ALFENTANIL 5 MG/ML, SOLUTION FOR INJECTION

ALFENTANIL 500 MICROGRAMS/ML, SOLUTION FOR INJECTION

PL 17507/0037

PL 17507/0074

UKPAR

TABLE OF CONTENTS

Lay summary .................................................. Page 2
Scientific discussion ........................................ Page 3
Steps taken for assessment ............................... Page 10
Summary of product characteristics .................. Page 11
Patient information leaflet ............................... Page 30
Labelling ....................................................... Page 39
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Alfentanil 5 mg/ml, Solution for Injection and Alfentanil 500 micrograms/ml, Solution for Injection (Product Licence numbers: 17507/0037 and 17507/0074).

Alfentanil is a potent and short-acting painkiller. It belongs to a group of medicines known as opioid analgesics, which relieve or prevent pain.

Alfentanil 5 mg/ml, Solution for Injection is used to control pain and breathing when using an artificial breathing machine in intensive care.

Alfentanil 500 micrograms/ml, Solution for Injection is used as a painkiller for therapeutic or exploratory surgical procedures.

Alfentanil 5 mg/ml and 500 micrograms/ml, Solution for Injection raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction ................................................. Page 4
Pharmaceutical assessment .......................... Page 5
Preclinical assessment ................................ Page 7
Clinical assessment ...................................... Page 8
Overall conclusions and risk benefit assessment  Page 9
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Alfentanil 5 mg/ml, Solution for Injection and Alfentanil 500 micrograms/ml, Solution for Injection (PL 7507/0037 and PL 17507/0074) to Auden Mckenzie (Pharma Division) Ltd on 23 March 2010. These medicines are only available on prescription.

The applicant claims that Alfentanil 5 mg/ml, Solution for Injection and Alfentanil 500 micrograms/ml, Solution for Injection are generic versions of Rapifen Intensive Care Solution for Injection and Rapifen 500 mcg/ml Solution for Injection, licensed to Janssen-Cilag Ltd since 31 of July 1989. The legal basis of these applications is acceptable and the ten year rule is complied with.

Alfentanil is a potent analgesic supplement for use before and during anaesthesia. The 5 mg/ml strength solution is indicated for analgesia and suppression of respiratory activity in mechanically ventilated patients on intensive care and to provide analgesic cover for painful manoeuvres. The 500 micrograms/ml strength solution is indicated for short procedures and outpatient surgery and for procedures of medium and long duration when given as a bolus followed by supplemental doses or by continuous infusion.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE: ALFENTANIL HYDROCHLORIDE

Formula: \( (C_{21}H_{32}N_{6}O_{3}, \text{HCl}) \)
MW: 453.0
CAS number: 69049-06-5 (anhydrous)
Chemical name: N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)-ethyl]-4-(methoxymethyl) piperidin-4-yl]-N-phenylpropanamide hydrochloride

Alfentanil hydrochloride is a white to off-white powder, readily soluble in water, soluble 1 in 5 of ethanol, 1 in < 2 of chloroform, 1 in < 2 of methanol and practically insoluble in ether.

Alfentanil has no chiral centres. Alfentanil hydrochloride can exist in the anhydrous and monohydrate form.

The method of manufacture of alfentanil hydrochloride is appropriate.

The proposed drug substance specification and its justification, analytical procedures and their validation, batch analyses and reference standards used by the drug substance manufacturer are satisfactory.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Active alfentanil hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting the retest period.

DRUG PRODUCT

Composition
The product excipients are sodium chloride, water for injections, sodium hydroxide and hydrochloric acid. The sodium hydroxide and hydrochloric acid are used for occasional pH adjustment only. Satisfactory certificates of analysis have been provided for all excipients. All excipients are Ph Eur and were tested in line with their Ph Eur monographs. There were no novel excipients used and no overages. None of the excipients are of human or animal origin.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.
**Finished Product Specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

Alfentanil 5 mg/ml is stored in type I Ph Eur clear glass ampoules containing 1 ml solution (10 ampoules per carton). Alfentanil 500 micrograms/ml, Solution for Injection is stored in type I Ph Eur clear glass ampoules containing 2 ml or 10 ml solution (5 or 10 ampoules per carton).

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months for unopened product and 24 hours for dilutions has been set, which is satisfactory. This medicinal product does not require any special storage conditions.

**Bioequivalence / Bioavailability**

These are parenteral products, therefore, bioequivalence studies are not necessary.

