SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rapifen™ Intensive Care

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alfentanil hydrochloride 5.44 mg equivalent to 5 mg alfentanil base per ml.

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

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rapifen Intensive Care is a potent opioid analgesic with a very rapid onset of action. It is indicated for analgesia and suppression of respiratory activity in mechanically ventilated patients on intensive care and to provide analgesic cover for painful manoeuvres. It will aid compliance with mechanical ventilation, and tolerance of the endotracheal tube. Intravenous bolus doses of Rapifen (0.5 mg/ml) may be used to provide additional pain relief during brief painful procedures such as physiotherapy, endotracheal suction, etc. Despite being mechanically ventilated, patients may be awake in the presence of adequate analgesia.

At the proposed doses, Rapifen Intensive Care has no sedative activity. Therefore supplementation with an appropriate hypnotic or sedative agent is recommended. Admixture is not advisable due to the need to individually titrate both agents.

Alfentanil given by infusion should only be given in areas where facilities are available to deal with respiratory depression and where continuous monitoring

is performed. Alfentanil should only be prescribed by physicians familiar with the use of potent opioids when given by continuous IV infusion.

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).

Method of Administration

For intravenous infusion.

Dosage

Adults

Rapifen Intensive Care should be diluted with sodium chloride intravenous infusion BP, glucose intravenous infusion BP, or compound sodium lactate intravenous infusion BP (Hartmann's solution). Such dilutions are compatible with plastic bags and giving sets. These dilutions should be used within 24 hours of preparation.

Once the patient has been intubated, mechanical ventilation can be initiated using the following dosage regimen:

The recommended initial infusion rate for mechanically ventilated adult patients is 2 mg per hour (equivalent to 0.4 ml per hour of undiluted Rapifen Intensive Care). For a 70 kg patient, this corresponds to approximately 30 micrograms per kilogram per hour.

More rapid control may initially be gained by using a loading dose. For example, a dose of 5 mg may be given in divided doses over a period of 10 minutes, during which time careful monitoring of blood pressure and heart rate should be performed. If hypotension or bradycardia occurs, the rate of administration should be reduced accordingly and other appropriate measures instituted.

The dose to produce the desired effects should then be individually determined and reassessed regularly to ensure that the optimum dose is being used.

In clinical trials, patient requirements have generally been met with doses of 0.5 to 10 mg alfentanil per hour.

Additional bolus doses of 0.5-1.0 mg alfentanil may be given to provide analgesia during short painful procedures.

Patients with liver impairment and hypothyroidism will require lower doses. Obese patients may require a dose based on their lean body mass.

The maximum recommended duration of treatment with alfentanil infusions is 4 days.

Present data suggest that clearance of alfentanil is unaltered in renal failure. However there is an increased free fraction and hence dosage requirements may be less than in the patient with normal renal function.

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.

Paediatric patients

Not recommended for use in children in intensive care.

4.3 Contraindications

Known intolerance of alfentanil or other morphinomimetics. Pregnancy, and concurrent administration with monoamine oxidase inhibitors.

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.

Cardiovascular warnings

Following administration of Rapifen Intensive Care, 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.

Like other opioids, alfentanil may cause bradycardia, an effect which 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 occurs, the rate of administration of alfentanil should be reduced and other appropriate measures 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.

Care must be taken if the patient has received monoamine oxidase inhibitors within the previous 2 weeks.

Significant respiratory depression and loss of consciousness will occur following administration of Rapifen Intensive Care in doses in excess of 1 mg and is dose-related. If necessary for assessment purposes, naloxone or other specific antagonists may be administered to reverse the opioid respiratory depression and other pharmacological effects of alfentanil. More than one dose of naloxone may be required in view of its short half life.

Muscle rigidity (morphine-like effect) may occur, in which case neuromuscular blocking drugs may be helpful.

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. 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 patient. 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.

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 post infusion period. Care should therefore be taken throughout the weaning period and adequate spontaneous respiration should be established and maintained in the absence of stimulation or ventilatory support. Resuscitation equipment and opioid antagonists should be readily available. Following cessation of the infusion, the patient should be closely observed for at least 6 hours. Prior use of opioid medication may enhance or prolong the respiratory depressant effects of alfentanil.

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.

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

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 Intensive

Care in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death (see warnings and precautions).

Effect of Rapifen Intensive Care on other drugs

Following the administration of Rapifen Intensive Care, 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 Intensive Care.

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 Intensive Care.

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 Intensive Care 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

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

Table 1	**Adverse Reactions reported in clinical trials and/or postmarketing**				
	Frequency Category				
					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				
Skin and Subcutaneous Tissue Disorders			Dermatitis Allergic; Hyperhidrosis	Pruritus	Erythema; Rash
Musculoskeletal and Connective Tissue Disorders		Muscle Rigidity			

Table 1	Adverse Reactions reported in clinical trials and/or postmarketing				
	Frequency Category				
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, which include the following:-

	Action:
Bradycardia:	Anticholinergics such as atropine or glycopyrrolate;
Hypoventilation or apnoea:	Oxygen administration, assisted or controlled respiration and an opioid antagonist may be required;

Muscle rigidity:	Intravenous neuromuscular blocking agents may be given.

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

In man, alfentanil at therapeutic doses has 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 were 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 approx. 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 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			
	$t_{1/2\beta}$ (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 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 CYPA4 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.

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

See Section 4.2 Posology and Method of administration.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store in the controlled drug store, at or below 25°C.

6.5 Nature and contents of container

Type I USP clear glass ampoules containing 1ml, packed in 5s or 10s.

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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