1 NAME OF THE MEDICINAL PRODUCT

Rapifen solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Rapifen contains alfentanil hydrochloride 544 micrograms, equivalent to 500 micrograms alfentanil base.

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.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Short procedures and outpatient surgery.
- Procedures of medium and long duration when given as a bolus followed by supplemental doses or by continuous infusion.

At very high doses, Rapifen may be used in adults as an anaesthetic induction agent in ventilated patients.

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

- an opioid analgesic in association with a hypnotic to induce anaesthesia
- an opioid analgesic in association with general anaesthesia and for both short and long surgical procedures

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with alfentanil in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

For intravenous administration.

Rapifen by the intravenous route can be administered to both adults and children. Rapifen should be used as bolus injections (short procedures) or bolus supplemented by increments or by infusion (long painful surgical procedures).

The dosage of Rapifen should be individualised according to age, bodyweight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.

Adults patients

The usual recommended dosage regimen is as follows:

Adults	*Initial*	*Supplemental*
Spontaneous respiration	500 mcg (1 ml)	250 mcg (0.5 ml)
Assisted ventilation	30-50 mcg/kg	15 mcg/kg

If desired, Rapifen can 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.

In spontaneously breathing patients, the initial bolus dose should be given slowly over about 30 seconds (dilution may be helpful).

After intravenous administration in unpremedicated adult patients, 1 ml Rapifen may be expected to have a peak effect in 90 seconds and to provide analgesia for 5-10 minutes. Periods of more painful stimuli may be overcome by the use of small increments of Rapifen. For procedures of longer duration, additional increments will be required.

In ventilated patients, the last dose of Rapifen should not be given later than about 10 minutes before the end of surgery to avoid the continuation of respiratory depression after surgery is complete.

In ventilated patients undergoing longer procedures, Rapifen may be infused at a rate of 0.5-1 microgram/kg/minute. Adequate plasma concentrations of alfentanil will only be achieved rapidly if this infusion is preceded by a loading dose of 50-100 microgram/kg given as a bolus or fast infusion over 10 minutes.

Lower doses may be adequate, for example where anaesthesia is being supplemented by other agents.

The infusion should be discontinued up to 30 minutes before the anticipated end of surgery.

Increasing the infusion rate may prolong recovery. Supplementation of the anaesthetic, if required, for periods of painful stimuli, is best managed by extra bolus doses of Rapifen (1-2 ml) or low concentrations of a volatile agent for brief periods.

Patients with severe burns presenting for dressing, etc, have received a loading dose of 18-28 mcg/kg/min for up to 30 minutes without requiring mechanical ventilation. In heart surgery, when used as a sole anaesthetic, doses in the range of 12-50 mg/hour have been used.

Paediatric patients

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

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 to2 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

Elderly (>65 years of age) and debilitated patients may require lower or less frequent dosing owing to a longer half-life of Rapifen in this age group (dilution may be helpful).

4.3 Contraindications

Obstructive airways disease or respiratory depression if not ventilating.

Concurrent administration with monoamine oxidase inhibitors or within 2 weeks of their discontinuation.

Administration in labour or before clamping of the cord during caesarean section due to the possibility of respiratory depression in the newborn infant.

Patients with a known intolerance to alfentanil and other morphinomimetics.

4.4 Special warnings and precautions for use

Warnings:

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). For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses.

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with alfentanil.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Neonatal Withdrawal Syndrome

If women take this drug 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 section 4.6).

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Following administration of Rapifen, a fall in blood pressure may occur. The magnitude of this effect may be exaggerated in the hypovolaemic patient or in the presence of concomitant sedative medication. Appropriate measures to maintain a stable arterial pressure should be taken.

Significant respiratory depression and loss of consciousness will occur following administration of Rapifen in doses in excess of 1 mg and is dose-related. This and the other pharmacological effects of Rapifen are usually of short duration and can be reversed by the specific opioid antagonists (e.g. naloxone). Additional doses of the antagonists may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.

Like other opioids, alfentanil may cause bradycardia, an effect that may be marked and rapid in onset but which can be antagonised by atropine. Particular care must be taken following treatment with drugs which may depress the heart or increase vagal tone, such as anaesthetic agents or beta-blockers, since they may predispose to bradycardia or hypotension. Heart rate and blood pressure should therefore be monitored carefully. If hypotension or bradycardia occur, appropriate measures should be instituted.

Cardiac arrest following bradycardia has been reported on very rare occasions in non-atropinised patients. Therefore it is advisable to be prepared to administer an anticholinergic drug.

<u>Risk from concomitant use of Central Nervous System (CNS) depressants, especially benzodiazepines or related drugs</u>

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. The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death. If a decision is made to administer Rapifen concomitantly with a CNS depressant, especially a benzodiazepine or a related drug, the lowest effective dose of both drugs should be administered, for the shortest period of concomitant use. Patients should be carefully monitored for signs and symptoms of respiratory depression and profound sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see Interactions).

Precautions:

It is wise to reduce the dosage in the elderly and debilitated patients. In hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism and liver or renal impairment the dosage should be titrated with care and prolonged monitoring may be required.

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

Rapifen may induce muscle rigidity during induction. Rigidity, which may also involve the thoracic muscles, can be avoided by the following measures:

- Slow IV injection (usually sufficient for lower doses);
- Premedication with a benzodiazepine;
- Administration of a muscle relaxant just prior to administration of Rapifen.