**Essential Similarity**

Both test and reference products have the same pharmaceutical form (solution for injection) and comparative impurity profiles. They can, therefore, be considered essentially similar.

**Product Literature**

All product literature (SPCs, PILs and labelling) are satisfactory. The package leaflets were submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflets are well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

**Conclusion**

It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

BACKGROUND
Alfentanil is a short-acting opioid anesthetic and analgesic derivative of fentanyl. It produces an early peak analgesic effect and fast recovery of consciousness. Alfentanil is effective as an anesthetic during surgery, for supplementation of analgesia during surgical procedures, and as an analgesic for critically ill patients.

INDICATIONS
The indications for these products are satisfactory.

DOSE & DOSE SCHEDULE
The posology for these products is satisfactory.

TOXICOLOGY
Satisfactory

CLINICAL PHARMACOLOGY
Satisfactory

EFFICACY
Satisfactory

SAFETY
Satisfactory

EXPERT REPORTS
The expert report is satisfactory and references the key literature.

PRODUCT LITERATURE
All product literature is medically satisfactory.

BIOEQUIVALENCE
These are parenteral products, therefore, bioequivalence studies are not necessary.

RECOMMENDATIONS
There are no clinical public health issues and the recommendation is to grant marketing authorisations for these preparations.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Alfentanil 5 mg/ml, Solution for Injection and Alfentanil 500 micrograms/ml, Solution for Injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of alfentanil is well established. The SPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with alfentanil. The risk benefit is therefore considered to be positive.
ALFENTANIL 5 MG/ML, SOLUTION FOR INJECTION

ALFENTANIL 500 MICROGRAMS/ML, SOLUTION FOR INJECTION

PL 17507/0037

PL 17507/0074

STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 10 August 2005</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 30 September 2005.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 14 July 2006</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 27 April 2009</td>
</tr>
<tr>
<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 20 November 2009</td>
</tr>
<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 11 December 2009</td>
</tr>
<tr>
<td>7</td>
<td>The application was determined on 23 March 2010</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Alfentanil 5 mg/ml, Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Alfentanil solution for injection contains 5 mg alfentanil (as hydrochloride) per ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.

A clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Alfentanil 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 Alfentanil 5 mg/ml (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, Alfentanil 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
For intravenous infusions.

Dosage
Alfentanil 5 mg/ml should be diluted with sodium chloride intravenous infusion BP, dextrose 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 Alfentanil 5 mg/ml). 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.

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

Adolescents and young adults will require higher than average doses. There is little experience of use of alfentanil to treat children in intensive care.

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.

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:

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.

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. Asystole 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 alfentanil 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.

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. 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.

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

4.5 Interaction with other medicinal products and other forms of interaction
Alfentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. Available human pharmacokinetic data indicate that the metabolism of alfentanil may be inhibited by fluconazole, erythromycin, diltiazem and cimetidine (known cytochrome P450 3A4 enzyme inhibitors). In vitro data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may also inhibit the metabolism of alfentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such 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 asystole can occur when Alfentanil 5 mg/ml is combined with non-vagolytic muscle relaxants.

Prior use of opioid premedication, barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non-selective CNS depressants may enhance or prolong the respiratory depressant effects of alfentanil.

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. Likewise, following the administration of alfentanil, the dose of other CNS-depressant drugs should be reduced.

4.6 Pregnancy and lactation
Animal studies are insufficient with respect to effects on pregnancy. Although no teratogenic or acute embryotoxic effects have been observed in animal experiments, the potential risk for humans is unknown.

Alfentanil should not be used in pregnancy unless clearly necessary. I.V. administration during childbirth (including Caesarean section) is not recommended, because alfentanil crosses the placenta and because the foetal respiratory centre is particularly sensitive to opiates. If, however, alfentanil is administered, an antidote should always be at hand for the child.

Alfentanil may appear in breast milk. It is therefore recommended that breast feeding is not initiated within 24 hours of treatment.
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 the 24 hours following administration.

