

**ALFENTANIL 500 MICROGRAMS / ML
SOLUTION FOR INJECTION
(ALFENTANIL HYDROCHLORIDE)**

PL 00156/0101

UKPAR

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PL 00156/0101

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Martindale Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Alfentanil 500 micrograms/ml Solution for Injection (PL 00156/0101) on 19th December 2007. This is a controlled drug, available only on special prescription, and is used exclusively for surgical procedures.

Alfentanil 500 micrograms/ml Solution for Injection contains the active ingredient alfentanil, as alfentanil hydrochloride, which belongs to a group of medicines called 'opioid analgesics', used to relieve or prevent pain. Alfentanil is a potent and short-acting painkiller that is used exclusively for surgical procedures.

The proposed product was considered to be a generic version of the reference product Rapifen 0.5mg/ml (PL 00242/0091, Janssen-Cilag Limited).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Alfentanil 500 micrograms/ml Solution for Injection outweigh the risk; hence a Marketing Authorisation has been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Martindale Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Alfentanil 500 micrograms/ml Solution for Injection (PL 00156/0101) on 19th December 2007. The product is a controlled drug, available only on special prescription.

The application was submitted as a national, abridged, complex application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Rapifen 0.5mg/ml (PL 00242/0091), marketed by Janssen-Cilag Limited and authorised on 27 July 1983.

Alfentanil 500 micrograms/ml Solution for Injection is an analgesic supplement for use before and during anaesthesia. It is indicated for use in 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.

The active ingredient, alfentanil, is a synthetic opioid derived from fentanyl. It is a potent μ -receptor agonist opioid with a very rapid onset of, and short lived, action, making it especially suitable for use as an adjunct to anaesthesia in short operative procedures and out-patient surgery, requiring spontaneous respiration. 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. The onset of action and duration of response is shorter than an equi-analgesic dose of fentanyl. The proposed product can be administered intravenously as a bolus injection followed by supplemental doses, or by continuous infusion. If desired, Alfentanil 500 micrograms/ml Solution for Injection can be diluted with sodium chloride injection BP, dextrose solution BP or compound sodium lactate injection BP (Hartmann's solution).

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

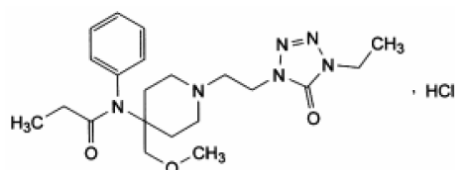
Alfentanil hydrochloride

Nomenclature:

INN: Alfentanil hydrochloride

Chemical name: *NN*-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl)-ethyl]-4-(methoxymethyl) piperidin-4-yl]-*N*-phenylpropanamide hydrochloride

Structure:



Molecular formula: $C_{21}H_{32}N_6O_3 \cdot HCl$

Molecular weight: 453

CAS No: 69049-06-5

Physical form: A white to off-white crystalline powder

Solubility: Freely soluble in water, soluble 1 in 5 of ethanol, 1 in < 2 of chloroform, 1 in < 2 of methanol and practically insoluble in ether

The active substance, alfentanil hydrochloride, is the subject of a European Pharmacopeia monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Confirmation has been provided that the materials used are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided based on the European Pharmacopeia monograph. Satisfactory details have been provided for the compendial and non-compendial test methods.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active alfentanil hydrochloride is stored in appropriate packaging. Specifications and Certificates of Analysis for all packaging components used have been provided. The primary packaging in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the active substance and supports a retest period of 24 months.

DRUG PRODUCT

Description & Composition

The drug product is presented as a clear, colourless solution.

Other ingredients consist of pharmaceutical excipients, namely sodium chloride, hydrochloric acid, and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Impurity profiles

Satisfactory comparative impurity data were presented for the test and reference products. The impurities were within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

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

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on validation batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory and complies with the requirements of the Ph. Eur. monograph. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The drug product is packed in Ph. Eur Type I transparent glass ampoules of size 2ml and 10ml, and Ph. Eur Type I transparent glass vials of size 50ml. The vials are sealed with halobutyl rubber stoppers and aluminium seals. The ampoules are packaged as packs of 10 and the vials are packaged individually, with the product information leaflets, in cardboard outer cartons.

All primary packaging satisfies Directive 2002/72/EC (as amended), and is suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, with storage instructions 'Do not store above 25°C'. This is satisfactory. For storage conditions of the diluted medicinal product, refer to the SPC.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application for a parenteral product.

