ALFENTANIL 500 MICROGRAMS/ML SOLUTION FOR INJECTION AND
ALFENTANIL 5MG/ML SOLUTION FOR INJECTION

PL 25215/0005-6

UKPAR

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ALFENTANIL 500 MICROGRAMS/ML SOLUTION FOR INJECTION AND ALFENTANIL 5MG/ML SOLUTION FOR INJECTION

PL 25215/0005-6

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Hameln Pharma R&D Gmbh Marketing Authorisations (licences) for the medicinal products Alfentanil 500 micrograms/ml Solution for Injection and Alfentanil 5mg/ml Solution for Injection (PL 25215/0005-6) on 5 May 2006 (following a change of ownership on 24 July 2006, these licences now belongs to Hameln Pharma Plus Gmbh). These products have been granted prescription only status.

Alfentanil is a synthetic opiate used primarily in pain elimination (analgesia). Alfentanil is also widely used as an anaesthetic or alongside anaesthesia.

Analgesic drugs similar to Alfentanil have been available in the European Union, including the UK, for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

Alfentanil 500 micrograms/ml Solution for Injection and Alfentanil 5mg/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.
ALFENTANIL 500 MICROGRAMS/ML SOLUTION FOR INJECTION AND
ALFENTANIL 5MG/ML SOLUTION FOR INJECTION

PL 25215/0005-6

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisation for the medicinal products Alfentanil 500 micrograms/ml Solution for Injection and Alfentanil 5mg/ml Solution for Injection (PL 25215/0005-6) to Hameln Pharma R&D Gmbh on 5 May 2006 and following a change of ownership on 24 July 2006, these licences now belongs to Hameln Pharma Plus Gmbh. These solutions for injection are prescription only medicines.

These are national applications for Alfentanil 500 micrograms/ml Solution for Injection and Alfentanil 5mg/ml Solution for Injection, submitted under EC Article 10.1. The applicant states that a subsequent Mutual Recognition Procedures are considered.

Alfentanil contains the active ingredient Alfentanil hydrochloride and is indicated as an analgesic supplement for use before and during anaesthesia. It is recommended for short procedures and outpatient surgery and procedures of medium and long duration when given as a bolus followed by supplemental doses or by continuous infusion. At very high doses, Alfentanil 500 micrograms/ml solution for injection may be used as an anaesthetic induction agent in ventilated patients.
1. INTRODUCTION

These national complex and standard abridged applications are for Alfentanil 500 micrograms/ml Injection and 5mg/ml Injection, sterile aqueous solutions for injection, presented as 1ml ampoules (5mg/ml) and 2ml and 10ml ampoules and vials (0.5mg/ml).

Alfentanil is a synthetic opiate agonist used primarily in analgesia. It is a member of the phenylpiperidine class of opiate agonists and is a derivative of fentanyl. Alfentanil has different pharmacokinetics and pharmacodynamics than fentanyl. Alfentanil is 5-8 times less potent than fentanyl and has a shorter onset and duration of action than fentanyl. In addition, alfentanil is less lipophilic than fentanyl but still more lipophylic than morphine. Alfentanil is widely used as an anaesthetic or adjuvant to anaesthesia.

Alfentanil Solution for Injection may be diluted with:
- Glucose 5%,
- Sodium chloride 0.9%,
- Glucose 5% - sodium chloride 0.9%
- Ringer lactate

These applications have been made under Article 10.1 (formerly 10.1 (a)(iii)) claiming essential similarity to Rapifen 0.5mg/ml Solution for Injection (PL 00242/0091) and Rapifen 5mg/ml Solution for Injection (PL 00242/0137) which were first authorised in the EU (UK) in 1983 and 1989, respectively, and are currently marketed in the UK by Janssen-Cilag Limited.

The active ingredient is manufactured by a suitable supplier and a letter of access dated 3rd January 2003 has been provided.

The proposed product has not been authorised to the applicant or to a related company in any other European Union (EU) member state, nor is it the subject of any pending application in any other EU member state.

Subsequent MRPs are being considered for both products.

The active ingredient is the subject of a Ph Eur monograph. No BP monograph currently exists for the finished product.

MODULE 1

1.2/1.3 Application form(s), Summary of Product Characteristics, Labelling & Package Leaflet

The MAA forms and SPC are acceptable.
1.4 Information about the Experts

1.4.1 Information about the Expert - Quality

A signed Expert Statement has been provided stating that the expert has performed the duties set out in Article 2 of the Council Directive 75/319/EEC in accordance with Part IC of the Annex to Council Directive 75/318/EEC.

1.5 Specific requirements for different types of applications

Bioavailability and Bioequivalence

The product is intended for parenteral use. Consequently, clinical studies to establish bioavailability and/or bioequivalence have not been conducted. This is reasonable.

MODULE 2

2.3 Quality Overall Summary

The quality overall summary is an accurate reflection of the data provided.

MODULE 3

3.2.S DRUG SUBSTANCE

3.2.S.1 General information

The drug substance will be reviewed for compliance with current guidelines and the Ph Eur monograph.

3.2.S.1.1 Nomenclature

Alfentanil hydrochloride

N-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)-ethyl]-4-(methoxymethyl) piperidin-4-yl]-N-phenylpropanamide monohydrochloride

3.2.S.1.2 Molecular formula

(C21H32N6O3 HCl) MW 453 CAS 70879-28-6
Polymorphs:

The applicant has provided data on the investigation of polymorphism in the drug substance and XRD diffraction data of four samples of alfentanil support the conclusion that the drug substance manufacturer is synthesising material of the same crystalline phase.

3.2.S.1.3 General properties

Alfentanil hydrochloride is a white to off-white powder, freely soluble in water, ethanol and methanol.

Melting point 140°C (with decomposition)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer

Manufacturer of the drug substance:

A letter of access from the manufacturer of the drug substance dated 3rd January 2003 has been provided.

3.2.S.2.2 Description of manufacturing process and process controls

A flow diagram and full description of the synthetic process and process controls has been provided. This information is satisfactory.

3.2.S.2.3 Control of materials

Control of materials is satisfactory.

3.2.S.3 Characterisation

3.2.S.3.1 Elucidation of structure and other characteristics

Structure and other characteristics have been elucidated satisfactorily.

3.2.S.3.2 Impurities

Impurities are appropriately controlled.
3.2.S.4  Control of drug substance

3.2.S.4.1  Specification

The active ingredient is the subject of a Ph Eur monograph.

A satisfactory specification has been provided.

3.2.S.4.2  Analytical procedures /
3.2.S.4.3  Validation of analytical procedures

The applicant has provided the same method and validation data as that submitted by the AIM in their DMF. The finished product manufacturer Hameln has provided appropriate validation data.

3.2.S.4.4  Batch analyses

Batch analysis data have been provided by the AIM in the DMF.

3.2.S.5  Reference standards or materials

The reference standard is stated as batch number B0594, the CoA confirms the purity level.

3.2.S.6  Container Closure System

Alfentanil hydrochloride is provided by the AIM in suitable packaging.

3.2.S.7  Stability

Appropriate stability data have been generated.

3.2.P  DRUG PRODUCT

3.2.P.1  Composition

The formulations are simple buffered aqueous solutions in WFI made isotonic with sodium chloride. The pH has been adjusted to pH 4.5 with 0.1N hydrochloric acid (0.5mg/ml) or 0.1N sodium hydroxide (5mg/ml).
Table 1: Qualitative composition of Alfentanil 0.5mg/ml Solution for Injection (ampoules and vials)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
<th>Reference to Standards*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil hydrochloride (corresponding to Alfentanil)</td>
<td>Active substance</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>Isotonicity agent</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Hydrochloric acid 0.1N</td>
<td>pH adjuster</td>
<td>Ph Helv</td>
</tr>
<tr>
<td>Water for injections</td>
<td>diluent</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Nitrogen</td>
<td></td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Total weight</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Qualitative composition of Alfentanil 5mg/ml Solution for Injection (ampoules)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
<th>Reference to Standards*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil hydrochloride (corresponding to Alfentanil)</td>
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</tr>
<tr>
<td>Sodium chloride</td>
<td>Isotonicity agent</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Sodium hydroxide 0.1N</td>
<td>pH adjuster</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Water for injections</td>
<td>diluent</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Nitrogen</td>
<td></td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Total weight</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No overage is included in the formulation.

**TSE**

Signed declarations have been provided by the suppliers of the excipients confirming that no material of animal origin is used in the manufacture or processing of these ingredients.
3.2.P.2 Pharmaceutical Development

The stated objective was to find a suitable formulation. The originator product Rapifen was analysed and the composition of the proposed formulation derived from analysis of the results.

Compatibility data were provided for Alfentanil 0.5mg/ml solution for injection. With standard solutions for infusion, tests were performed with recommended dilutions and it was concluded that the proposed products are compatible with Glucose 5%, sodium chloride 0.9%, Glucose 5% - sodium chloride 0.9%, and Ringer lactate.

The product is sterilised using a suitable method.

The vials and ampoules are intended for single use only. They should be used immediately after opening and any unused solution should be discarded.

The brand leader product contains antioxidant. The proposed formulation does not contain antioxidant, therefore, precautions are taken to minimise exposure to oxygen during the manufacturing process.

No justification for the choice of rubber stoppers has been provided although the applicant states that compatibility has been demonstrated in stability studies.

The applicant has stated that the results of the stability testing indicate that there is no loss of active due to sorption to the container or closure system and also no leaching of components to the solution. The applicant has stated that vials were stored upside down on stability (this affects the 0.5mg/mL finished product only, 5ml/mL only available in ampoules).