4.8 Undesirable effects
The most frequently reported ADRs (incidence ≥ 10%) are: nausea and vomiting. Undesirable effects listed below in Table 1 have been reported in a clinical trial 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 (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000), and not known (frequency cannot be estimated from the available data). Adverse drug 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>
<thead>
<tr>
<th>Table 1</th>
<th>Adverse drug reactions reported in clinical trials and/or postmarketing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body System/Organ Class</strong></td>
<td><strong>Frequency Category</strong></td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Adverse drug 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>
<thead>
<tr>
<th></th>
<th>Dizziness</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Loss of consciousness (Postoperative period), Convulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not known</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Eye disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Blurred/double vision</td>
</tr>
</tbody>
</table>

| **Not known**            | Miosis                                                     |

<table>
<thead>
<tr>
<th><strong>Cardiac disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Bradycardia, Tachycardia</td>
</tr>
</tbody>
</table>

| **Uncommon**             | Arrhythmia                                                 |

| **Not known**            | Cardiac arrest                                             |

<table>
<thead>
<tr>
<th><strong>Vascular Disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Hypotension, Hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Respiratory, thoracic, and mediastinal disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Apnoea, Respiratory depression</td>
</tr>
</tbody>
</table>

| **Uncommon**                                          | Cough, Recurrence of respiratory depression, Laryngospasm, Hiccup |

<p>| <strong>Not known</strong>                                         | Respiratory arrest (including fatal)                     |</p>
<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very common</strong></td>
<td>Nausea, Vomiting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Pruritis, Sweating</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Injection site pain, Shivering</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Pyrexia</td>
</tr>
</tbody>
</table>

a: Listed are only those adverse drug reactions that were not identified in clinical trials

### 4.9 Overdose
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:** O₂ 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 narcotic antagonist (eg naloxone) should be available to treat respiratory depression.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
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 narcotic 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
After bolus injections ranging from 2.4 to 125 µg/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' α₁-acid-glycoprotein. It is not bound to the blood cells. Pharmacokinetics were comparable in rats, dogs and man. In children, alfentanil has been shown to have a much shorter half-life than adults, whereas the elderly show a longer half-life for alfentanil, after IV bolus doses.

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 injections
Hydrochloric acid*
Sodium hydroxide*
* for occasional pH adjustment only

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

6.3 Shelf life
24 months (unopened).
24 hours (dilutions).

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Type I Ph Eur clear glass ampoules containing 1 ml.
10 ampoules per carton.

6.6 Special precautions for disposal
If desired, Alfentanil Solution for Injection 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.

7 MARKETING AUTHORISATION HOLDER
Auden McKenzie (Pharma Division) Ltd
Mckenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL

8 MARKETING AUTHORISATION NUMBER(S)
PL 17507/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/03/2010
NAME OF THE MEDICINAL PRODUCT
Alfentanil 500 micrograms/ml, Solution for Injection.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Alfentanil solution for injection contains 500 micrograms alfentanil (as hydrochloride).

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Solution for injection.

A clear colourless solution.

CLINICAL PARTICULARS

4.1 Therapeutic indications
As an analgesic supplement for use before and during anaesthesia.

It is indicated for:

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

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

4.2 Posology and method of administration
For intravenous administration.

Alfentanil by the intravenous route can be administered to both adults and children. The dosage of alfentanil should be individualised according to age, body weight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia. The usual recommended dosage regimen is as follows:

<table>
<thead>
<tr>
<th>Adults</th>
<th>Initial</th>
<th>Supplemental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous respiration</td>
<td>500 µg (1 ml)</td>
<td>250 µg (0.5 ml)</td>
</tr>
<tr>
<td>Assisted ventilation</td>
<td>30-50 µg/kg</td>
<td>15 µg/kg</td>
</tr>
<tr>
<td>Children</td>
<td>Initial</td>
<td>Supplemental</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>--------------</td>
</tr>
<tr>
<td>Assisted ventilation</td>
<td>30-50 µg/kg</td>
<td>15 µg/kg</td>
</tr>
</tbody>
</table>

*Dosage adjustments:* Children may require higher or more frequent dosing owing to a shorter half-life of alfentanil in this age group. The elderly and debilitated may require lower or less frequent dosing owing to a longer half-life of alfentanil in this age group (dilution may be helpful). See also Section 4.4 Special Warnings and Precautions.

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 Solution for Injection 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. For procedures of longer duration, additional increments will be required.

In ventilated patients, the last dose of alfentanil 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 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, in geriatric patients or 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 Solution for Injection (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 µg/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.

If desired, Alfentanil Solution for Injection 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.
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:*

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 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.

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.

Asystole 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 CO₂, 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 0.5 mg dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Alfentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. Available human pharmacokinetic data indicate that the metabolism of alfentanil may be inhibited by fluconazole, erythromycin, diltiazem and cimetidine (known cytochrome P450 3A4 enzyme inhibitors). In vitro data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may also inhibit the metabolism of alfentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such 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 asystole can occur when alfentanil is combined with non-vagolytic muscle relaxants.