EXPERT REPORT

The quality overview is written by an appropriately qualified expert and is satisfactory. A satisfactory Curriculum Vitae has been provided for the pharmaceutical expert.

PRODUCT INFORMATION:

Summary of Product Characteristics

The approved SPC is satisfactory.

Patient Information Leaflet

The approved PIL is in line with the final SPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

Conclusion

The proposed product, Alfentanil 500 micrograms/ml Solution for Injection, has been shown to be a generic version of the reference product, Rapifen 0.5mg/ml, with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

The quality grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, complex application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Alfentanil 500 micrograms/ml Solution for Injection is an analgesic supplement for use before and during anaesthesia. It is indicated for:

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

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

CLINICAL PHARMACOLOGY

No new data are submitted and none are required for this type of application.

EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical expert report

Alfentanil 500 micrograms/ml Solution for Injection is to be administered as an intravenous injection and contains the same active substance, in the same concentration, as the currently authorised reference product, Rapifen 0.5mg/ml. Thus, in accordance with the “Note for Guidance on the Investigation of Bioavailability and Bioequivalence”, (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

SAFETY

No new data are submitted and none are required for this type of application. Safety is reviewed in the clinical expert report

EXPERT REPORT

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSION

The grounds for establishing the proposed product as a generic version of the reference product, Rapifen 0.5mg/ml (PL 00242/0091), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. When used as indicated, Alfentanil 500 micrograms/ml Solution for Injection has a favourable benefit-to-risk ratio. Therefore, the grant of a Marketing Authorisation is recommended on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

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

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

The applicant's Alfentanil 500 micrograms/ml Solution for Injection (PL 00156/0101) has been demonstrated to be a generic version of the reference product Rapifen 0.5mg/ml (PL 00242/0091, Janssen-Cilag Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with alfentanil hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation application on 22nd May 2002
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 18th July 2002
- 3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 18th July 2002
- 4 The applicant responded to the MHRA's request, providing further information for the clinical sections on 23rd July 2002
- 5 Following assessment of the application the MHRA requested further information relating to the quality dossier on 20th March 2003, 22nd June 2004, 10th December 2004, 9th January 2007, and 29th August 2007.
- 6 The applicant responded to the MHRA's request, providing further information for the quality sections on 3rd June 2004, 19th August 2004, 28th September 2006, 21st March 2007, and 17th December 2007 respectively
- 7 The application was determined on 19th December 2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Alfentanil 500 micrograms/ml Solution for Injection is as follows:

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 545 micrograms, equivalent to 500 micrograms alfentanil base.

Also contains Sodium Chloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

A clear, colourless solution, free from visible particles.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

As an analgesic supplement for use before and during anaesthesia.

It is indicated for:

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

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For intravenous administration.

Alfentanil 500 micrograms/ml Solution for Injection by the intravenous route can be administered to both adults and children. The dosage of Alfentanil 500 micrograms/ml Solution for 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 as follows:

<i>Adults</i>	<i>Initial</i>	<i>Supplemental</i>
Spontaneous respiration	500 micrograms (1ml)	250 micrograms (0.5ml)
Assisted ventilation	30-50 micrograms / kg	15 micrograms / kg
<i>Children</i>	<i>Initial</i>	<i>Supplemental</i>
Assisted ventilation	30-50 micrograms / kg	15 micrograms / kg

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

Use in children:

Children may require higher or more frequent dosing owing to a shorter half-life of alfentanil in this age group.

Use in elderly and debilitated patients:

Lower or less frequent dosing may be required owing to a longer half-life of alfentanil in this age group (dilution may be helpful).

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

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

In ventilated patients undergoing longer procedures, Alfentanil 500 micrograms/ml Solution for Injection may be infused at a rate of 0.5-1.0 microgram/kg/minute. Adequate plasma concentrations of alfentanil will only be achieved rapidly if this infusion is preceded by a loading dose of 50-100 microgram/kg, given as a bolus or fast infusion over 10 minutes. Even 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. Therefore supplementation of the anaesthetic, if required, for periods of painful stimuli, is best managed by extra bolus doses of Alfentanil 500 micrograms/ml Solution for Injection (1-2ml) or low concentrations of a volatile agent for brief periods.

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

4.3 CONTRAINDICATIONS

Obstructive airways disease or respiratory depression if not ventilating.

