Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rapifen 500 micrograms/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 500 micrograms of alfentanil (as hydrochloride).

2ml ampoules contain: 1000 micrograms of alfentanil.
10ml ampoules contain: 5000 micrograms of alfentanil.

Each 2 ml ampoule contains 7.08 mg of sodium.
Each 10 ml ampoule contains 35.4 mg sodium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
Ampoules containing a clear, aqueous, sterile solution for injection or infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults:
As an analgesic supplement for use before and during anaesthesia. It is indicated:

i) As an induction agent in general anaesthesia.
ii) As the sole intravenous anaesthetic agent for short minor surgical procedures.
iii) For the induction of anaesthesia, and as an adjunct in the maintenance of general anaesthesia and analgesia.
iv) For the provision of analgesia and suppression of respiratory activity in mechanically ventilated patients in intensive care and to provide analgesic cover for painful procedures.

In paediatrics:
Rapifen is indicated for use in neonates, infants, children and adolescents as:

i) An opioid analgesic in association with a hypnotic to induce anaesthesia
ii) An opioid analgesic in association with general anaesthesia and for both short and long surgical procedures.

4.2 Posology and method of administration

For intravenous use.
Rapifen should be administered intravenously either by bolus injection (short procedures) or bolus supplemented by increments or by infusion (long painful surgical procedures).

The dosage should be individualised. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs including human cytochrome P450 3A4 inhibitors (see section 4.5), type of anaesthesia to be used and type and duration of the surgical procedures.

All administrations of Rapifen must be under cardiovascular monitoring for bradycardia and hypotension. To avoid bradycardia, a small intravenous (I.V.) dose of an anticholinergic agent just before anaesthetic induction may be administered.

Adult patients

1. As an induction agent:

An intravenous bolus of equal to or greater than 120 mcg/kg given slowly.

2. As the sole intravenous anaesthetic agent in short minor surgical procedures where spontaneous respiration is desired:

Single doses of 7 mcg/kg up to 500 mcg (1 ml), with supplemental doses of 3.5 mcg/kg or 250 mcg (0.5 ml). The initial bolus dose should be given slowly over approximately 30 seconds. Analgesia after 1 ml lasts for 5-10 minutes, peaking at 90 seconds.

3. For longer procedures utilising controlled ventilation:

a) Single bolus doses of 30-50 mcg/kg with supplemental bolus doses of 15 mcg/kg.
b) By infusion, with an initial loading dose of 50-100 mcg/kg given over 10-15 minutes, and thereafter at approximately 0.5-1 mcg/kg/min.

Infusion rates in excess of 1 mcg/kg/min during maintenance of anaesthesia have been associated with prolonged recovery and delayed life threatening, respiratory arrest and depression up to 1.5 hours after cessation of infusion. A rate below this value should be titrated to individual patient response with a progressive reduction of infusion rate.

Lower doses will be adequate where anaesthesia is being supplemented by other agents, and in patients with hepatic disease, in elderly or obese patients, in those who are taking fluconazole, erythromycin, diltiazem, cimetidine, ketoconazole, itraconazole or ritonavir concurrently and in patients who are slow metabolisers due to genetic polymorphism.

Infusion should be discontinued 10-20 minutes before the anticipated end of surgery. Supplementation of the anaesthetic if required is best achieved by single injections of 7-15 mcg/kg. Large doses by infusion are not suitable if early spontaneous ventilation is desired.

4. Use in intensive care unit:

Following intubation, mechanical control of ventilation may be achieved by the following regimens:
The usual initial infusion rate is 2 mg/hr or 30 mcg/kg/hr. A more rapid control may be gained by using a loading dose of 5 mg in divided doses over a period of 10 minutes, under close cardiovascular monitoring for bradycardia and hypotension. Subsequently, dosage should be adjusted by careful and continuous titration in each individual patient to produce the desired effects. The usual rate during prolonged infusion is 0.4-0.5 mcg/kg/min, which should be tapered off towards the end of the infusion period. Reassessment should be carried out regularly to ensure that the optimum dose is being used. Additional bolus doses of 0.5-1 mg may be given to provide analgesia during short painful procedures, under careful cardiovascular monitoring.

Paediatric patients

Assisted ventilation equipment should be available for use in children of all ages, even for short procedures in spontaneously breathing children.

It is not recommended for use in treating children in intensive care as there is little experience.

Data in children, particularly those aged 1 month to 1 year are limited (see section 5.2).