The use of opioid premedication, barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non-selective CNS depressants may enhance or prolong the respiratory depressant effects of alfentanil.

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. Likewise, following the administration of alfentanil, the dose of other CNS-depressant drugs should be reduced.
4.6 Pregnancy and lactation
Animal studies are insufficient with respect to effects on pregnancy. Although no teratogenic or acute embryotoxic effects have been observed in animal experiments, the potential risk for humans is unknown.

Alfentanil should not be used in pregnancy unless clearly necessary. I.V. administration during childbirth (including Caesarean section) is not recommended, because alfentanil crosses the placenta and because the foetal respiratory centre is particularly sensitive to opiates. If, however, alfentanil is administered, an antidote should always be at hand for the child.

Alfentanil may appear in breast milk. It is therefore recommended that breast feeding is not initiated within 24 hours of treatment.

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 the 24 hours following administration.

4.8 Undesirable effects
The most frequently reported ADRs (incidence ≥ 10%) are: nausea and vomiting. Undesirable effects listed below in Table 1 have been reported in a clinical trial 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 (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000), and not known (frequency cannot be estimated from the available data). Adverse drug 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'.

<p>| Table 1 Adverse drug reactions reported in clinical trials and/or postmarketing |
|-------------------------------------------------|-----------------|------------------|
| <strong>Body System/Organ Class</strong>                     | Clinical trials | Spontaneous Reports^a |
| <strong>Frequency Category</strong>                          |                 |                  |
| <strong>Immune system disorders</strong>                     |                 |                  |
| <strong>Uncommon</strong>                                    | Allergic reactions (such as anaphylaxis, bronchospasm, urticaria) |                  |
| <strong>Psychiatric Disorders</strong>                       |                 |                  |</p>
<table>
<thead>
<tr>
<th>Common</th>
<th>Somnolence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Disorientation, Agitation, Euphoria</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Muscle rigidity (may also involve thoracic muscles) Myoclonic movements, Dizziness</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Headache</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Loss of consciousness (Postoperative period), Convulsion</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Blurred/double vision</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Miosis</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Bradycardia, Tachycardia</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Arrhythmia</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Hypotension, Hypertension</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal</strong></td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Common</td>
<td>Apnoea, Respiratory depression</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cough, Recurrence of respiratory depression, Laryngospasm, Hiccup</td>
</tr>
<tr>
<td>Not known</td>
<td>Respiratory arrest (including fatal outcome)</td>
</tr>
</tbody>
</table>

**Gastrointestinal disorders**

<table>
<thead>
<tr>
<th>Very common</th>
<th>Nausea, Vomiting</th>
</tr>
</thead>
</table>

**Skin and subcutaneous tissue disorders**

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Pruritis, Sweating</th>
</tr>
</thead>
</table>

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th>Uncommon</th>
<th>Injection site pain, Shivering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Pyrexia</td>
</tr>
</tbody>
</table>

a: Listed are only those adverse drug reactions that were not identified in clinical trials

### 4.9 Overdose

The manifestations of alfentanil overdose are generally an extension of its pharmacological action, which include the following:

<table>
<thead>
<tr>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>Hypoventilation or</td>
</tr>
</tbody>
</table>
apnoea 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

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 man, alfentanil at therapeutic doses had no detrimental effects of 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 narcotic 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

After bolus injections ranging from 2.4 to 125 µg/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' $\alpha_1$ acid-glycoprotein. It is not bound to the blood cells. Pharmacokinetics were comparable in rats, dogs and man. In children, alfentanil has been shown to have a much shorter half-life than adults, whereas the elderly show a longer half-life for alfentanil.

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 injections
Sodium hydroxide*
Hydrochloric acid*
* for occasional pH adjustment only

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

6.3 Shelf life
24 months (unopened).
24 hours (dilutions).

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Type I Ph Eur clear glass ampoules containing 2 ml or 10 ml.
5 or 10 ampoules per carton.

6.6 Special precautions for disposal
If desired, Alfentanil Solution for Injection 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.
MARKETING AUTHORISATION HOLDER
Auden Mckenzie (Pharma Division) Ltd
Mckenzie House
Bury Street
Ruislip
Middlesex
HA4 7TL

MARKETING AUTHORISATION NUMBER(S)
PL 17507/0074

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/03/2010

DATE OF REVISION OF THE TEXT
23/03/2010
Please read all of this leaflet carefully before taking your medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What is ALFENTANIL and what is it used for?
2. Before you are given ALFENTANIL
3. How you will be given ALFENTANIL
4. Possible side effects
5. Storing ALFENTANIL
6. Further information

1. What is ALFENTANIL and what is it used for?

What is ALFENTANIL?
ALFENTANIL 5 mg/ml, Solution for Injection is a potent and short-acting painkiller. It belongs to a group of medicines known as opioid analgesics which relieve or prevent pain.