It is stated in the SPC that the products may be diluted with 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and sodium chloride (0.9%) injection or lactate Ringers injection and that such dilutions are compatible with plastic bags and giving sets. Data have been provided demonstrating that such dilutions are chemically and physically stable up to 48 hours.

Overall the extent of the development was adequate considering the nature of the product.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The drug product is manufactured at an appropriate site.
3.2.P.3.2 Batch formula

0.5mg/ml product:
Satisfactory batch formulae have been provided for batches of 600 litres (=50,000 ampoules @ 10ml) and for 200 litres (=90,000 ampoules @ 2ml) and for 100 litres (=40,000 vials @ 2ml) and 300 litres (=25,000 vials @ 10ml).

5mg/ml product, 1ml ampoules:
Satisfactory batch formula has been provided for 200 litres.

3.2.P.3.3/4 Description of manufacturing process and process controls

Satisfactory flow diagrams of the manufacturing process have been provided, together with details of in process controls.

3.2.P.3.5 Process validation and/ or evaluation

Three full scale validation batches were produced for each filling volume in order to qualify the process, filtration and testing stages for the 0.5mg/ml and 5mg/ml products.

Process validation data have been provided for appearance, pH, osmolality, density, assay, assay of chloride and bioburden demonstrating compliance with in process controls. The applicant has provided details of the validation of the autoclaves used for the vials and for the depyrogenation of containers and leak testing of containers. Full results of the validation and revalidation programme have been provided and demonstrate that satisfactory process validation has been performed.

3.2.P.4 Control of excipients

All excipients used are Ph Eur grade material, except for 0.1N hydrochloric acid which is Ph Helv.

3.2.P.5 Control of drug product

3.2.P.5.1 Specification(s)

There are no current BP monographs for the finished products.

Proposed release and shelf-life specifications for the finished products are satisfactory.

3.2.P.5.2 Analytical procedures /
3.2.P.5.3 Validation of analytical procedures

All test methods are Ph Eur except for identification by TLC, identification by HPLC, impurities by HPLC, assay by HPLC and assay of chlorides.

LOD / LOQ values for alfentanil hydrochloride are satisfactory.

Analytical methods have been validated by submission of a comprehensive validation package.

3.2.P.5.4 Batch analyses

Batch analysis data have been provided on the finished products demonstrating conformance to the proposed specifications.

3.2.P.6 Reference Standard

The purity of the reference materials used for determination of alfentanil hydrochloride and Ph Eur Impurity E has been confirmed.

3.2.P.7 Container closure system

Clear, neutral glass, Type I Ph Eur ampoules and vials.

The applicant has stated that the vial stoppers comply with the Ph. Eur. requirements for Rubber Closures for Containers for use with Aqueous Parenteral Preparations’ and has provided appropriate test specifications supported by certificates of analysis.

3.2.P.8 Stability

0.5mg/ml product:
Stability studies have been performed on three batches each packaged in 2ml ampoules and vials and 10ml ampoules and vials.

5mg/ml product:
Stability studies have been performed on three batches packaged in 1ml ampoules.

Batches were stored up to 36 months in real time conditions and up to 6 months in accelerated conditions.

Appearance, particulate matter, pH, extractable volume, assay and impurities were tested. Identity, osmolality, sterility and bacterial endotoxins were tested at the beginning and end of shelf-life.
Stability data provided show acceptable impurity levels and would support the proposed shelf-life of 3 years. See comments above under analytical validation.

**PHARMACEUTICAL RECOMMENDATION**

Marketing Authorisation may be granted.
PRECLINICAL ASSESSMENT

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

1. INTRODUCTION

These are complex and standard abridged applications for Marketing Authorisation submitted under Article 10.1 of Directive 2001/83/EC for Alfentanil 500 micrograms/ml Solution for Injection and Alfentanil 5mg/ml Solution for Injection (PL 25215/0005-6).

These applications cross-refer to Rapifen 0.5 mg/ml Solution for Injection (PL 00242/0091) and Rapifen 5mg/ml Solution for Injection (PL 0242/0137), that were first authorised in the EU (UK) in 1983 and 1989, respectively. The reference products are currently marketed in the UK by Janssen-Cilag Ltd.

2. BACKGROUND

Alfentanil is a synthetic opioid derived from fentanyl. It is a potent µ-receptor agonist opioid with a very rapid onset of action.

Alfentanil is a potent analgesic, which achieves its effects by an action at µ opioid receptors in the brain. It shows a 29-fold higher affinity than morphine, the respective \( K_a \) values being 0.84 mg.kg\(^{-1}\) for alfentanil and 24 mg.kg\(^{-1}\) for morphine. Alfentanil has no activity at \( \kappa \), \( \sigma \) or \( \delta \) opioid receptors. In animal studies (e.g. rat tail withdrawal test) alfentanil has a peak effect within 1 minute of intravenous injection, compared with 30 minutes for morphine.

When given by a single intravenous injection to human subjects, alfentanil has maximal effects in 2-3 minutes and a duration of action of about 10 minutes. Alfentanil produces dose-dependent analgesia in patients with pain. Its effects on pain perception make it a useful component of anaesthesia where doses of 5-10 \( \mu \)g.kg\(^{-1}\) are used in spontaneously ventilating patients, with much larger doses (up to 250 \( \mu \)g.kg\(^{-1}\)) being used in ventilated patients. Alfentanil may cause respiratory depression like any opioid; the curve of the respiratory response to carbon dioxide is shifted to the right and the slope may be decreased. Alfentanil usually produces a small reduction in the systemic vascular resistance, and a decrease in systolic and diastolic blood pressure of about 20% can be expected. There is usually a small fall in the heart rate.

The pharmacokinetics of alfentanil have been studied only after intravenous injection, as the drug is not used orally due to the extent of presystemic metabolism. Plasma protein binding is high, about 90%, although this decreases at concentrations above 0.1 mg.l\(^{-1}\). Alfentanil is bound primarily to \( \alpha_1 \) acid glycoprotein. As the p\( K_a \) of alfentanil is 6.5, about 90% of the drug is unionised at pH 7.4, which is unusual for an opioid (cf. fentanyl, 9%). This allows rapid transfer across the blood-brain barrier. As alfentanil also has a very small central volume of distribution compared with other similar opioids (about 20% that of fentanyl), plasma concentrations are relatively high after intravenous injection, which also leads to rapid transfer to the receptor compartment. All these effects combine to produce the very fast onset of effect of this drug, which is usually apparent within 1 minute, despite alfentanil being less lipophilic than most opioids.
The plasma concentration-time profile of alfentanil following intravenous injection is best fitted biexponentially, with a terminal plasma half-life of 80.4 minutes. Alfentanil half-lives are quite variable between individuals and this may be partly explained by the fact that the main route of elimination is by CYP 3A4, a cytochrome P450 which is known to vary greatly in activity between individuals. Little of the drug is excreted unchanged; it is mostly metabolised in the liver with a small degree of biliary conjugation and excretion. The terminal half-life is shorter in children, and longer in the elderly, although no particular hazard is associated with it so long as dosage is based on patient response. Renal insufficiency has little effect on elimination, but may increase the volume of distribution. Hepatic failure may be expected to impair elimination and prolong the therapeutic effect.

3. **INDICATIONS**

The Applicant has submitted the following indications:

**Alfentanil 500 micrograms/ml injection:**

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 500 micrograms/ml solution for injection may be used as an anaesthetic induction agent in ventilated patients.

**Alfentanil 5mg/ml injection:**

Alfentanil 5 mg/ml solution for injection 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 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.

4. **DOSE & DOSE SCHEDULE**

The Applicant has submitted the following dosing recommendations:

**Alfentanil 500 micrograms/ml solution for injection:**

Alfentanil 500 micrograms/ml injection by the intravenous route can be administered to both adults and children. The dosage of Alfentanil 500 micrograms/ml injection should be individualised according to age, bodyweight, physical status, underlying
pathological condition, use of other drugs and type of surgery and anaesthesia. The usual recommended dosage regimen is shown in Table 1 Dosage regimen:

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

If desired, Alfentanil 500 micrograms/ml injection can be mixed with sodium chloride injection BP, glucose injection BP or Ringer-Lactate BP (Hartmann's solution). Such dilutions are compatible with plastic bags and giving sets. These dilutions should be used within 24 hours of preparation.

Children may require higher or more frequent dosing owing to a shorter half-life of Alfentanil 500 micrograms/ml in this age group (dilution may be helpful).

In obese patients (more than 20 % above ideal total body weight), the dosage of alfentanil should be determined on the basis of lean body weight.

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

After intravenous administration in unpremedicated adult patients, 1 ml Alfentanil 500 micrograms/ml 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 500 micrograms/ml injection. For procedures of longer duration, additional increments will be required.

In ventilated patients, the last dose of Alfentanil 500 micrograms/ml should not be given later than about 10 minutes before the end of surgery to avoid the continuation of respiratory depression after surgery is complete.

In ventilated patients undergoing longer procedures, Alfentanil 500 micrograms/ml injection 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 micrograms/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 500 micrograms/ml 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.

Patients with **renal impairment**: No dosage adjustment is needed.

Patients with **hepatic impairment**: Dose should be modified depending on the clinical response and degree of hepatic impairment, however no quantitative recommendations are available.

**Administration Guidelines**

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

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

Continuous infusions longer than 4 days have not been studied.

**Alfentanil 5 mg/ml solution for injection**

At the proposed doses, Alfentanil 5 mg/ml solution for injection 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.

