SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfentanil 500 micrograms/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of Alfentanil 500 micrograms/ml solution for injection contains:
Alfentanil hydrochloride hydrate 543.8 micrograms, equivalent to 500 micrograms alfentanil base

This medicine contains:
- 7.1 mg (or 0.31 mmol) sodium per 2 ml ampoule, that is to say essentially ‘sodiumfree’.
- 35.4 mg (or 1.54 mmol) sodium) per 10 ml ampoule, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
- 177 mg (or 7.70 mmol) sodium per 50 ml vial, equivalent to 9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

The product is a clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults, as an 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.

Alfentanil 500 micrograms/ml is indicated for use in neonates, infants, and children as:
- an opioid in association with a hypnotic to induce anaesthesia
- a narcotic analgesic in association with general anaesthesia and for both short and long surgical procedures

At very high doses, Alfentanil 500 micrograms/ml solution for injection may be used as an anaesthetic induction agent in ventilated patients.

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).

Alfentanil 500 micrograms/ml by the intravenous route can be administered to both adults and children. Alfentanil 500 micrograms/ml should be used as bolus injections (short procedures) or bolus supplemented by increments or by infusion (long painful surgical procedures). The dosage of Alfentanil 500 micrograms/ml should be individualised according to age, bodyweight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.

Adult patients

The usual recommended dosage regimen is shown in Table 1 Dosage regimen:

Table 1 Dosage regimen

	Initial	*Supplemental*
Spontaneous respiration	500 microgram (1 ml)	250 microgram (0.5 ml)
Assisted ventilation	30 – 50 microgram/kg	15 microgram/kg

If desired, Alfentanil 500 micrograms/ml can be mixed with sodium chloride injection BP, glucose injection BP or Ringer-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 obese patients (more than 20 % above ideal total body weight), the dosage of alfentanil should be determined on the basis of lean body weight.

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 Alfentanil 500 micrograms/ml 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 Alfentanil 500 micrograms/ml. For procedures of longer duration, additional increments will be required.

In ventilated patients, the last dose of Alfentanil 500 micrograms/ml 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, Alfentanil 500 micrograms/ml may be infused at a rate of 0.5 – 1 micrograms/kg/minute. Adequate plasma concentrations of alfentanil will only be achieved rapidly if this infusion is preceded by a loading dose of 50 – 100 micrograms/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 Alfentanil 500 micrograms/ml (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 micrograms/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 (0-27 days): The pharmacokinetics are very variable in neonates, particularly in those born preterm. Clearance and protein binding are lower, and a lower dose of alfentanil may be required. Neonates should be closely monitored and the dose of alfentanil 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 alfentanil 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 alfentanil makes it difficult to provide dosing recommendations for younger children. For older children a bolus dose of 10 to 20 micrograms/kg alfentanil 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 micrograms/kg alfentanil at appropriate intervals can be administered.

To maintain analgesia in children during surgery, an Alfentanil 500 micrograms/ml infusion rate of 0.5 to2 micrograms/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 microgram/kg/min.

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

Elderly or debilitated patients

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

Method of administration

Alfentanil is administered intravenously by injection or infusion and should only be given by individuals trained in the administration of general anaesthetics and the management of the respiratory effects of potent opioids. Pulse oximetry or some other means for measuring respiratory function is recommended. Visually inspect parenteral products for particulate matter and discoloration prior to administration.

Infuse iv slowly over 3 minutes. Injections rates of < 1 minute are associated with an increased incidence of hypotension.

Continuous infusions longer than 4 days have not been studied.

4.3 Contraindications

Hypersensitivity to the active substance, to other opioids, or to any of the excipients listed in section 6.1.

Obstructive airway 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 new-born infant.

4.4 Special warnings and precautions for use

Warnings:

Following administration of alfentanil, 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 alfentanil in doses in excess of 1 mg and is dose-related. This and the other pharmacological effects of alfentanil 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.

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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of Alfentanil and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Alfentanil concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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.

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.

Alfentanil 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 alfentanil.

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 alfentanil 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.

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).

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.

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.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Paediatric population
There may be a higher risk of respiratory complications when alfentanil 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 alfentanil is commenced. Assisted ventilation equipment should be available for use in children of all ages, even for short procedures in spontaneously breathing children.

If alfentanil 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 alfentanil to ensure the return of spontaneous respiration has been achieved.

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

This medicine contains:
- 7.1 mg (or 0.31 mmol) sodium per 2 ml ampoule, that is to say essentially ‘sodium-free’.
- 35.4 mg (or 1.54 mmol) sodium) per 10 ml ampoule, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
- 177 mg (or 7.70 mmol) sodium per 50 ml vial, equivalent to 9% 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

Sedative medicines such as benzodiazepines or related drugs

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Other Central Nervous System (CNS) depressants

Drugs such as barbiturates, 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 alfentanil in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death. The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

Effect of alfentanil on other drugs

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

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 alfentanil.