What is ALFENTANIL used for?
ALFENTANIL is used to control pain and breathing when using an artificial breathing machine in intensive care.

ALFENTANIL 5 mg/ml, Solution for Injection will be diluted and given as an infusion (a ‘drip’) into a vein.

2. Before you are given ALFENTANIL

Always inform your doctor if you are pregnant, think you might be pregnant or are trying to become pregnant.

Always tell your doctor about any medicines (other prescribed by a doctor or that you have bought) which you have taken recently or are taking now.

Do not use ALFENTANIL:
- if you are taking, or have recently been taking (within the last two weeks), any of the antidepressant medicines known as monoamine oxidase inhibitors (MAOIs), including moclobemide.
- if you think that you may have had an allergic or any other type of reaction to ALFENTANIL or a similar medicine in the past. An allergic reaction may be recognized as a rash, itching, swollen face or lips, or shortness of breath.
- if you are pregnant or think that you are pregnant.

If any of the above applies to you, tell the doctor.

Warnings
Medicines like ALFENTANIL 5 mg/ml, Solution for Injection may cause a drop in blood pressure and breathing rate. These effects are usually short-lived. It may also cause the heart to beat more slowly.

Particular care has to be taken following treatment with other medicines which have similar effects. Blood pressure and heart rate are therefore monitored during administration of ALFENTANIL and any unwanted effects of this nature can be reversed with other medicines. Rarely, the rhythm of the heart may be altered and this will be treated if it occurs.

The doctor who will be giving ALFENTANIL 5 mg/ml, Solution for Injection will be aware of the possibility of all these unwanted effects and will take steps to avoid them.
Special Precautions
Your doctor will take special precautions when giving you ALFENTANIL if any of the points listed below applies to you:

- The dose of ALFENTANIL 5 mg/ml, Solution for Injection is normally reduced in elderly patients, and those with some thyroid problems or liver disease.
- Your dose will be carefully monitored if you have a history of lung disease, alcoholism, kidney problems or if you have been on long term opioid therapy.
- ALFENTANIL can make the muscles stiff. Your doctor will take measures to avoid this happening.
- As with all strong opioid painkillers, good pain relief is accompanied by a lowering of the breathing rate. This may last into the recovery period or occur again during this time. This effect may be increased if you have recently used similar medicines for pain relief. Your breathing will therefore be carefully monitored until it returns to normal.

Taking other medicines
Always tell your doctor if you are taking any other medicines because taking some medicines together can be harmful. Remember that the doctor at the hospital may not have been informed if you have recently begun a course of treatment for another illness.

Some medicines may affect the length of time it takes for the effects of ALFENTANIL to wear off:
- cimetidine, a medicine for ulcers, stomach-ache and heartburn
- erythromycin, an antibiotic
- diltiazem, a medicine used for a certain type of heart disorder.

Some medicines will have some of the same effects as ALFENTANIL. When one or more of these medicines is used at the same time as ALFENTANIL, the effects of either may be increased.
- beta-blockers (used to treat high blood pressure and disorders of the heart rhythm)
- anaesthetic agents
- drugs which depress the central nervous system (such as tranquillizers and sleeping pills)
- benzodiazepines e.g. clonazepam, clonazepam (used to treat epilepsy)
- barbiturates e.g. phenobarbitone
- other strong opioid painkillers.

It may also be necessary to adjust the dose of ALFENTANIL 5 mg/ml, Solution for Injection if you are taking the following:
- certain medicines for fungal infections, e.g. fluconazole, ketoconazole and itraconazole;
- certain medicines called antiviral protease inhibitors, e.g. ritonavir.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking this medicine.

Pregnancy and breast feeding
If you are pregnant, or think you may be, you should inform your doctor. He/she will decide whether or not you should be given ALFENTANIL.

ALFENTANIL may get into breast milk. It is therefore recommended that you should not breast feed for 24 hours after treatment.

Driving and using machines
You should not drive or operate machinery for 24 hours after being given ALFENTANIL as you may be less alert than usual.

3. How you will be given ALFENTANIL

Your doctor will decide how much ALFENTANIL 5 mg/ml, Solution for Injection you need. This will depend, for example, on the type of surgery, your body weight, age and general health.