**Method of administration**

For intravenous infusions.

**Dosage**

Alfentanil 5 mg/ml solution for injection 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 Alfentanil 5 mg/ml solution for injection. 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.

5. TOXICOLOGY

No new toxicological data on alfentanil is presented and none is required for this application.

6. CLINICAL PHARMACOLOGY

6.1. PHARMACODYNAMICS / PHARMACOKINETICS

No new data on the pharmacodynamics or pharmacokinetics of alfentanil is presented and none is required for this application.

Sections 5.1 and 5.2 of the proposed SPC contain accurate information.

6.2. BIOEQUIVALENCE
No bioequivalence testing has been carried out. This is acceptable due to the aqueous nature of the solutions for intravenous administration and the presence of the active substance in identical concentrations in the reference products and the applicant’s corresponding solutions (see Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98)).

7. **EFFICACY**

No new data on the efficacy of alfentanil is presented and none is required for this application.

8. **SAFETY**

No new data on the safety of alfentanil is presented and none is required for this application.

9. **EXPERT REPORTS**

The Clinical Expert Report is sufficiently concise. All the relevant areas are adequately covered.

The expert’s curriculum vitae documents his appropriate qualification. The Preclinical Expert Report has been signed off by the clinical expert. The pharmaceutical expert is also suitably qualified according to his curriculum vitae.

10. **SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

These are satisfactory.

11. **PATIENT INFORMATION LEAFLET (PIL)**

The PIL is satisfactory.

12. **LABELLING**

All labelling is satisfactory.

13. **APPLICATION FORM (MAA)**

The MAA form is satisfactory.

14. **DISCUSSION**

These complex and standard abridged application for Alfentanil 500 micrograms/ml solution for injection and 5mg/ml solution for injection cross-reference to Rapifen 0.5 mg/ml and Rapifen 5mg/ml Solution for Injection, respectively, which were first authorised in the UK in 1983 and 1989. The clinical expert argues that the efficacy and safety of alfentanil as an analgesic supplement before and during anaesthesia have been sufficiently documented in the past.
The Clinical Expert Report provides a brief review of the pharmacodynamics and pharmacokinetics of alfentanil. The review of the efficacy and clinical safety of alfentanil for the claimed indications is considered deficient.

As these solutions and their respective reference products are aqueous in nature, and since they are all intended for parenteral administration, there is no requirement for bioequivalence testing. (cf. section 5.1.6 from CPMP/EWP/QWP/1401/98).

15. **MEDICAL CONCLUSION**

A Product Licence may be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Alfentanil 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 indication is for analgesia during short procedures and outpatient surgery or procedures of medium and long duration when given as a bolus followed by supplemental doses or by continuous infusion. At very high doses, Alfentanil 500 micrograms/ml solution for injection may also be used as an anaesthetic induction agent in ventilated patients.

The efficacy of Alfentanil was demonstrated in all clinical studies presented.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no significant preclinical or clinical safety concerns were identified. When used as indicated, Alfentanil has a favourable benefit-to-risk ratio. The hazard associated with Alfentanil appears to be low and acceptable when considered in relation to its therapeutic benefits.
ALFENTANIL 500 MICROGRAMS/ML SOLUTION FOR INJECTION AND ALFENTANIL 5MG/ML SOLUTION FOR INJECTION

PL 25215/0005-6

STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 20 January 2003</td>
</tr>
<tr>
<td>2</td>
<td>Following assessment of the application the MHRA requested further information relating to the clinical dossier on 22 August 2003</td>
</tr>
<tr>
<td>3</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 3 October 2003</td>
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<tr>
<td>4</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 6 May 2005</td>
</tr>
<tr>
<td>5</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 27 June 2005</td>
</tr>
<tr>
<td>6</td>
<td>The application was determined on 5 May 2006</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

Alfentanil 500 micrograms/ml solution for injection (PL 25215/0005) has the following product summary:

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alfentanil 500 micrograms/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

The product is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

As an analgesic supplement for use before and during anaesthesia.

It is indicated for:

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

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

4.2. Posology and method of administration

Alfentanil 500 micrograms/ml by the intravenous route can be administered to both adults and children. The dosage of Alfentanil 500 micrograms/ml should be individualised according to age, bodyweight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.
The usual recommended dosage regimen is shown in Table 1 Dosage regimen:

**Table 1 Dosage regimen**

<table>
<thead>
<tr>
<th>Adults</th>
<th>Initial</th>
<th>Supplemental</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Spontaneous respiration</em></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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children</th>
<th>Initial</th>
<th>Supplemental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assisted ventilation</td>
<td>30 – 50 µg/kg</td>
<td>15 µg/kg</td>
</tr>
</tbody>
</table>

If desired, Alfentanil 500 micrograms/ml can be mixed with sodium chloride injection BP, glucose injection BP or Ringer-Lactate injection BP (Hartmann’s solution). Such dilutions are compatible with plastic bags and giving sets. These dilutions should be used within 24 hours of preparation.

Children may require higher or more frequent dosing owing to a shorter half-life of Alfentanil 500 micrograms/ml in this age group (dilution may be helpful).

In obese patients (more than 20 % above ideal total body weight), the dosage of alfentanil should be determined on the basis of lean body weight.

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

After intravenous administration in unpremedicated adult patients, 1 ml Alfentanil 500 micrograms/ml may be expected to have a peak effect in 90 seconds and to provide analgesia for 5 – 10 minutes. Periods of more painful stimuli may be overcome by the use of small increments of Alfentanil 500 micrograms/ml. For procedures of longer duration, additional increments will be required.

In ventilated patients, the last dose of Alfentanil 500 micrograms/ml should not be given later than about 10 minutes before the end of surgery to avoid the continuation of respiratory depression after surgery is complete.

In ventilated patients undergoing longer procedures, Alfentanil 500 micrograms/ml may be infused at a rate of 0.5 – 1 µg/kg/minute. Adequate plasma concentrations of alfentanil will only be achieved rapidly if this infusion is preceded by a loading dose of 50 – 100 µg/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 500 micrograms/ml (1 – 2 ml) or low concentrations of a volatile agent for brief periods.

Patients with severe burns presenting for dressing, etc., have received a loading dose of 18 – 28 µ/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.

Patients with renal impairment: No dosage adjustment is needed.

Patients with hepatic impairment: Dose should be modified depending on the clinical response and degree of hepatic impairment, however no quantitative recommendations are available.

Administration Guidelines

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

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

Continuous infusions longer than 4 days have not been studied.

4.3. Contraindications

Alfentanil hydrochloride is contraindicated in patients with known hypersensitivity to the drug and other opioids.

Obstructive airway disease or respiratory depression if not ventilating.

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

Administration in labour or before clamping of the cord during Caesarian section due to the possibility of respiratory depression in the new-born infant.

4.4. Special warnings and precautions for use

Warnings
Alfentanil should be administered only by persons specifically trained in the use of intravenous and general anaesthetic agents and the management of respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

Alfentanil hydrochloride administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of alfentanil at anaesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. Alfentanil may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anaesthesia; 2) administration of up to 1/4 of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of alfentanil at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of alfentanil and a full paralyzing dose of a neuromuscular blocking agent when alfentanil is used in rapidly administered anaesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered alfentanil. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Patients receiving monitored anaesthesia care should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure; oxygen supplementation should be immediately available and provided where clinically indicated; oxygen saturation should be continuously monitored; the patient should be observed for early signs of hypertension, apnea, upper airway obstruction and/or oxygen desaturation.

Severe and unpredictable potentiation of monoamine oxidase (MAO) inhibitors has been reported for other opioid analgesics, and rarely with alfentanil. Therefore when alfentanil is administered to patients who have received MAO inhibitors within 14 days, appropriate monitoring and ready availability of vasodilators and beta-blockers for the treatment of hypertension is recommended.

**Precautions**

Delayed respiration depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. Therefore, vital signs must be monitored continuously.
**General**
The initial dose of alfentanil should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of alfentanil should be determined on the basis of lean body weight. In one clinical trial, the dose of alfentanil required to produce anaesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of alfentanil may be reduced and postoperative recovery may be prolonged.

Induction doses of alfentanil should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of alfentanil may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by alfentanil may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anaesthetic induction dose of alfentanil, requirements for volatile inhalation anaesthetics of alfentanil infusion are reduced by 30 to 50% for the first hour of maintenance. Alfentanil infusions should be discontinued at least 10-15 minutes prior to the end of surgery during general anaesthesia. During administration of alfentanil for monitored anaesthesia care, infusions may be continued to the end of the procedure. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by alfentanil may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further add to respiratory depression. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of alfentanil, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

**Head injuries**
Alfentanil may obscure the clinical course of patients with head injuries.

**Impaired respiration**
Alfentanil should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anaesthesia, this can be managed by assisted or controlled respiration.

**Impaired hepatic or renal function**

In patients with liver or kidney dysfunction, alfentanil should be administered with caution due to the importance of these organs in the metabolism and excretion of alfentanil.

**Pediatric use**

Adequate data to support the use of alfentanil in children under 12 years of age are not presently available.

### 4.5. Interactions with other medicinal products and other forms of interaction

Monoamine oxidase (MAO) inhibitors may potentiate the effects of narcotics. It is not recommended to take alfentanil who have received MAO inhibitors within 14 days.

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 P450 3A4 enzyme inhibitors (e.g. ketoconazole, ritonavir) may also inhibit the metabolism of alfentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such active substances requires special patient care and observation, in particular, it may be necessary to lower the dose of alfentanil.

Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when alfentanil is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anaesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anaesthetics are reduced by 30 to 50% for the first sixty (60) minutes following alfentanil induction.

Treatment with drugs which may depress the heart or increase vagal tone, such as beta-blockers and anaesthetic agents, may predispose to bradycardia or hypertension. Bradycardia and possibly asystole can occur when alfentanil is combined with non-vagolytic muscle relaxants.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
4.6. Pregnancy and lactation

Pregnancy

Alfentanil has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration for alfentanil in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. Alfentanil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

There are insufficient data to support the use of alfentanil in labor and delivery. Placental transfer of the drug has been reported: therefore, use in labor and delivery is not recommended.

Nursing Mothers

In one study of nine women undergoing postpartum tubal ligation, significant levels of alfentanil were detected in colostrum four hours after administration of 60 µg/kg of alfentanil, with no detectable levels present after 28 hours. Caution should be exercised when alfentanil is administered to a nursing woman.

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4.7. Effects on ability to drive and use machines

No studies on the effects of alfentanil on the ability to drive and use machines have been performed. However, where early discharge is envisaged patients should be advised not to drive or operate machinery for 24 hours following administration.

4.8. Undesirable effects

Undesirable effects in patients receiving alfentanil are generally mild and transient.

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity, particularly of the truncal muscles. Alfentanil may produce muscular rigidity that involves the skeletal muscles of the neck and extremities.

The adverse experience profile from patients receiving alfentanil for monitored anaesthesia care is similar to the profile established with alfentanil during general anaesthesia. Respiratory events reported during monitored anaesthesia care included hypoxia, apnea, and bradypnea. Other adverse events reported by patients receiving alfentanil for monitored anaesthesia care, in order of decreasing frequency, were nausea, hypotension, vomiting, pruritus, confusion, somnolence and agitation.

Summarising the adverse effects reported in the currently available literature (clinical trials and case reports, representing 2029 patients), the incidence of adverse reactions probably or possibly related to alfentanil sorted according to the affected organ system is shown in Table 1.

Table 1. Adverse reactions probably or possibly related to alfentanil sorted by frequency and organ system

<table>
<thead>
<tr>
<th>Frequency category</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common:</td>
<td>Gastrointestinal adverse reactions (16.95%)</td>
</tr>
</tbody>
</table>
- Common: Cardiovascular adverse reactions (3.3%), Central nervous adverse reactions (3.25%), Respiratory adverse reactions (2.0%)
- Uncommon: Skin adverse reactions (1.1%), Adverse reactions in body as whole (0.9%), Sensory organ adverse reactions (0.2%), Urogenital adverse reactions (0.15%), Muscle/skeleton adverse reactions (0.15%)
- Rare: --
- Very rare: --

A more detailed summary of probably or possibly to alfentanil use related adverse events is compiled in Table 2. Nausea and vomiting are the most frequent observed adverse events, then cardiovascular reactions and respiratory effects. All other adverse events reported are uncommon and rare.

### Table 2. Frequency of adverse reactions possibly or probably related to alfentanil, reported in clinical trials

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse event</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥ 10%) nausea</td>
<td>headache</td>
<td>11.29</td>
</tr>
<tr>
<td>Common (1-10%)</td>
<td>hypotension</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>pain on injection site</td>
<td>2.07</td>
</tr>
<tr>
<td></td>
<td>Pruritus/itching</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>respiratory depression/hypoxemia</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>sleepiness/dizziness/drowsiness/vomiting</td>
<td>1.08</td>
</tr>
<tr>
<td>Uncommon (0.1-1%)</td>
<td>bradycardia</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>coughing</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>excitation</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>hypertension</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>laryngospasm/bronchospasm</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>muscle rigidity</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>shivering/feeling of cold</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>tachycardia</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>urinary retention</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>visual disturbances</td>
<td>0.20</td>
</tr>
<tr>
<td>Rare (0.01-0.1%)</td>
<td>singultus</td>
<td>0.05</td>
</tr>
<tr>
<td>Very rare (≤ 0.01%)</td>
<td>--</td>
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</tr>
</tbody>
</table>

### 4.9. Overdose

Overdosage would be manifested by extension of the pharmacological actions of alfentanil hydrochloride. No experience of overdosage with alfentanil was reported during clinical trials. The duration of respiratory depression...
following overdosage with alfentanil may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics-Narcotic (opioid analgesic), ATC code: N01AH02 (Alfentanil)

Alfentanil hydrochloride is an opioid analgesic with a rapid onset of action. At doses of 8-40 µg/kg for surgical procedures lasting up to 30 minutes, alfentanil provides analgesic protection against hemodynamic responses to surgical stress with recovery times generally comparable to those seen with equipotent fentanyl dosages.

For longer procedures, doses of up to 75 µg/kg attenuate hemodynamic responses to laryngoscopy, intubation and incision, with recovery time comparable to fentanyl. At doses of 50-75 µg/kg followed by a continuous infusion of 0.5-3.0 µg/kg/min, alfentanil attenuates the catecholamine response with more rapid recovery and reduced need for postoperative analgesics as compared to patients administered enflurane. At doses of 5 µg/kg, alfentanil provides analgesia for the conscious but sedated patient. Based on patient response, doses higher than 5 µg/kg may be needed. Elderly or debilitated patients may require lower doses.

Alfentanil has an immediate onset of action. At dosages of approximately 105 µg/kg, alfentanil produces hypnosis as determined by EEG patterns; an aesthetic ED90 of 182 µg/kg for alfentanil in unpremedicated patients has been determined, based upon the ability to block response to placement of a nasopharyngeal airway. Based on clinical trials, induction dosage requirements range from 130-245 µg/kg. For procedures lasting 30-60 minutes, loading dosages of up to 50 µg/kg produce the hemodynamic responses to endotracheal intubation and skin incision comparable to those from fentanyl. A pre-intubation loading dose of 50-75 µg/kg prior to a continuous infusion attenuates the response to laryngoscopy, intubation and incision. Subsequent administration of alfentanil infusion administered at a rate of 0.5-3 µg/kg/min with nitrous oxide/oxygen attenuates sympathetic responses to surgical stress with more rapid recovery than enflurane.

Requirements for volatile inhalation anaesthetics were reduced by 30 to 50% during the first 60 minutes of maintenance in patients administered anaesthetic doses (above 130 µg/kg) of alfentanil as compared to patients given doses of 4-5 mg/kg thiopental for anaesthetic induction. At anaesthetic induction dosages, alfentanil provides a deep level of anaesthesia during the
first hour of anaesthetic maintenance and provides attenuation of the hemodynamic response during intubation and incision.

Following an anaesthetic dose of alfentanil, requirements for alfentanil infusion are reduced by 30 to 50% for the first hour of maintenance.

Patients with compromised liver function and those over 65 years of age have been found to have reduced plasma clearance and extended terminal elimination of alfentanil, which may prolong postoperative recovery.

Bradycardia may be seen in patients administered alfentanil. The incidence and degree of bradycardia may be more pronounced when alfentanil is administered in conjunction with non-vagolytic neuromuscular blocking agents or in the absence of anticholinergic agents such as atropine.

Administration of intravenous diazepam immediately prior to or following high doses of alfentanil has been shown to produce decreases in blood pressure that may be secondary to vasodilation; recovery may also be prolonged.

Patients administered doses up to 200 µg/kg of alfentanil have shown no significant increase in histamine levels and no clinical evidence of histamine release.

Skeletal muscle rigidity is related to the dose and speed of administration of alfentanil. Muscular rigidity will occur with an immediate onset following anaesthetic induction dosages. Preventative measures may reduce the rate and severity.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Although higher doses may produce apnea and a longer duration of respiratory depression, apnea may also occur at low doses.

During monitored anaesthesia care, attention must be given to the respiratory effects of alfentanil injection. Decreased oxygen saturation, apnea, decreased respiratory rate, and upper airway obstruction can occur.

5.2. Pharmacokinetic properties

High intrasubject and intersubject variability in the pharmacokinetic disposition of alfentanil has been reported.

The pharmacokinetics of alfentanil can be described as a three-compartment model with sequential distribution half-lives of 1 and 14 minutes; and a terminal elimination half-life of 90-111 minutes (as compared to a terminal elimination half-life of approximately 475 minutes for fentanyl and approximately 265 minutes for sufentanil at doses of 250 µg). The liver is the major site of biotransformation.

Alfentanil has an apparent volume of distribution of 0.4-1 L/kg, which is approximately one-fourth to one-tenth that of fentanyl, with an average plasma clearance of 5 ml/kg/min as compared to approximately 8 ml/kg/min for fentanyl.

Only 1.0% of the dose is excreted as unchanged drug; urinary excretion is the major route of elimination of metabolites. Plasma protein binding of alfentanil is approximately 92%.
In one study involving 15 patients administered alfentanil with nitrous oxide/oxygen, a narrow range of plasma alfentanil concentrations, approximately 310-340 ng/ml, was shown to provide adequate anaesthesia for intra-abdominal surgery, while lower concentrations, approximately 190 ng/ml, blocked responses to skin closure. Plasma concentrations between 100-200 ng/ml provided adequate anaesthesia for superficial surgery.

Repeated or continuous administration of alfentanil produces increasing plasma concentrations and an accumulation of the drug, particularly in patients with reduced plasma clearance.

5.3. Preclinical safety data

**Single and repeated dose toxicity:** Alfentanil may be assessed as a drug having low toxic potential at therapeutic doses. Toxic reactions occur principally as extension of the specific pharmacodynamic effects. Consequently, symptoms secondary due to suppression of the function of the central nervous system dominate in the event of acute overdose, e.g., respiratory suppression. Lesions of the cortical regions and the limbic system may be produced in rats after supratherapeutic doses.