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

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early postoperative period. Care should be taken after infusions or large doses of Rapifen to ensure that adequate spontaneous breathing has been established and maintained in the absence of stimulation before discharging the patient from the recovery area. Resuscitation equipment and narcotic antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's response to CO_2, thus affecting respiration postoperatively.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per 5 mg dose, i.e. essentially 'sodium-free'.

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)

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 enhance or prolong the respiratory depressant effects of opioids. If other narcotic or CNS depressant drugs are used concurrently with alfentanil, the effects of the drugs can be expected to be additive. When patients have received such drugs, the dose of alfentanil required will be less than usual. Concomitant use with Rapifen in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death (see warnings and precautions).

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

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

In combination with alfentanil, the blood concentrations of propofol are 17% higher than in the absence of alfentanil. 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 (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.

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. Bradycardia and possibly cardiac arrest can occur when Rapifen is combined with non-vagolytic muscle relaxants.

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

Serotonergic drugs
Coadministration of alfentanil with a serotonergic agent, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), or Monoamine Oxidase Inhibitors (MAOIs), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

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.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Administration to nursing women is not recommended as alfentanil may be secreted in breast milk and may cause respiratory depression in the infant.

4.7 Effects on ability to drive and use machines

Where 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. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. 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 is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely.

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).

Adverse reactions from spontaneous reports during worldwide postmarketing experience with Alfentanil that met threshold criteria are included. Unlike for clinical trials, precise frequencies cannot be provided for spontaneous reports. The frequency for these reports is therefore classified as 'not known'.

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 Drug dependence (see section 4.4)
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				

Table 1	**Adverse Reactions reported in clinical trials and/or postmarketing**				
	Frequency Category				
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 Drug withdrawal syndrome		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

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

The manifestations of alfentanil overdose are generally an extension of its pharmacological action. They include the following symptoms (on the left) and advice for treatment (on the right):

Symptom	*Action*
Bradycardia	Anticholinergics such as atropine or glycopyrrolate.
Hypoventilation or apnoea	O_2 administration, assisted or controlled respiration and an opioid antagonist may be required.
Muscle rigidity	Intravenous neuromuscular blocking agents may be given.

If hypotension is severe or persists, the possibility of hypovolaemia should be considered and controlled with appropriate parenteral fluid administration.

The suggested treatments given above do not preclude the use of other clinically indicated counter measures.

Body temperature and adequate fluid intake should be maintained and the patient observed for 24 hours. A specific opioid antagonist (e.g. naloxone) should be available to treat respiratory depression.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: opioid anesthetics, ATC code: N01AH02

The analgesic potency of Rapifen is one quarter that of fentanyl. The duration of action of Rapifen is one third that on an equianalgesic dose of fentanyl and is clearly dose-related. Its depressant effects on respiratory rate and alveolar ventilation are also of shorter duration than those of fentanyl.

The onset of action of Rapifen is four times more rapid than that of an equianalgesic dose of fentanyl. The peak analgesic and respiratory depressant effects occur within 90 seconds.

In man, alfentanil at therapeutic doses had no detrimental effects on myocardial performance. The cardiovascular stability is remarkable both in healthy and poor-risk patients. The only changes seen in blood pressure and heart rate are transient, slight decreases occurring immediately after induction. The incidence and degree of respiratory depression is less and of shorter duration after alfentanil than with fentanyl. Like other opioid analgesics, alfentanil increases the amplitude of the EEG and reduces its frequency. Alfentanil reduces intraocular pressure by about 45%. It blocks increases in plasma cortisol and in plasma antidiuretic and growth hormones throughout surgery and prevents increases in plasma catecholamines up to but not during or after cardiopulmonary bypass in patients undergoing open heart surgery.

5.2 Pharmacokinetic properties

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

After bolus injections ranging from 2.4 to 125 mcg/kg, plasma levels in man decay triexponentially with a terminal half life of approximately 90 minutes. Total distribution volume varies from 0.4 to 1.0 L/kg, indicating a limited distribution of alfentanil to the tissues. Plasma clearance, varying from 3.3 to 8.3 ml/kg/min represents approximately one third of liver plasma flow indicating that elimination of alfentanil is not flow dependent. Since only 0.4% of the dose is excreted with the urine as unchanged drug, elimination of alfentanil occurs mainly by metabolism.

These main parameters in patients undergoing surgery are similar to those in healthy volunteers. Only when the drug was given as the sole anaesthetic in a continuous high infusion over about 5 hours was the clearance of alfentanil reduced resulting in a plasma half-life of about 200 minutes, the distribution volume not being markedly changed.

Plasma protein binding of alfentanil is 92%, mainly due to a strong binding to the 'acute phase' α_1 acid-glycoprotein. It is not bound to the blood cells. Pharmacokinetics were comparable in rats, dogs and man. The elderly show a longer half-life for Rapifen after IV bolus doses.

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 12-14 years; ***n= 3***	1.1-1.9	5.5-7.4	0.3-0.6

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.

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 effects 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

See ‘Dosage and dosage schedules’.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store in a controlled drug store. This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Colourless glass one-point-cut ampoules (PhEur, Type I).

Pack size: packs of 10 x 2 ml ampoules; packs of 5 and 10* x 10 ml ampoules.

*Not all pack sizes maybe marketed.

6.6 Special precautions for disposal

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 usage of soap, alcohol, and other cleaning materials that may cause chemical or physical abrasions to the skin.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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