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

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

Patients with a known intolerance to alfentanil or other morphinomimetics.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE***Warnings:***

Following administration of Alfentanil 500 micrograms/ml Solution for Injection, a fall in blood pressure may occur. The magnitude of this effect may be exaggerated in the hypovolaemic patient or in the presence of concomitant sedative medication. Appropriate measures to maintain a stable arterial pressure should be taken.

Significant respiratory depression will occur following administration of Alfentanil 500 micrograms/ml Solution for Injection in doses in excess of 1mg and is dose-related. This and the other pharmacological effects of Alfentanil 500 micrograms/ml Solution for Injection are usually of short duration and can be reversed by specific opioid antagonists (e.g. naloxone). Additional doses of the antagonists may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.

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

and blood pressure should therefore be monitored carefully. If hypotension or bradycardia occurs, appropriate measures should be instituted.

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

Precautions:

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

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

Alfentanil 500 micrograms/ml Solution for Injection may induce muscle rigidity during induction. Rigidity, which may also involve the thoracic muscles, can be avoided by the following measures:

- Slow iv injection (usually sufficient for lower doses);
- Premedication with a benzodiazepine;
- Administration of a muscle relaxant just prior to administration of Alfentanil 500 micrograms/ml Solution for Injection

Non-epileptic (myo) clonic movements can occur.

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early post-operative period. Care should be taken after infusions or large doses of alfentanil to ensure that adequate spontaneous breathing has been established and maintained in the absence of stimulation before discharging the patient from the recovery area. Resuscitation equipment and narcotic antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's response to CO₂, thus affecting respiration postoperatively.

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Alfentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. Available human pharmacokinetic data indicate that the metabolism of alfentanil may be inhibited by fluconazole, erythromycin, diltiazem and cimetidine (known cytochrome P450 3A4 enzyme inhibitors). *In vitro* data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may also inhibit the metabolism of alfentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of Alfentanil 500 micrograms/ml Solution for Injection.

Treatment with drugs which may depress the heart or increase vagal tone, such as beta-blockers and anaesthetic agents, may predispose to bradycardia or hypotension. Bradycardia and possibly asystole can occur when Alfentanil 500 micrograms/ml Solution for Injection is combined with non-vagolytic muscle relaxants.

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

If other narcotic or CNS depressant drugs are used concurrently with alfentanil, the effects of the drugs can be expected to be additive. When patients have received such drugs the dose of alfentanil required will be less than usual. Likewise, following the administration of alfentanil, the dose of other CNS depressant drugs should be reduced.

4.6 PREGNANCY AND LACTATION

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

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

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Where early discharge is envisaged patients should be advised not to drive or operate machinery for 24 hours following administration.

4.8 UNDESIRABLE EFFECTS

Adverse events reported in association with Alfentanil 0.5mg/ml Injection use in clinical trials are listed below by decreasing frequency within each body system.

Frequency estimate: Very common >10%; Common >1% to <10%; Uncommon >0.1% to <1%.

Application Site Disorders

Uncommon: Injection site pain

Body as a Whole – General Disorders

Uncommon: Shivering, Allergic reactions (such as anaphylaxis, bronchospasm, urticaria)

Cardiovascular Disorders, General

Common: Hypotension, Hypertension

Central & Peripheral Nervous System Disorders

Common: Muscle rigidity (which may also involve the thoracic muscles), Myoclonic movements, Dizziness

Uncommon: Headache

Gastro-Intestinal System Disorders

Very Common: Nausea, Vomiting

Heart Rate and Rhythm Disorders

Common: Bradycardia, Tachycardia

Uncommon: Arrhythmia

Isolated reports: Asystole

Psychiatric Disorders

Common: Somnolence

Uncommon: Disorientation, Agitation, Euphoria

Respiratory System Disorders

Common: Apnoea, Respiratory depression

Uncommon: Cough, Recurrence of respiratory depression, Laryngospasm, Hiccup

Skin and Appendages Disorders

Uncommon: Pruritus, Sweating

Vision Disorders

Uncommon: Blurred/double vision

4.9 OVERDOSE

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

	<i>Action</i>
Bradycardia	Anticholinergics such as atropine or glycopyrrolate.
Hypoventilation or apnoea	O ₂ administration assisted or controlled respiration and an opioid antagonist may be required.
Muscle rigidity	Intravenous neuromuscular blocking agent may be given.

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

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

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

5 PHARMACOLOGICAL PROPERTIES**5.1 PHARMACODYNAMIC PROPERTIES**

Pharmacotherapeutic group: Analgesics-Narcotics (opiod analgesic)

ATC code: N01AH02 (Alfentanil)

The analgesic potency of alfentanil is one quarter that of fentanyl.