The intravenous LD$_{50}$ of alfentanil is 43-51 mg/kg in rats, 72-74 mg/kg in mice, 72-82 mg/kg in guinea pigs and 60-88 mg/kg in dogs. On the basis of experimental data in rats, a therapeutic index of 1080 was calculated after intravenous administration of alfentanil.

Alfentanil is indicated for short-term use only. Subchronic and chronic toxicity data should not be required. Theoretically, alfentanil hydrochloride can produce drug dependence of the morphine type and therefore has the potential for being abused.

**Carcinogenesis, mutagenesis, and impairment of fertility:**
No long-term animal studies of alfentanil have been performed to evaluate carcinogenic potential. No structural chromosome mutations were produced in the in vivo micronucleus test in female rats at single intravenous doses of alfentanil as high as 20 mg/kg body weight (approximately 40 times the upper human dose), equivalent to a dose of 103 mg/m$^2$ body surface area. No dominant lethal mutations were produced in the in vivo dominant lethal test in male and female mice at the maximum intravenous dose of 20 mg/kg (60 mg/m$^2$). No mutagenic activity was revealed in the in vitro Ames Salmonella typhimurium test, with and without metabolic activation.

**Reproductive effects of alfentanil cannot be fully excluded, if administered at supratherapeutic doses in particular. Alfentanil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Caution should be exercised when alfentanil is administered to a nursing woman.**

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.
Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were not observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride, hydrochloric acid and water for injections

6.2. Incompatibilities

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

6.3. Shelf life

Shelf-life before first opening

3 years.

Shelf-life after dilution

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

Shelf-life after first opening (vials)

The product should be used immediately after opening the container.

6.4. Special precautions for storage

No special precautions for storage

6.5. Nature and contents of container
Clear glass ampoules (Ph Eur Type I, one point cut) containing 1 mg/2 ml
Clear glass ampoules (Ph Eur Type I, one point cut) containing 5 mg/10 ml
Clear glass (Ph Eur Type I) vials containing 1 mg/2 ml
Clear glass (Ph Eur Type I) vials containing 5 mg/10 ml
Original pack containing 5 or 10 ampoules of 2 ml each.
Original pack containing 5 or 10 ampoules of 10 ml each.
Original pack containing 5 or 10 vials of 2 ml each.
Original pack containing 5 or 10 vials of 10 ml each.

6.6. Instruction for use and handling (use, and disposal)

Alfentanil 500 micrograms/ml solution for injection may be diluted with
sodium chloride injection BP, glucose injection BP, or Ringer-Lactate
injection BP (Hartmann’s solution) to a concentration of 25-80 pg/ml. Such
dilutions are compatible with plastic bags and giving sets.

Any unused solution from opened ampoules or vials should be discarded.
Any unused product or waste material should be disposed of in accordance
with local requirements.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Hameln Pharma Plus GmbH
Langes Feld 13
Hameln
31789
Germany

8. MARKETING AUTHORISATION NUMBER

PL 25215/0005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

05/05/2006 – 04/05/2011

10. DATE OF (PARTIAL) REVISION OF THE TEXT

05/05/2006
Alfentanil 5 mg/ml solution for injection (PL 25215/0006) has the following product summary:

1. NAME OF THE MEDICINAL PRODUCT

Alfentanil 5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of Alfentanil 5 mg/ml solution for injection contains:
Alfentanil hydrochloride, monohydrate 5.44 mg, equivalent to 5.0 mg alfentanil base

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

The product is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Alfentanil 5 mg/ml solution for injection 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 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.

4.2. Posology and method of administration

At the proposed doses, Alfentanil 5 mg/ml solution for injection 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.
**Method of administration**
For intravenous infusions.

**Dosage**
Alfentanil 5 mg/ml solution for injection 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 Alfentanil 5 mg/ml solution for injection. 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**
Alfentanil hydrochloride is contraindicated in patients with known hypersensitivity to the drug and other opioids.

Obstructive airway disease or respiratory depression if not ventilating.

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

Administration in labour or before clamping of the cord during Caesarian section due to the possibility of respiratory depression in the new-born infant.

4.4. Special warnings and precautions for use

**Warnings**

Alfentanil should be administered only by persons specifically trained in the use of intravenous and general anaesthetic agents and the management of respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

Alfentanil hydrochloride administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of alfentanil at anaesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. Alfentanil may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by:

1) routine methods of administration of neuromuscular blocking agents for balanced opioid anaesthesia; 2) administration of up to 1/4 of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of alfentanil at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of alfentanil and a full paralyzing dose of a neuromuscular blocking agent when alfentanil is used in rapidly administered anaesthetic dosages (above 130 µg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered alfentanil. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Patients receiving monitored anaesthesia care should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure; oxygen supplementation should be immediately available and
provided where clinically indicated; oxygen saturation should be continuously monitored; the patient should be observed for early signs of hypertension, apnea, upper airway obstruction and/or oxygen desaturation.

Severe and unpredictable potentiation of monoamine oxidase (MAO) inhibitors has been reported for other opioid analgesics, and rarely with alfentanil. Therefore when alfentanil is administered to patients who have received MAO inhibitors within 14 days, appropriate monitoring and ready availability of vasodilators and beta-blockers for the treatment of hypertension is recommended.

**Precautions**

Delayed respiration depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. Therefore, vital signs must be monitored continuously.

**General**

The initial dose of alfentanil should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of alfentanil should be determined on the basis of lean body weight. In one clinical trial, the dose of alfentanil required to produce anaesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of alfentanil may be reduced and postoperative recovery may be prolonged.

Induction doses of alfentanil should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction.

Diazepam administered immediately prior to or in conjunction with high doses of alfentanil may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by alfentanil may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anaesthetic induction dose of alfentanil, requirements for volatile inhalation anaesthetics of alfentanil infusion are reduced by 30 to 50% for the first hour of maintenance.

Alfentanil infusions should be discontinued at least 10-15 minutes prior to the end of surgery during general anaesthesia. During administration of alfentanil for monitored anaesthesia care, infusions may be continued to the end of the procedure.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by alfentanil may last longer than the duration of the opioid
antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO2 stimulation which may persist into or recur in the postoperative period.

Intraoperative hyperventilation may further add to respiratory depression. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of alfentanil, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

**Head injuries**
Alfentanil may obscure the clinical course of patients with head injuries.

**Impaired respiration**
Alfentanil should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anaesthesia, this can be managed by assisted or controlled respiration.

**Impaired hepatic or renal function**
In patients with liver or kidney dysfunction, alfentanil should be administered with caution due to the importance of these organs in the metabolism and excretion of alfentanil.

**Pediatric use**
Adequate data to support the use of alfentanil in children under 12 years of age are not presently available.

**4.5. Interactions with other medicinal products and other forms of interaction**

Monoamine oxidase (MAO) inhibitors may potentiate the effects of narcotics. It is not recommended to take alfentanil who have received MAO inhibitors within 14 days.

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 P450 3A4 enzyme inhibitors (e.g. ketoconazole, ritonavir) may also inhibit the metabolism of alfentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such active substances requires special patient care and observation, in particular, it may be necessary to lower the dose of alfentanil.

Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when alfentanil is administered in combination with other CNS depressants such as barbiturates, tranquillizers, opioids, or
inhalation general anaesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anaesthetics are reduced by 30 to 50% for the first sixty (60) minutes following alfentanil induction.

Treatment with drugs which may depress the heart or increase vagal tone, such as beta-blockers and anaesthetic agents, may predispose to bradycardia or hypertension.

Bradycardia and possibly asystole can occur when alfentanil is combined with non-vagolytic muscle relaxants.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

4.6. **Pregnancy and lactation**

*Pregnancy*

Alfentanil has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration for alfentanil in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. Alfentanil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Labor and Delivery*

There are insufficient data to support the use of alfentanil in labor and delivery. Placental transfer of the drug has been reported: therefore, use in labor and delivery is not recommended.

*Nursing Mothers*

In one study of nine women undergoing postpartum tubal ligation, significant levels of alfentanil were detected in colostrum four hours after administration of 60 µg/kg of alfentanil, with no detectable levels present after 28 hours. Caution should be exercised when alfentanil is administered to a nursing woman.

4.7. **Effects on ability to drive and use machines**
No studies on the effects of alfentanil on the ability to drive and use machines have been performed. However, where early discharge is envisaged patients should be advised not to drive or operate machinery for 24 hours following administration.

4.8. Undesirable effects

Undesirable effects in patients receiving alfentanil are generally mild and transient.

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity, particularly of the truncal muscles. Alfentanil may produce muscular rigidity that involves the skeletal muscles of the neck and extremities.

The adverse experience profile from patients receiving alfentanil for monitored anaesthesia care is similar to the profile established with alfentanil during general anaesthesia. Respiratory events reported during monitored anaesthesia care included hypoxia, apnea, and bradypnea. Other adverse events reported by patients receiving alfentanil for monitored anaesthesia care, in order of decreasing frequency, were nausea, hypotension, vomiting, pruritus, confusion, somnolence and agitation.

Summarising the adverse effects reported in the currently available literature (clinical trials and case reports, representing 2029 patients), the incidence of adverse reactions probably or possibly related to alfentanil sorted according to the affected organ system is shown in Table 1.