- Neonates (0 to 27 days): The pharmacokinetics are very variable in neonates, particularly in those born preterm. Clearance and protein binding are lower, and a lower dose of Rapifen may be required. Neonates should be closely monitored and the dose of Rapifen titrated according to the response.
- Infants and toddlers (28 days to 23 months): Clearance may be higher in infants and toddlers compared to that in adults. For maintenance of analgesia, the rate of infusion of Rapifen may need to be increased.
- Children (2 to 11 years): Clearance may be slightly higher in children and the rate of infusion may need to be increased.
- Adolescents: The pharmacokinetics of alfentanil in adolescents are similar to those in adults and no specific dosing recommendations are required.

Dosing recommendations for paediatric patients

The wide variability in response to Rapifen makes it difficult to provide dosing recommendations for younger children. For older children a bolus dose of 10 to 20 mcg/kg Rapifen for induction of anaesthesia (i.e. to supplement propofol or inhalation anaesthesia) or as an analgesic is considered appropriate. Supplemental boluses of 5 to 10 mcg/kg Rapifen at appropriate intervals can be administered.

To maintain analgesia in children during surgery, a Rapifen infusion rate of 0.5 to 2 mcg/kg/min may be administered. The dose must be titrated up or down according to the needs of the individual patient. When combined with an intravenous anaesthetic agent the recommended dose is approximately 1 mcg/kg/min.

There may be a higher risk of respiratory complications and muscle rigidity when Rapifen is administered to neonates and very young children. Necessary precautions are detailed in section 4.4.

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

A correlation has been shown in the elderly between the development of hypotension and both dose and plasma concentration of alfentanil. Hypotension may be avoided by reducing both the dose and the speed of injection, which should be over 3 to 5 minutes. The effect of the initial dose should be taken into account in determining supplemental doses.

Obese patients:
Should have dosage calculated according to their lean body mass.

Hepatic impairment:
Will require reduced doses.

Renal impairment:
Clearance of alfentanil is unaltered in renal failure. However, there is an increased free fraction and hence dosage requirements may be less.
Prior to infusion, the product should be diluted using standard infusion solutions. Rapifen may be mixed with sodium chloride injection BP, dextrose injection BP or compound sodium lactate injection BP (Hartmann's solution). Such dilutions are compatible with plastic bags and giving sets. These dilutions should be used within 24 hours of preparation.

4.3 Contraindications

Obstructive airways disease or respiratory depression, if not being ventilated. Administration during labour or Caesarean section, prior to clamping of the cord. Concurrent administration with monoamine oxidase inhibitors or within 2 weeks of discontinuation of them. Patients with a known hypersensitivity or idiosyncratic response to alfentanil or other opioids. Patients with a known hypersensitivity to any of the excipients.

4.4 Special warnings and precautions for use

Rapifen is intended for use in hospitals only, by those trained in anaesthesia and familiar with the use of potent opioids when given by continuous infusion or by the intravenous route.

Rapifen can be abused in a manner similar to other opioid agonists.

As with all potent opioids, respiratory depression is dose-related and can be reversed by a specific opioid antagonist, 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 post-operative period. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's responses to CO_2, thus affecting respiration post-operatively.

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical 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).

Induction of muscle rigidity, which may also involve the thoracic muscles, can occur, but can be avoided by the following measures: slow iv injection (ordinarily sufficient for lower doses), premedication with benzodiazepines and the use of muscle relaxants.

Non-epileptic (myo)clonic movements can occur.

After Rapifen use, but especially after infusions or large doses, the anaesthetist should satisfy himself that adequate spontaneous breathing has been established and is maintained in the absence of stimulation before discharging the patient from the recovery area. Respiratory arrests have generally occurred within 90 minutes of cessation of infusion.

Careful cardiovascular monitoring is necessary during Rapifen administration, particularly when the loading dose and any subsequent bolus doses are administered. Bradycardia and possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic, or when Rapifen is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.

Opioids may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

The likelihood of bradycardia should be particularly borne in mind if other drugs which themselves may give rise to bradycardia e.g. beta-blockers, suxamethonium, halothane, are being used, or where patients have existing conduction defects. An anti-cholinergic drug and isoprenaline should be available.

The use of rapid bolus injections of opioids should be avoided in patients with compromised intracerebral compliance; in such patients the transient decrease in mean arterial pressure has occasionally been accompanied by a short-lasting reduction of the cerebral perfusion pressure.

Patients on chronic opioid therapy or with history of opioid abuse may require higher doses.