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 alfentanil.

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 alfentanil 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

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.

Although no teratogenic or acute embryotoxic effects have been observed in animal experiments, insufficient data are available to evaluate any harmful effects in humans.

Consequently, it is necessary to consider possible risks and potential advantages before administering this drug to pregnant patients.

Labour and Delivery

Intravenous administration during labour (including caesarian section) is not recommended because alfentanil crosses the placenta and because the foetal respiratory centre is particularly sensitive to opioids, which may result in respiratory depression in the neonate. If alfentanil is administered nevertheless, assisted ventilation equipment must be immediately available for use if required. 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 must be considered.

Breast-feeding

Alfentanil may be secreted in breast milk and may cause respiratory depression in the infant Therefore, breast-feeding or use of expressed breast milk is not recommended for 24 hours following the administration of alfentanil.

4.7 Effects on ability to drive and use machines

No studies on the effects of alfentanil on the ability to drive and use machines have been performed.
However, 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* o

The medicine has been prescribed to treat a medical or dental problem and o
You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and

- *However, you would not be committing an offence (called 'statutory defence') if:*
    - o *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; Unresponsiv-e 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; Laryngospa-sm; Respiratory Depression (including fatal outcome)	Bronchosp-asm; Epistaxis	Respiratory Arrest; Cough
Gastrointestinal Disorders	Nausea; Vomiting				
Skin and Subcutaneous Tissue Disorders			Dermatitis Allergic; Hyperhidr-osis	Pruritus	Erythema; Rash
Musculoskeletal and Connective Tissue Disorders		Muscle Rigidity			
Renal and urinary disorders			Urinary retention		
General Disorders and Administration Site Conditions		Chills; Injection Site Pain; Fatigue	Pain, Drug withdrawal syndrome		Pyrexia
Injury, Poisoning and Procedural Complications		Procedural Pain	Agitation Postoper-ative; Airway Complica-tion of Anaesthesia; Confusion Postope-rative	Anaesthetic Compli-cation Neurolo-gical; Procedural Compli-cation; Endotra-cheal Intubation Compli-cation	

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 alfentanil 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 - Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, which include the following:

	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 agent 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 anaesthetics, ATC code: N01AH02 (Alfentanil)

The analgesic potency of alfentanil is one quarter that of fentanyl. The duration of action of alfentanil 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 alfentanil 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 humans, 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 halflife 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 alfentanil after IV bolus doses.

Special Populations

Paediatric population

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			
	t1/2β (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, 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 metabolized by CYP3A4. CYP3A4 activity is low in neonates and increases after birth to reach 30 to 40% of adult levels at 1 month of age. Activity of CYP3A4 increases further to 45% at 6 months, 80% at 12 months.

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, hydrochloric acid and water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

Shelf-life before first opening
3 years.

Shelf-life after dilution
Chemical and physical in-use stability of the dilutions (see section 6.6) has been demonstrated for 48 hours.
From the microbiological point of view, the dilutions should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Shelf-life after first opening
The product should be used immediately after opening the container.

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

Clear glass ampoules (Ph Eur Type I, one point cut) containing 1 mg/2 ml

Clear glass ampoules (Ph Eur Type I, one point cut) containing 5 mg/10 ml

Clear glass (Ph Eur Type I) vials containing 1 mg/2 ml

Clear glass (Ph Eur Type I) vials containing 5 mg/10 ml

Clear glass (Ph Eur Type I) vials containing 25 mg/50 ml

Vials are closed with bromobutyl rubber stoppers and aluminium caps.

Pack sizes:

Original pack containing 5 or 10 ampoules of 2 ml each.

Original pack containing 5 or 10 ampoules of 10 ml each.

Original pack containing 5 or 10 vials of 2 ml each.

Original pack containing 5 or 10 vials of 10 ml each. Original pack containing 1, 5 or 10 vials of 50 ml each

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Alfentanil 500 micrograms/ml solution for injection may be diluted with sodium chloride injection BP, glucose injection BP, or Ringer-Lactate injection BP (Hartmann's solution) to a concentration of 25-80 µg/ml. Such dilutions are compatible with plastic bags and giving sets.
Any unused solution from opened ampoules or vials should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

hameln pharma ltd
Nexus, Gloucester Business Park
Gloucester, GL3 4AG, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 01502/0115

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/09/2020

10 DATE OF REVISION OF THE TEXT

12/10/2022