ALFENTANIL 5 mg/ml, Solution for Injection should be mixed with sodium chloride injection, dextrose injection or compound sodium lactate injection (Hartmann’s solution). These dilutions should be used within 24 hours of preparation.

The usual recommended dosage is as follows:

Adults:
Your initial dose will be 2 mg per hour. Sometimes a higher initial dose (for example 5 mg) is given over a period of 10 minutes to achieve more rapid control.

Adolescents and young adults will be given higher than the average adult dose.

Elderly:
The above amounts of ALFENTANIL 5 mg/ml, Solution for Injection will be reduced.

Patients with liver problems and hypothyroidism (underactive thyroid) will also need their dose of ALFENTANIL to be reduced from the normal adult dosage.
Children:
ALFENTANIL 5 mg/ml, Solution for Injection is not usually used to treat children in intensive care.

The usual maximum treatment time with ALFENTANIL infusions is 4 days.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, using Alfentanil can cause side-effects, although not everybody gets them.

To give you an idea of how many patients might get side effects, they have been listed as very common, common, uncommon, rare and very rare. These mean the following:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>More than 1 in 10 people.</td>
</tr>
<tr>
<td>Common</td>
<td>up to 1 in 10 people.</td>
</tr>
<tr>
<td>Uncommon</td>
<td>up to 1 in 100 people.</td>
</tr>
<tr>
<td>Rare</td>
<td>up to 1 in 1,000 people.</td>
</tr>
<tr>
<td>Very rare</td>
<td>fewer than 1 in 10,000 people.</td>
</tr>
</tbody>
</table>

These are the side effects we know about for ALFENTANIL 5 mg/ml, Solution for Injection:

- Very common: Feeling or being sick.
- Common: Low blood pressure (hypotension); high blood pressure (hypertension); muscle stiffness, twitching, dizziness, slow or fast heart beat, feeling sleepy, stopping breathing temporarily, lowered breathing rate.
- Uncommon: Pain at the site of the injection, shivering, allergic reaction (such as difficulty in breathing, skin rash or itching, or swollen face), headache, irregular heart beat, feeling disorientated, agitation, feeling 'high' (euphoria), cough, continued lowered breathing rate, tightness of the throat, hiccups, itching of the skin, sweating, blurred or 'double' vision.

If you think your medicine has affected you in any other way, you should tell the doctor.
See also Section 2, Before you are given ALFENTANIL 5 mg/ml, Solution for Injection, above.

5. Storing ALFENTANIL

Keep out of the reach and sight of children.

You must not be given ALFENTANIL 5 mg/ml, Solution for Injection after the expiry date (month and year) printed after 'EXP' on the carton. The expiry date refers to the last day of that month.

Dilutions made with ALFENTANIL 5 mg/ml, Solution for Injection must be used within 24 hours of preparation.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further Information

What ALFENTANIL contains:
The name of your medicine is ALFENTANIL 5 mg/ml, Solution for Injection and its active ingredient is ALFENTANIL. Each millilitre contains 5 milligrams of ALFENTANIL (as the hydrochloride).

The solution for injection also contains sodium chloride, water for injections, sodium hydroxide and hydrochloric acid.

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

What ALFENTANIL looks like and contents of the pack:
It is a solution for injection which comes in 1 millilitre (ml) clear glass ampoules. It is a clear colourless solution.

ALFENTANIL 5 mg/ml, Solution for Injection is supplied in packs of 10 x 1 ml ampoules.

Marketing authorisation holder:
Auden McKenzie (Pharma Division) Ltd.
McKenzie House
Bury Street
Budip
Middlesex
HA4 7YL
UK
Manufacturer:
SNS Pharmaceuticals Ltd
30 Stadium Business Centre
North End Road
Middlesex
HA9 0HT
UK

This leaflet was last approved in February 2010.

For information in large print, on tape, on CD or in Braille, phone 01895 627 420.

ALFENTANIL Intensive Care 5mg/ml Solution for Injection
PL 17507/0037

Auden Mckenzie
Please read all of this leaflet carefully before taking your medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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What is ALFENTANIL used for?
ALFENTANIL is used as a painkiller exclusively for surgical procedures having a therapeutic or exploratory purpose:
- Therapeutic purpose – Operations to try and rectify known problems.
- Exploratory purpose – Operations to determine the cause of unexplained symptoms.