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

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

5.2 PHARMACOKINETIC PROPERTIES

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

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

Plasma protein binding of alfentanil is 92%, mainly due to a strong binding to the 'acute phase' α_1 acid-glycoprotein. It is not bound to the blood cells.

Pharmacokinetics were comparable in rats, dogs and man. In children, alfentanil has been shown to have a much shorter half-life than adults, whereas the elderly show a longer half-life for alfentanil, after IV bolus doses.

5.3 PRECLINICAL SAFETY DATA

Preclinical effects observed were only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium Chloride
Hydrochloric Acid 10%*
Water for Injections
* For pH adjustment only

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

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

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

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

The ampoules and vial are packed in a cardboard carton along with a patient leaflet.

Pack sizes: 10 x 2ml ampoules
 10 x 10ml ampoules
 1 x 50ml vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Alfentanil 500 micrograms/ml Solution for Injection is for single use only. Discard any unused contents.

Alfentanil 500 micrograms/ml Solution for Injection may be diluted with sodium chloride injection BP, dextrose injection BP or compound sodium lactate BP (Hartmann's solution).

Alfentanil 500 micrograms/ml Solution for Injection does not contain any antimicrobial preservative.

From a microbiological point of view, the diluted product 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 not normally be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

7 MARKETING AUTHORISATION HOLDER

MARTINDALE PHARMACEUTICALS LTD.
Bampton Road,
Harold Hill,
Romford,
Essex,
RM3 8UG.
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00156/0101

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/12/2007

10 DATE OF REVISION OF THE TEXT

19/12/2007

PRODUCT INFORMATION LEAFLETS

PATIENT INFORMATION LEAFLET

C91 130

Alfentanil 500 micrograms/ml Solution for Injection

This leaflet is a summary of the information for patients who are given Alfentanil 500 micrograms/ml Solution for Injection. You should ask your doctor or nurse if you are unsure about any aspect of this medication.

What you should know about Alfentanil Injection.

Alfentanil 500 micrograms/ml Solution for Injection contains alfentanil hydrochloride equivalent to 500 micrograms alfentanil base per ml. Also contains Sodium Chloride and Water for Injections. May contain dilute hydrochloric acid. The solution is supplied in clear glass ampoules containing either 1mg of alfentanil base in 2ml or 5mg of alfentanil base in 10ml or in vials containing 25mg of alfentanil base in 50ml. Alfentanil is one of a group of medicines known as opioid analgesics which relieve or prevent pain.

Licence holder: Martindale Pharmaceuticals Ltd.
Bampton Road, Romford, RM3 8UG UK.

Manufacturer: Martindale Pharmaceuticals

Uses

Alfentanil is a potent and short-acting painkiller that is used exclusively for surgical procedures.

Warnings

Before receiving this medicine always inform your doctor if any of the following apply to you:

- If you are taking, or have recently been taking (within the last two weeks), any of the antidepressant drugs known as monoamine oxidase inhibitors (MAOIs).
- If you are allergic to any of the ingredients listed above or any similar medicines. Allergic reactions may include a rash, itching, swollen face or lips, or shortness of breath.
- If you suffer from breathing difficulties.
- If you have problems with liver, kidney, lungs or thyroid gland.
- If you have been using opioid analgesics (e.g. Codeine, Fentanyl, Morphine) for a long period, or if you have a history of opioid abuse (e.g. Heroin).
- If you suffer from alcoholism.

If you are pregnant or breast-feeding your doctor should take this into account before prescribing this product. It is important that he/she is aware of your condition.

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

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 alfentanil 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), drugs for epilepsy (such as Clonazepam or Phenobarbital), and other strong opioid painkillers will have some of the same effects as alfentanil. When one or more of these medicines is used at the same time as alfentanil, the effects of either may be increased.

It may also be necessary to adjust the dose of alfentanil if you are taking the following:

- certain medicines for fungal infections, e.g. Fluconazole, Ketoconazole and Itraconazole;
- certain medicines called antiviral protease inhibitors, e.g. Ritonavir.

You should not drive or operate machinery for 24 hours after being given alfentanil as you may be less alert than usual.

PATIENT INFORMATION LEAFLET (Continued)

Alfentanil 500 micrograms/ml Solution for Injection

Dose

Alfentanil 500 micrograms/ml Solution for Injection should only be given by injection into a vein.

Under some circumstances your doctor may prescribe a dose higher than those stated here.

