 150)	475
Volume of Distribution (L/kg)	0.4-1.0	4.8
Protein Binding (%)	92%	84%
Plasma Clearance (mL/min)	356	574
Hepatic Metabolism	1% unchanged drug in urine	10% unchanged drug in urine

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 *Section 4.4 – Special Warning and Precautions for Use*).

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 *Section 4.4 – Special Warning and Precautions for Use*).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride

Water for injection

6.2 INCOMPATIBILITIES

See Section 4.2 Dose and Method of Administration.

6.3 SHELF LIFE

5 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light. Ampoules should be removed only for immediate use.

6.5 NATURE AND CONTENTS OF CONTAINER

1mg alfentanil in 2mL glass ampoules in cartons of 5 ampoules. AUST R 50506

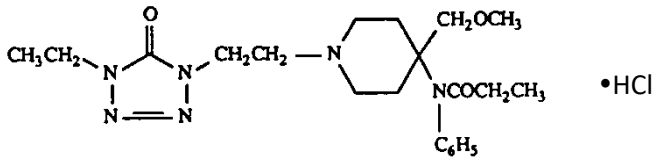
5mg alfentanil in 10mL glass ampoules in cartons of 5 ampoules. AUST R 50508

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Alfentanil hydrochloride

CAS number

71195-58-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8 – Controlled Drug

8 SPONSOR

PIRAMAL CRITICAL CARE PTY LIMITED
Level 20, Tower A, The Zenith
821 Pacific Highway
Chatswood
NSW 2067
Australia

9 DATE OF FIRST APPROVAL

14th October 1994

10 DATE OF REVISION

26 March 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
NA	Boxed warning added as per TGA request letter following opioid reforms
4.3	Contraindication added as per TGA request letter following opioid reforms
4.4	Precautions and warnings class statements added as per TGA request letter following opioid reforms
8	Updated new sponsor details