ALFENTANIL 500 micrograms/ml, Solution for Injection may be given as part of a general anaesthetic or for day-case surgery. It is particularly useful if you are going home the same day as your operation as the effects wear off quickly. It may also be used for longer operations in patients whose breathing is assisted. You will be given ALFENTANIL 500 micrograms/ml, Solution for Injection along with an anaesthetic while your operation is carried out. It will be given by an injection into a vein.

2. Before you are given ALFENTANIL

Always inform your doctor if you are pregnant, think you might be pregnant or are trying to become pregnant.

Always tell your doctor about any medicines (either prescribed by a doctor or that you have bought) which you have taken recently or are taking now.

Do not use ALFENTANIL:
- if you suffer from any illness which causes breathing difficulties. You should make sure that you discuss this with your doctor. It may be possible to use ALFENTANIL if your breathing is to be assisted during and/or after surgery.
- if you are taking, or have recently been taking (within the last two weeks), any of the antidepressant medicines known as monoamine oxidase inhibitors (MAOIs), including moclobemide.
- if you think that you may have had an allergic or any other type of reaction to ALFENTANIL or a similar medicine in the past. An allergic reaction may be recognized as a rash, itching, swollen face or lips, or shortness of breath.
- during labour; or before the cord is clamped during Caesarean section, as ALFENTANIL may affect the baby’s breathing.

If any of the above applies to you, tell the doctor.

Warnings
Medicines like ALFENTANIL 500 micrograms/ml, Solution for Injection may cause a drop in blood pressure and breathing rate. These effects are usually short-lived. It may also cause the heart to beat more slowly.

Particular care has to be taken following treatment with other medicines which have similar effects. Blood pressure and heart rate are therefore monitored during administration of ALFENTANIL and any unwanted effects of this nature can be reversed with other medicines. Rarely, the rhythm of the heart may be altered and this will be treated if it occurs.
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- Your dose will be carefully monitored if you have a history of lung disease, alcoholism, kidney problems or if you have been on long term opioid therapy.
- ALFENTANIL can make the muscles stiff. Your doctor will take measures to avoid this happening.
- As with all strong opioid painkillers, good pain relief is accompanied by a lowering of the breathing rate. This may last into the recovery period or occur again during this time. This effect may be increased if you have recently used similar medicines for pain relief. Your breathing will therefore be carefully monitored until it returns to normal.

Taking other medicines
Always tell your doctor if you are taking any other medicines because taking some medicines together can be harmful. Remember that the doctor at the hospital may not have been informed if you have recently begun a course of treatment for another illness.

Some medicines may affect the length of time it takes for the effects of ALFENTANIL to wear off:
- cimetidine, a medicine for ulcers, stomach-ache and heartburn
- erythromycin, an antibiotic
- dilazem, a medicine used for a certain type of heart disorder.

Some medicines will have some of the same effects as ALFENTANIL. When one or more of these medicines is used at the same time as ALFENTANIL, the effects of either may be increased.
- beta-blockers (used to treat high blood pressure and disorders of heart rhythm)
- anaesthetic agents
- drugs which depress the central nervous system (such as tranquillisers and sleeping pills)
- benzodiazepines e.g. clonazepam, clonazepam (used to treat epilepsy)
- barbiturates e.g. phenobarbital
- other strong opioid painkillers.

It may also be necessary to adjust the dose of ALFENTANIL 500 micrograms/ml, Solution for Injection if you are taking the following:
- certain medicines for fungal infections, e.g. fluconazole, ketoconazole and itraconazole;
- certain medicines called antiviral protease inhibitors, e.g. ritonavir.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking this medicine.

Pregnancy and breast feeding
If you are pregnant, or think you may be, you should inform your doctor. He/she will decide whether or not you should be given ALFENTANIL.

ALFENTANIL may get into breast milk. It is therefore recommended that you should not breast feed for 24 hours after treatment.

Driving and using machines
You should not drive or operate machinery for 24 hours after being given ALFENTANIL as you may be less alert than usual.

3. How you will be given ALFENTANIL

Your doctor will decide how much ALFENTANIL 500 micrograms/ml, Solution for Injection you need. This will depend, for example, on the type of surgery, your body weight, age and general health.

The usual recommended dosage is as follows:

Adults:
**If you are to breathe by yourself** your initial dose will be 500 micrograms (1 ml), followed by further injections of 250 micrograms (0.5 ml), if necessary. Your initial dose will be given slowly, over about 30 seconds.

**If you are on a ventilator** your initial dose will be 30-50 micrograms per kilogram bodyweight, followed by further injections of 15 micrograms per kilogram, if necessary.