<table>
<thead>
<tr>
<th>Frequency category</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common:</td>
<td>Gastrointestinal adverse reactions (16.95%)</td>
</tr>
<tr>
<td>Common:</td>
<td>Cardiovascular adverse reactions (3.3%), Central nervous adverse reactions (3.25%), Respiratory adverse reactions (2.0%)</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Skin adverse reactions (1.1%), Adverse reactions in body as whole (0.9%), Sensory organ adverse reactions (0.2%), Urogenital adverse reactions (0.15%), Muscle/skeleton adverse reactions (0.15%)</td>
</tr>
<tr>
<td>Rare:</td>
<td>- --</td>
</tr>
<tr>
<td>Very rare:</td>
<td>- --</td>
</tr>
</tbody>
</table>

A more detailed summary of probably or possibly to alfentanil use related adverse events is compiled in Table 2. Nausea and vomiting are the most
frequent observed adverse events, then cardiovascular reactions and respiratory effects. All other adverse events reported are uncommon and rare.

Table 2. Frequency of adverse reactions possibly or probably related to alfentanil, reported in clinical trials

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse event</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥ 10%)</td>
<td>nausea</td>
<td>11.29</td>
</tr>
<tr>
<td>Common (1-10%)</td>
<td>headache</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>hypotension</td>
<td>2.07</td>
</tr>
<tr>
<td></td>
<td>pain on injection site</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>Pruritus/itching</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>respiratory depression/ hypoxemia</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>sleepiness/dizziness/drowsiness</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td>vomiting</td>
<td>5.62</td>
</tr>
<tr>
<td>Uncommon (0.1-1%)</td>
<td>bradycardia</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>coughing</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>excitation</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>hypertension</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>laryngospasm/bronchospasm</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>muscle rigidity</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>shivering/feeling of cold</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>tachycardia</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>urinary retention</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>visual disturbances</td>
<td>0.20</td>
</tr>
<tr>
<td>Rare (0.01-0.1%)</td>
<td>singultus</td>
<td>0.05</td>
</tr>
<tr>
<td>Very rare (≤ 0.01%)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

4.9. Overdose

Overdosage would be manifested by extension of the pharmacological actions of alfentanil hydrochloride. No experience of overdosage with alfentanil was reported during clinical trials. The duration of respiratory depression following overdosage with alfentanil may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics-Narcotic (opioid analgesic), ATC code: N01AH02 (Alfentanil)
Alfentanil hydrochloride is an opioid analgesic with a rapid onset of action.

At doses of 8-40 µg/kg for surgical procedures lasting up to 30 minutes, alfentanil provides analgesic protection against hemodynamic responses to surgical stress with recovery times generally comparable to those seen with equipotent fentanyl dosages. For longer procedures, doses of up to 75 µg/kg attenuate hemodynamic responses to laryngoscopy, intubation and incision, with recovery time comparable to fentanyl. At doses of 50-75 µg/kg followed by a continuous infusion of 0.5-3.0 µg/kg/min, alfentanil attenuates the catecholamine response with more rapid recovery and reduced need for postoperative analgesics as compared to patients administered enflurane. At doses of 5 µg/kg, alfentanil provides analgesia for the conscious but sedated patient. Based on patient response, doses higher than 5 µg/kg may be needed. Elderly or debilitated patients may require lower doses.

Alfentanil has an immediate onset of action. At dosages of approximately 105 µg/kg, alfentanil produces hypnosis as determined by EEG patterns; an aesthetic ED₉₀ of 182 µg/kg for alfentanil in unpremedicated patients has been determined, based upon the ability to block response to placement of a nasopharyngeal airway. Based on clinical trials, induction dosage requirements range from 130-245 µg/kg. For procedures lasting 30-60 minutes, loading dosages of up to 50 µg/kg produce the hemodynamic responses to endotracheal intubation and skin incision comparable to those from fentanyl. A pre-intubation loading dose of 50-75 µg/kg prior to a continuous infusion attenuates the response to laryngoscopy, intubation and incision. Subsequent administration of alfentanil infusion administered at a rate of 0.5-3 µg/kg/min with nitrous oxide/oxygen attenuates sympathetic responses to surgical stress with more rapid recovery than enflurane.

Requirements for volatile inhalation anaesthetics were reduce by 30 to 50% during the first 60 minutes of maintenance in patients administered anaesthetic doses (above 130 µg/kg) of alfentanil as compared to patients given doses of 4-5 mg/kg thiopental for anaesthetic induction. At anaesthetic induction dosages, alfentanil provides a deep level of anaesthesia during the first hour of anaesthetic maintenance and provides attenuation of the hemodynamic response during intubation and incision.

Following an anaesthetic dose of alfentanil, requirements for alfentanil infusion are reduced by 30 to 50% for the first hour of maintenance. Patients with compromised liver function and those over 65 years of age have been found to have reduced plasma clearance and extended terminal elimination of alfentanil, which may prolong postoperative recovery. Bradycardia may be seen in patients administered alfentanil. The incidence and degree of bradycardia may be more pronounced when alfentanil is administered in conjunction with non-vagolytic neuromuscular blocking agents or in the absence of anticholinergic agents such as atropine.

Administration of intravenous diazepam immediately prior to or following high doses of alfentanil has been shown to produce decreases in blood pressure that may be secondary to vasodilation; recovery may also be prolonged.
Patients administered doses up to 200 µg/kg of alfentanil have shown no significant increase in histamine levels and no clinical evidence of histamine release.

Skeletal muscle rigidity is related to the dose and speed of administration of alfentanil. Muscular rigidity will occur with an immediate onset following anaesthetic induction dosages. Preventative measures may reduce the rate and severity.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Although higher doses may produce apnea and a longer duration of respiratory depression, apnea may also occur at low doses.

During monitored anaesthesia care, attention must be given to the respiratory effects of alfentanil injection. Decreased oxygen saturation, apnea, decreased respiratory rate, and upper airway obstruction can occur.

5.2. Pharmacokinetic properties

High intrasubject and intersubject variability in the pharmacokinetic disposition of alfentanil has been reported.

The pharmacokinetics of alfentanil can be described as a three-compartment model with sequential distribution half-lives of 1 and 14 minutes; and a terminal elimination half-life of 90-111 minutes (as compared to a terminal elimination half-life of approximately 475 minutes for fentanyl and approximately 265 minutes for sufentanil at doses of 250 µg). The liver is the major site of biotransformation.

Alfentanil has an apparent volume of distribution of 0.4-1 L/kg, which is approximately one-fourth to one-tenth that of fentanyl, with an average plasma clearance of 5 ml/kg/min as compared to approximately 8 ml/kg/min for fentanyl. Only 1.0% of the dose is excreted as unchanged drug; urinary excretion is the major route of elimination of metabolites. Plasma protein binding of alfentanil is approximately 92%.

In one study involving 15 patients administered alfentanil with nitrous oxide/oxygen, a narrow range of plasma alfentanil concentrations, approximately 310-340 ng/ml, was shown to provide adequate anaesthesia for intra-abdominal surgery, while lower concentrations, approximately 190 ng/ml, blocked responses to skin closure. Plasma concentrations between 100-200 ng/ml provided adequate anaesthesia for superficial surgery. Repeated or continuous administration of alfentanil produces increasing plasma concentrations and an accumulation of the drug, particularly in patients with reduced plasma clearance.

5.3. Preclinical safety data

Single and repeated dose toxicity: Alfentanil may be assessed as a drug having low toxic potential at therapeutic doses. Toxic reactions occur
principally as extension of the specific pharmacodynamic effects. Consequently, symptoms secondary due to suppression of the function of the central nervous system dominate in the event of acute overdose, e.g., respiratory suppression. Lesions of the cortical regions and the limbic system may be produced in rats after supratherapeutic doses.

The intravenous LD$_{50}$ of alfentanil is 43-51 mg/kg in rats, 72-74 mg/kg in mice, 72-82 mg/kg in guinea pigs and 60-88 mg/kg in dogs. On the basis of experimental data in rats, a therapeutic index of 1080 was calculated after intravenous administration of alfentanil.

Alfentanil is indicated for short-term use only. Subchronic and chronic toxicity data should not be required. Theoretically, alfentanil hydrochloride can produce drug dependence of the morphine type and therefore has the potential for being abused.

**Carcinogenesis, mutagenesis, and impairment of fertility:**
No long-term animal studies of alfentanil have been performed to evaluate carcinogenic potential. No structural chromosome mutations were produced in the in vivo micronucleus test in female rats at single intravenous doses of alfentanil as high as 20 mg/kg body weight (approximately 40 times the upper human dose), equivalent to a dose of 103 mg/m$^2$ body surface area. No dominant lethal mutations were produced in the in vivo dominant lethal test in male and female mice at the maximum intravenous dose of 20 mg/kg (60 mg/m$^2$). No mutagenic activity was revealed in the in vitro Ames Salmonella typhimurium test, with and without metabolic activation.

Reproductive effects of alfentanil cannot be fully excluded, if administered at supratherapeutic doses in particular. Alfentanil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Caution should be exercised when alfentanil is administered to a nursing woman.

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were not observed.

6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of excipients**

Sodium chloride, sodium hydroxide and water for injections
6.2. Incompatibilities

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

6.3. Shelf life

Shelf-life before first op

3 years.

Shelf-life after dilution

Chemical and physical in-use stability of the dilutions (see section 6.6) has been demonstrated for 48 hours.

From the microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

No special precautions for storage

6.5. Nature and contents of container

Clear glass ampoules (Ph Eur Type I, one point cut) containing 5 mg/1 ml.