It is recommended to reduce the dosage in the elderly and in debilitated patients.

Opioids should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism; pulmonary disease; decreased respiratory reserve; alcoholism; impaired hepatic or renal function. Such patients also require prolonged post-operative monitoring.

Use in intensive care units:
Alfentanil lacks sedative or hypnotic activity at the proposed doses. Supplementation with an appropriate hypnotic or sedative agent such as midazolam or diazepam, is recommended.

Although all the effects of alfentanil can be reversed by naloxone, acceleration of the recovery process by this means should be resisted wherever possible. Rapid reversal is likely to cause opioid withdrawal and exaggerated responses to painful stimuli, and should be reserved for the very rare occasions where the benefits outweigh the disadvantages.

Although muscle rigidity is often a feature of high Rapifen doses, only one patient in the clinical ICU infusion programme developed mild symptoms. Nevertheless, rigidity may occur after supplementary bolus doses and immediate administration of a neuromuscular blocking agent may be necessary.

In some patients, an increasing requirement for Rapifen has been observed over the course of several days. These patients have also often required greater doses of other drugs such as midazolam used concomitantly.
Alfentanil may give rise to an increase in intracranial pressure. This should be borne in mind when considering use in patients with head injuries.

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.

Paediatric population:
There may be a higher risk of respiratory complications when Rapifen is administered to neonates and very young children than when it is used in older children and adults. For this reason, young paediatric subjects should be monitored immediately after administration of Rapifen is commenced. Assisted ventilation equipment should be available for use in children of all ages, even for short procedures in spontaneously breathing children.

If Rapifen is used in neonates and young infants, the simultaneous use of a muscle relaxant should be considered because of the risk of muscle rigidity. All children should be monitored for a sufficient period of time following cessation of treatment with Rapifen to ensure the return of spontaneous respiration has been achieved.

Due to variable pharmacokinetics in neonates a lower dose of Rapifen may be required. Neonates should be closely monitored and the dose of Rapifen titrated according to the response. (See section 4.2)

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 Section 4.5).

For Rapifen 2 ml ampoule: This medicine contains less than 1 mmol sodium (23 mg) per 2 ml ampoule, that is to say essentially 'sodium-free'.

For Rapifen 10 ml ampoule: This medicinal product contains 35.4 mg sodium per 10 ml ampoule, equivalent to 1.8 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs Modifying the Effect of Alfentanil

Central Nervous System (CNS) depressants
Drugs such as barbiturates, benzodiazepines or related drugs, neuroleptics, general anaesthetics and other, non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depression of 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 Section 4.4). 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 Section 4.4).
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.

Cytochrome P450 3A4 (CYP3A4) inhibitors
Alfentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. *In vitro* data suggest that potent cytochrome P450 3A4 enzyme inhibitors (eg 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 (see section 4.2).
Treatment with drugs which may depress the heart or increase vagal tone, such as beta-blockers and anaesthetic agents, may predispose to bradycardia or hypotension. The use of opioid premedication may enhance or prolong the respiratory depressant effects of alfentanil.

Monoamine Oxidase Inhibitors (MAOI)
It is usually recommended to discontinue MAO-inhibitors 2 weeks prior to any surgical or anesthetic procedure (see section 4.3).

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.

4.6 Fertility, 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. 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.
Intravenous administration during childbirth (including caesarian section) is not recommended because alfentanil 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.
Breast-feeding
Alfentanil 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.

4.7 Effects on ability to drive and use machines

When early discharge is envisaged, patients should be advised not to drive or operate machinery for at least 24 hours following administration.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It may be an offence to drive while under the influence of this medicine.

4.8 Undesirable effects

Adverse Reactions
The most frequently reported adverse reactions (incidence ≥10%) are: nausea and vomiting. Undesirable effects listed below in Table 1 have been reported in clinical trials (1157 subjects) and/or from spontaneous reports from post-marketing experience. The following terms and frequencies are applied:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available clinical trial data).