ALFENTANIL 500 micrograms/ml, Solution for Injection may be mixed with sodium chloride injection, dextrose injection or compound sodium lactate injection (Hartmann’s solution). These dilutions should be used within 24 hours of preparation.
ALFENTANIL 500 micrograms/ml, Solution for Injection may also be given as an infusion (a drip). A typical infusion would consist of an initial dose of 50-100 micrograms per kilogram, followed by 0.5 1 microgram/kilogram/minute, continued until approximately 30 minutes before the end of your operation. The rate of infusion will depend on your response and on the type of operation.

*In elderly patients and patients who are weak due to ill health*, the above amounts of ALFENTANIL 500 micrograms/ml, Solution for Injection will be reduced.

**Children:**
The amount given to children will always depend on how much they weigh. Children may require higher or more frequent dosing than adults.

*In children on a ventilator,* the initial dose will be 30-50 micrograms per kilogram bodyweight, followed by further injections of 15 micrograms per kilogram, if necessary.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **Possible side effects**

Like all medicines, using Alfentanil can cause side-effects, although not everybody gets them.

To give you an idea of how many patients might get side effects, they have been listed as very common, common, uncommon, rare and very rare. These mean the following:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>More than 1 in 10 people.</td>
</tr>
<tr>
<td>Common</td>
<td>up to 1 in 10 people.</td>
</tr>
<tr>
<td>Uncommon</td>
<td>up to 1 in 100 people.</td>
</tr>
<tr>
<td>Rare</td>
<td>up to 1 in 1,000 people.</td>
</tr>
<tr>
<td>Very rare</td>
<td>fewer than 1 in 10,000 people.</td>
</tr>
</tbody>
</table>

These are the side effects we know about for ALFENTANIL 500 micrograms/ml Solution for Injection:

- **Very common**: Feeling or being sick.
- **Common**: Low blood pressure (hypotension); high blood pressure (hypertension), muscle stiffness, twitching, dizziness, slow or fast heart beat, feeling sleepy, stopping breathing temporarily, lowered breathing rate.
- **Uncommon**: Pain at the site of the injection, shivering, allergic reaction (such as difficulty in breathing, skin rash or itching, or swelling face), headache, irregular heart beat, feeling disoriented, agitation, feeling 'high' (euphoria), cough, continued lowered breathing rate, tightness of the throat, hiccups, itching of the skin, sweating, blurred or 'double' vision.

If you think your medicine has affected you in any other way, you should tell the doctor.

See also Section 2, Before you are given ALFENTANIL 500 micrograms/ml, Solution for Injection, above.

5. **Storing ALFENTANIL**

Keep out of the reach and sight of children.

You must not be given ALFENTANIL 500 micrograms/ml, Solution for Injection after the expiry date (month and year) printed after "EXP" on the carton. The expiry date refers to the last day of that month.

Dilutions made with ALFENTANIL 500 micrograms/ml, Solution for Injection must be used within 24 hours of preparation.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **Further Information**

**What ALFENTANIL contains:**
The name of your medicine is ALFENTANIL 500 micrograms/ml, Solution for Injection and its active ingredient is ALFENTANIL. Each millilitre contains 500 micrograms of ALFENTANIL (as the hydrochloride).

The solution for injection also contains sodium chloride, water for injections, sodium hydroxide and hydrochloric acid.

This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 mg dose, i.e. essentially 'sodium-free'.

**What ALFENTANIL looks like and contents of the pack:**

It is a solution for injection which comes in 2 millilitre (ml) and 10 ml clear glass ampoules. It is a clear colourless solution.

ALFENTANIL 500 micrograms/ml, Solution for Injection is supplied in packs of 5 x 2 ml ampoules, 5 x 10 ml ampoules, 10 x 2 ml ampoules and 10 x 10 ml ampoules. Not all pack sizes may be marketed.
Marketing authorisation holder:
Auden Mckenzie (Pharma Division) Ltd.
Mckenzie House
Bury Street
Rainlip
Middlesex
HA1 7TL
UK

Manufacturer:
SNS Pharmaceuticals Ltd
30 Stadium Business Centre
North End Road
Middlesex
HA9 0HT
UK

This leaflet was last approved in February 2010.

For information in large print, on tape, on CD or in Braille, phone 01895 627 420
Labeling

Label:
Carton:
Label:

Alfentanil
500 micrograms/ml,
Solution for Injection

1mg in 2ml

IV POM CD

BN: xxxx EXP: xx/yyyy

PL No: 17507/0074
Auden Mckenzie
(Pharma Division) Ltd