Original pack containing 5 or 10 ampoules of 1 ml each.

6.6. Instruction for use and handling (use, and disposal)

Alfentanil 5 mg/ml solution for injection should be diluted with sodium chloride intravenous infusion BP, glucose intravenous infusion BP, or compound sodium lactate intravenous infusion BP (Hartmann’s solution) to a convenient concentration. Such dilutions are compatible with plastic bags and giving sets.

Any unused solution from opened ampoules should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
8. MARKETING AUTHORISATION NUMBER

PL 25215/0006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/05/2006

10. DATE OF REVISION OF THE TEXT

05/05/2006
PATIENT INFORMATION LEAFLET

Alfentanil 500 micrograms/ml solution for injection (PL 25215/0005):

Patient information leaflet

Read all of this leaflet carefully because it will provide you with important information about your medicine. Please read it carefully before your medicine is administered. If, after reading it, you still have some queries, please consult your doctor or pharmacist. Keep this leaflet, you may need to read it again.

Alfentanil 500 micrograms/ml solution for injection

What is in your medicine?
Alfentanil 500 micrograms/ml is a clear and sterile solution for injection contained in clear glass ampoules or vials. Each 1 ml of this solution contains 500 micrograms of the active substance alfentanil.

Other ingredients:
The solution also contains sodium chloride, hydrochloric acid and water for injections.

Pack sizes:
Alfentanil 500 micrograms/ml is available in packs of 5 and 10 ampoules or vials each containing 2 ml or 10 ml of solution.

PL holder:
Hameln Pharma plus gmbh
Langes Feld 15, 31790 Hameln, Germany

Manufacturer:
Hameln Pharmaceuticals gmbh
Langes Feld 13, 31790 Hameln, Germany

Distributor:
Hameln Pharmaceuticals Ltd
Gloucester, United Kingdom

About your medicine:
Alfentanil 500 micrograms/ml is a potent and short-acting painkiller that is used for surgical procedures.

Before you receive Alfentanil 500 micrograms/ml solution for injection:
Before taking or receiving any medicine you should ask your doctor or pharmacist for advice. Tell them if you are pregnant, think you might be pregnant or are trying to become pregnant.

You should not be given Alfentanil 500 micrograms/ml solution for injection:
- if you think you may have had an allergic reaction to Alfentanil 500 micrograms/ml or to a similar medicine in the past
- if you suffer from lung or breathing disorder. The doctor can give you Alfentanil 500 micrograms/ml if your breathing has to be assisted by a ventilator.
- if you are taking or have been taking (within the last two weeks) an antidepressant known as monoamine oxidase inhibitor (MAOI).
- during labour or before clamping of the cord during Caesarean section due to the possibility of breathing difficulties in the baby.

Take special care with Alfentanil 500 micrograms/ml solution for injection:
Alfentanil 500 micrograms/ml may cause a drop in blood pressure and breathing rate (incl. respiratory arrest). It may also cause the heart to beat more slowly. Rarely the rhythm of the heart may be altered. Particular care has to be taken following treatment with other medicines which have similar effects. Therefore vital signs as blood pressure and heart rate are monitored during administration of Alfentanil 500 micrograms/ml.

Unwanted effects caused by Alfentanil 500 micrograms/ml can be reversed by other medicines.
Alfentanil 500 micrograms/ml will be used with caution if you suffer from lung diseases like respiratory depression, respiratory arrest or potentially compromised respiration because medicines like Alfentanil 500 micrograms/ml may decrease respiratory drive and increase airway resistance.
If the function of your liver or kidneys is reduced or if you have been on long term opioid therapy, the doctor will use Alfentanil 500 micrograms/ml with caution because of the influence of these organs on the amount of medicine in your body.

For elderly, debilitated and obese patients the dosage will be adjusted to their physical condition.
The doctor will be aware that Alfentanil 500 micrograms/ml may obscure the clinical course if you have head injuries.
Alfentanil 500 micrograms/ml 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. Your breathing will therefore be carefully monitored until it returns to normal.
1. NAME OF THE MEDICINAL PRODUCT
Alfentanil 500 micrograms/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Alfentanil 500 micrograms/ml solution for injection contains
Alfentanil hydrochloride, microcrystalline 53.6 micrograms, eqv.
to 500 micrograms of alfentanil base
For excipients, see 3.1.

3. PHARMACEUTICAL FORM
Solution for injection
The product is a white and colorless solution.

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

4.2 Posology and method of administration
Alfentanil 500 micrograms/ml by the intravenous route can be administered to both adults and children. The dosage of Alfentanil should only be given according to the instructions of a qualified medical practitioner.

Table: Dosage regime

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Supplementary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>500 micrograms</td>
<td>1500 micrograms</td>
</tr>
<tr>
<td>Child</td>
<td>5 micrograms</td>
<td>15 micrograms</td>
</tr>
</tbody>
</table>

If desired, Alfentanil 500 micrograms/ml can be mixed with sodium citrate injection 5% or Intralipid® 20% emulsion for intravenous administration. It should not be mixed with other drugs, antacids, or other injectable fluids.

Children may require higher or more frequent dosing owing to a greater proportion of body fat and a lower dose related to lean body weight.

In unconscious patients, the initial bolus dose should be limited to less than 15 micrograms/kg (1 microgram/0.08 per cent of body weight) and may be repeated if necessary.

4.3 Special warnings and precautions for use
Wernicke's
Alfentanil should be administered only by persons specifically trained in the use of intravenous and general anaesthetic agents and the management of respiratory complications of parenteral drug administration.

An opioid antagonist, resuscitation and inhalation equipment should be readily available.

Because of the possibility of delayed respiratory depression, monitoring of the respiratory status should be performed well after surgery.

4.4 Special precautions for use

4.5 Interactions with other medicinal products and other forms of interaction

4.6 Overdose

4.7 Effects on ability to drive and use machines

5. PHARMACOLOGICAL PROPERTIES

5.1 Preclinical safety data

6. MARKETING AUTHORISATION HOLDER

7. PHARMACOVIGILANCE

8. MARKETING AUTHORISATION NUMBER

MHRA PAR ALFENTANIL 500 MICROGRAMS/ML SOLUTION FOR INJECTION AND ALFENTANIL 5MG/ML SOLUTION FOR INJECTION (PL 25215/0005-6)
Pregnancy and labour/delivery
If you are pregnant or think you may be pregnant, you should inform your doctor. He/she will decide whether or not you should be given Alfentanil 500 micrograms/ml.

Breast feeding
Alfentanil 500 micrograms/ml may get into breast milk. It is recommended that you should not breast feed for 28 hours after treatment.

Driving and using machines
Do not drive or operate any machines for 24 hours after being given Alfentanil 500 micrograms/ml because you may be less alert than usual.

Taking other medicines
Tell your doctor about any medicines that you are taking, or have recently taken, including any you have bought yourself. Fluconazole, a medicine used for the treatment of mycotic infections, cinemidone, a medicine for ulcers, stomach-ache and heartburn, erythromycin, an antibiotic and diltiazem, a medicine used for a certain type of heart disorder, may affect the length of time it takes for the effects of Alfentanil 500 micrograms/ml to wear off.

Medicines such as 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, e.g. chlorpromazine) and other strong painkillers will have some of the same effects as Alfentanil 500 micrograms/ml. When one or more of these medicines is used at the same time as Alfentanil 500 micrograms/ml, the effects of either may be increased.

It may also be necessary to adjust the dose of Alfentanil 500 micrograms/ml if you are taking the following certain medicines for mycotic infections, e.g. ketoconazole, or certain medicines called antiviral protease inhibitors, e.g. ritonavir.

Monoamine oxidase inhibitors (MAOIs), medicines acting as antidepressant drugs, may potentiate the effect of narcotics. It is therefore not recommended to take Alfentanil 500 micrograms/ml for patients who have received MAO inhibitors within 14 days.

How Alfentanil 500 micrograms/ml solution for injection will be used:
Alfentanil 500 micrograms/ml will be given as an injection or an infusion into a vein. Your doctor will decide how much Alfentanil 500 micrograms/ml you need. This will depend, for example, on the type and duration 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.

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.

Your last dose of Alfentanil 500 micrograms/ml will be given no later than ten minutes before the end of your surgery.

Alfentanil 500 micrograms/ml may be mixed with sodium chloride injection BP, glucose injection BP or Ringer-Lactate injection BP (Hartmann’s injection). These dilutions should be used within 24 hours of preparation.

Alfentanil 500 micrograms/ml 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 will be reduced.

**Children:**
The amount given to children will always depend on how much they weigh.

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.

Possible side effects of Alfentanil 500 micrograms/ml solution for injection:
Like all medicines Alfentanil 500 micrograms/ml can have side effects.

Occasionally, Alfentanil 500 micrograms/ml may cause side effects such as feeling sick (nausea), headache, vomiting, stiffness of the muscles, pain on the injection site, low blood pressure, itching of the skin, confusion, dizziness and drowsiness. It may also cause your heart or breathing rate deviate from the normal frequency. Additionally, some cases of excitement, urinary retention, visual disturbance and hiccups have been reported.

If you notice any side effects not mentioned in this leaflet, please inform your doctor.

**How Alfentanil 500 micrograms/ml solution for injection should be stored:**
The doctor will not give you this medicine after the date printed following "Exp. date".

Keep out of the reach and sight of children.

Date of preparation of leaflet: May 2006.
be avoided not to draw or operate machinery for 24 hours fol-
lowing administration.