Table 1	**Adverse Reactions reported in clinical trials and/or postmarketing**				
	Frequency Category				
System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare ≥1/10,000 to <1/1,000**	**Not Known**
Immune System Disorders					Hypersensitivity (including anaphylactic reaction, anaphylactoid reaction and urticaria)
Psychiatric Disorders		Euphoric Mood		Agitation; Crying	Disorientation
Nervous System Disorders		Movement Disorder; Dizziness; Sedation; Dyskinesia	Headache; Somnolence; Unresponsive to Stimuli		Loss of Consciousness (postoperative period); Convulsion; Myoclonus
Eye Disorders		Visual Disturbance			Miosis
Cardiac Disorders		Bradycardia; Tachycardia	Arrhythmia; Heart Rate Decreased		Cardiac Arrest
Vascular Disorders		Hypotension; Hypertension; Blood Pressure Decreased; Blood Pressure Increased		Vein Pain	
Respiratory, Thoracic and Mediastinal Disorders		Apnoea	Hiccups; Hypercapnia; Laryngospasm; Respiratory Depression (including fatal outcome)	Bronchospasm; Epistaxis	Respiratory Arrest; Cough
Gastrointestinal Disorders	Nausea; Vomiting				
Skin and Subcutaneous Tissue Disorders			Dermatitis Allergic; Hyperhidrosis	Pruritus	Erythema; Rash
Musculoskeletal and Connective Tissue Disorders		Muscle Rigidity			

General Disorders and Administration Site Conditions		Chills; Injection Site Pain; Fatigue	Pain		Pyrexia
Injury, Poisoning and Procedural Complications		Procedural Pain	Agitation Postoperative; Airway Complication of Anaesthesia; Confusion Postoperative	Anaesthetic Complication Neurological; Procedural Complication; Endotracheal Intubation Complication	

Paediatric population
The 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 frequently in neonates, although the number of neonates included in clinical studies was small. Severe rigidity and jerking can occur less commonly and may be accompanied by transient impaired ventilation, especially with high doses of Rapifen or with a rapid rate of intravenous injection.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms
The manifestations of Rapifen overdose are an extension of its pharmacologic actions. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnoea to apnoea.

Treatment
In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific 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 hypovolaemia should be considered and, if present, it should be controlled with appropriate parenteral fluid administration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: opioid anaesthetics, ATC Code: N01A H02

Alfentanil is a potent, fast and short acting opioid analgesic, chemically related to fentanyl. After intravenous administration of alfentanil, action sets in almost instantly; the onset of action amounts to only one quarter of that of an equianalgesic dose of fentanyl. The maximum analgesic and respiratory depressant effect occurs within 1-2 minutes (30 minutes with morphine).

The duration of action of alfentanil is only one third of that of an equianalgesic dose of fentanyl and is clearly dose-related. For analgesia lasting longer than 60 minutes, an infusion is preferable. Its depressant effects on respiratory rate and alveolar

ventilation are also 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 anaesthesia. 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.

5.2 Pharmacokinetic properties

Alfentanil is a synthetic opioid with μ-agonist pharmacological effects.

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

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

Elimination
Alfentanil is rapidly eliminated after intravenous administration. Terminal elimination half-lives of 83-223 min have been reported. The plasma clearance in subjects below 40 years averages 356 ml/min, and decreases approximately 8% per decade increase above 40 years of age.

Because of this pharmacokinetic profile, alfentanil is not stored in the tissues. During average-length to long-lasting surgery, analgesia can be maintained by repeating alfentanil injections or by a continuous infusion, subsequent to a bolus dose.

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

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

Pharmacokinetic Parameters of Alfentanil in Paediatric Subjects			
	$t_{1/2\beta}$ (hr)	**CL (mL/kg/min)**	**Vd_{ss} (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 & Toddlers 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	1.1-1.9	5.5-7.4	0.3-0.6

12-14 years; ***n= 3***			
Note: Data for neonates, infants & toddlers, and children are given as range of mean values. CL = clearance, Vd_{ss} = volume of distribution at steady state, $t_{1/2\beta}$ = 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 metabolised 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 Section 4.4.).

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.).

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in section 4.2, *Posology and Administration*.

6.3 Shelf life

Unopened: 5 years
Once opened: Use immediately. Discard any unused contents.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Colourless Ph.Eur Type I glass ampoules
Pack size: packs of 10 x 2 ml ampoules, packs of 5 and 10* x 10ml ampoules.

**Not all pack sizes may be marketed.*

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused contents.
Wear gloves while opening ampoule. Accidental dermal exposure should be treated by rinsing the affected area with water.
Avoid use of soap, alcohol, and other cleaning materials that may cause chemical or physical abrasions to the skin.

7 MARKETING AUTHORISATION HOLDER

Piramal Critical Care B.V.
Rouboslaan 32 (ground floor)
2252 TR
Voorschoten
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA22583/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 June 1992

Date of last renewal: 09 June 2007

10 DATE OF REVISION OF THE TEXT

October 2022