4.8 Undesirable effects

undesirable effects associated with alfentanil are generally mild and transient.
The most common undesirable reactions of alfentanil are respiratory.
Alfentanil may cause increased respiratory rate and frequency and times of
narcotic muscles. Patients may experience signs of exaggerated respiratory
response to mild stimuli. The response may be more noticeable in patients
who have respiratory compromise. Such signs may include tachypnoea and

Table 1. Adverse reactions probably or possibly related to alfentanil and frequencies expressed as a percentage of the number of patients treated.

<table>
<thead>
<tr>
<th>Common</th>
<th>Very common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1.1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.07%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.08%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1.08%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.15%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.99%</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>0.10%</td>
</tr>
<tr>
<td>Rigidity</td>
<td>0.11%</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>0.20%</td>
</tr>
<tr>
<td>Angina</td>
<td>0.01%</td>
</tr>
<tr>
<td>Very rare</td>
<td>1.01%</td>
</tr>
</tbody>
</table>

4.9 Overdose

Overdose would be manifested by extension of the pharma-
cological actions of alfentanil hydrochloride. No experience of
overdose with alfentanil was reported during clinical trials.
If an overdose is suspected, the patient should be observed and
assisted if necessary. The patient should be treated symptomatically.
Respiratory depression is the major route of elimination of alfentanil.
A naloxone test can be performed to determine the effectiveness
of naloxone in reversing alfentanil-induced respiratory depression.

5.3 Pharmacokinetic properties

Alfentanil is predominantly metabolized by hepatic pathways.
Approximately 50% of alfentanil is metabolized to alfentanil-3- and
4-OH metabolites. Approximately 10% of alfentanil is excreted in

5.1 Pharmacological properties

Pharmacotherapeutic group: Anaesthetics-Narcotic (opiate anal-
gesics). ATC code: N01BA02 (Alfentanil).

5.2 Preclinical safety data

Single and repeated dose toxicity: Alfentanil may be re-
covered in breast milk in the mother but the level is not
likely to be harmful to the child.

5.4 Special warnings and precautions for use

5.5 Technical and pharmacokinetic data

5.6 Nature and contents of container

5.7 Marketing Authorisation holder

humira par alfentanil 500 micrograms/ml solution for injection
and alfentanil 5mg/ml solution for injection (pl 2515/0005-6)

MHRA PAR ALFENTANIL 500 MICROGRAMS/ML SOLUTION FOR INJECTION AND ALFENTANIL 5MG/ML SOLUTION FOR INJECTION (PL 2515/0005-6)
Alfentanil 5 mg/ml solution for injection (25215/0006):

Patient information leaflet

Read all of this leaflet carefully because it will provide you with important information about your medicine. Please read it carefully before your medicine is administered. If, after reading it, you still have some queries, please consult your doctor or pharmacist. Keep this leaflet, you may need to read it again.

Alfentanil 5 mg/ml solution for injection

What is in your medicine?
Alfentanil 5 mg/ml is a clear and sterile solution for injection contained in clear glass ampoules. Each 1 ml of this solution contains 5.0 mg of the active substance alfentanil.

Other ingredients:
The solution also contains sodium chloride, sodium hydroxide and water for injections.

Pack sizes:
Alfentanil 5 mg/ml is available in packs of 5 and 10 ampoules containing 1 ml of solution.

PL holder:
hameln pharmaceuticals gmbh
Langes Feld 13, 31789 Hameln, Germany

Manufacturer:
hameln pharmaceuticals gmbh
Langes Feld 13, 31789 Hameln, Germany

Distributor:
hameln pharmaceuticals ltd
Gloucester, United Kingdom

About your medicine:
Alfentanil 5 mg/ml is a potent and short-acting painkiller that is used for surgical procedures.

Before you receive Alfentanil 5 mg/ml solution for injection:
Before taking or receiving any medicine you should ask your doctor or pharmacist for advice. Tell them if you are pregnant, think you might be pregnant or are trying to become pregnant.

You should not be given Alfentanil 5 mg/ml solution for injection:
- if you think you may have had an allergic reaction to Alfentanil 5 mg/ml or to a similar medicine in the past.
- if you suffer from lung or breathing disorder. The doctor can give you Alfentanil 5 mg/ml if your breathing has to be assisted by a ventilator.
- if you are taking or have been taking (within the last two weeks) an antidepressant known as monoamine oxidase inhibitor (MAOI).
- during labour or before clamping of the cord during Caesarean section due to the possibility of breathing difficulties in the baby.

Take special care with Alfentanil 5 mg/ml solution for injection:
Alfentanil 5 mg/ml may cause a drop in blood pressure and breathing rate (incl. respiratory arrest). It may also cause the heart to beat more slowly. Rarely the rhythm of the heart may be altered. Particular care has to be taken following treatment with other medicines which have similar effects. Therefore vital signs as blood pressure and heart rate are monitored during administration of Alfentanil 5 mg/ml. Unwanted effects caused by Alfentanil 5 mg/ml can be reversed by other medicines.

Alfentanil 5 mg/ml will be used with caution if you suffer from lung diseases like respiratory depression, respiratory arrest or potentially compromised respiration because medicines like Alfentanil 5 mg/ml may decrease respiratory drive and increase airway resistance.

If the function of your liver or kidneys is reduced or if you
have been on long term opioids therapy, the doctor will use Alfentanil 5 mg/ml with caution because of the influence of these organs on the amount of medicine in your body.

For elderly, debilitated and obese patients the dosage will be adjusted to their physical condition.

The doctor will be aware that Alfentanil 5 mg/ml may obscure the clinical course if you have head injuries.

Alfentanil 5 mg/ml 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. Your breathing will therefore be carefully monitored until it returns to normal.

Pregnancy and labour/delivery
If you are pregnant or think you may be pregnant, you should inform your doctor. He/she will determine whether or not you should be given Alfentanil 5 mg/ml.

Breast feeding
Alfentanil 5 mg/ml may get into breast milk. It is recommended that you should not breast feed for 28 hours after treatment.

Driving and using machines
Do not drive or operate any machines for 24 hours after being given Alfentanil 5 mg/ml because you may be less alert than usual.

Taking other medicines
Tell your doctor about any medicines that you are taking, or have recently taken, including any you have bought yourself. Fluconazole, a medicine used for the treatment of mycotic infections, cimetidine, a medicine for ulcers, stomach-ache and heartburn; erythromycin, an antibiotic and diltiazem, a medicine used for a certain type of heart disorder, may affect the length of time it takes for the effects of Alfentanil 5 mg/ml to wear off.

Medicines such as 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, e.g. barbiturate) and other strong opioid painkillers will have some of the same effects as Alfentanil 5 mg/ml. When one or more of these medicines is used at the same time as Alfentanil 5 mg/ml, the effects of either may be increased.

It may also be necessary to adjust the dose of Alfentanil 5 mg/ml if you are taking the following: certain medicines for mycotic infections, e.g. ketoconazole, or certain medicines called antiviral protease inhibitors, e.g. ritonavir.

Monoamine oxidase inhibitors (MAOIs), medicines acting as antidepressant drugs, may potentiate the effect of narcotics. It is therefore not recommended to take Alfentanil 5 mg/ml for patients who have received MAO inhibitors within 14 days.

How Alfentanil 5 mg/ml solution for injection will be used:
Alfentanil 5 mg/ml will be diluted and given as an infusion (a drip) into a vein. Your doctor will decide how much Alfentanil 5 mg/ml you need. This will depend on, for example, your body weight, age and general health.

Possible side effects of Alfentanil 5 mg/ml solution for injection:
Like all medicines Alfentanil 5 mg/ml can have side effects. Occasionally, Alfentanil 5 mg/ml may cause side effects such as feeling sick (nausea), headache, vomiting, stiffness of the muscles, pain on the injection site, low blood pressure, itching of the skin, confusion, dizziness and drowsiness. It may also cause your heart or breathing rate deviate from the normal frequency. Additionally, some cases of excitation, urinary retention, visual disturbance and hiccup have been reported. If you notice any side effects not mentioned in this leaflet, please inform your doctor.

How Alfentanil 5 mg/ml solution for injection should be stored:
The doctor will not give you this medicine after the date printed following "Exp. date".

Keep out of the reach and sight of children.

Date of preparation of leaflet: June 2005.
LABELLING

Alfentanil 500 micrograms/ml solution for injection (25215/0005):

1 x 1mg in 2ml ampoule carton:

1 x 1mg in 2ml vial carton:
2 x 1mg in 2ml ampoule carton:

2 x 1mg in 2ml vial carton:
1 x 5mg in 10ml ampoule carton:

1 x 5mg in 10ml vial carton:
2 x 5mg in 10ml ampoule carton:

2 x 5mg in 10ml vial carton:
Alfentanil 5 mg/ml solution for injection (25215/0005):

1 x 1mg in 2ml ampoule carton:

1 x 1mg in 2ml vial carton:
2 x 1mg in 2ml ampoule carton:

MHRA PAR ALFENTANIL 500 MICROGRAMS/ML SOLUTION FOR INJECTION AND ALFENTANIL 5MG/ML SOLUTION FOR INJECTION (PL 25215/0005-6)

2 x 1mg in 2ml vial carton:
1mg in 2ml ampoule carton label:

1mg in 2ml vial carton label:
1x 5mg in 10ml ampoule carton:

1x 5mg in 10ml vial carton:
2 x 5mg in 10ml ampoule carton:

MHRA PAR ALFENTANIL 500 MICROGRAMS/ML SOLUTION FOR INJECTION AND ALFENTANIL 5MG/ML SOLUTION FOR INJECTION (PL 25215/0005-6)