Adults

The dosage should be individualised according to age, bodyweight, general health, underlying disease, use of other drugs and type of surgery and anaesthesia.

The Elderly and Debilitated Patients

A lower or less frequent dose may be required.

Children

Children may require higher or more frequent dosing. The dose will be dependant on their weight.

Side Effects

Side effects that may occur include breathing difficulties, apnoea (stop in breathing) hypotension (low blood pressure), hypertension (high blood pressure), bradycardia (slowing of the heart rate) tachycardia (increased heart rate), and somnolence (sleepiness). Nausea (feeling sick), vomiting and dizziness may be experienced.

In patients receiving large doses of Alfentanil 500 micrograms/ml Solution for Injection, myoclonic movements (muscle jerks) and muscle rigidity (possibly involving the thoracic (chest) muscles) have rarely been reported shortly after the administration of Alfentanil 500 micrograms/ml Solution for Injection.

Other reported adverse reactions are laryngospasm (a spasm of the throat causing difficulty in breathing), slight transient hypotension (drop in blood pressure), allergic reactions (such as anaphylaxis (shock), bronchospasm (shortness of breath) and urticaria (hives)), asystole (stop in heart beat) and arrhythmias (irregular heart beat).

Uncommon side effects include: injection site pain, shivering, headache, disorientation, agitation (restlessness with anxiety), euphoria (feeling of well-being), cough, hiccups, pruritus (itching), sweating, and blurred/double vision.

If you have any of these or any other unwanted effects not listed here, report them to your doctor.

This product has an expiry date on the carton and bottle label. The doctor or nurse will check that the product has not passed this date. This product will be stored below 25°C and protected from light.

Keep out of the reach and sight of children.

Product licence number: PL 0156/0101

Prepared: January 2007

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Pharmaceuticals 
Bampton Road, Harold Hill, Romford,
Essex RM3 8UG, UK.

TECHNICAL LEAFLET

Alfentanil 500 micrograms/ml Solution for Injection

Alfentanil 500 micrograms/ml Solution for Injection contains alfentanil hydrochloride equivalent to 500 micrograms alfentanil base per ml. The solution is supplied in clear glass ampoules containing either 1mg of alfentanil base in 2ml or 5mg of alfentanil base in 10ml or in vials containing 25mg of alfentanil base in 50ml.

Clinical Particulars

Therapeutic Indications: As an analgesic supplement for use before and during anaesthesia. It is indicated for:

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

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

Posology and Method of Administration: For intravenous administration Alfentanil 500 micrograms/ml Solution for Injection by the intravenous route can be administered to both adults and children. The dosage of Alfentanil 500 micrograms/ml Solution for 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 as follows:

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

If desired, Alfentanil 500 micrograms/ml Solution for Injection can be mixed with Sodium Chloride Injection BP, Dextrose Injection BP or Compound Sodium Lactate Injection BP (Hartmann's solution). Such dilutions are compatible with plastic bags and giving sets. These dilutions should be used within 24 hours of preparation.

Use in children: Children may require higher or more frequent dosing owing to a shorter half-life of alfentanil in this age group.

Use in elderly and debilitated patients: Lower or less frequent dosing may be required owing to a longer half-life of alfentanil (dilution may be helpful).

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

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

In ventilated patients undergoing longer procedures, alfentanil may be infused at a rate of 0.5 - 1.0 micrograms/kg/minute. Adequate plasma concentrations of alfentanil will only be achieved rapidly if this infusion is preceded by a loading dose of 50-100 micrograms/kg given as a bolus or fast infusion over 10 minutes. Even 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. Therefore supplementation of the anaesthetic, if required, is best managed by extra bolus doses of Alfentanil 500 micrograms/ml Solution for Injection (1-2ml) or low concentrations of a volatile agent for brief periods.

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

Contra-indications

- Obstructive airways disease or respiratory depression if not ventilating.
- Concurrent administration with monoamine oxidase inhibitors or within 2 weeks of their discontinuation.
- Administration in labour or before clamping of the cord during Caesarean section due to the possibility of respiratory depression in the new-born infant.
- Patients with a known intolerance to alfentanil or other morphinomimetics.

Special warnings and precautions for use**Warnings:**

Following administration of Alfentanil 500 micrograms/ml Solution for Injection, a transient fall in blood pressure may occur. The magnitude of this effect may be exaggerated in the hypovolaemic patient or in the presence of concomitant sedative medication. Appropriate measures to maintain a stable arterial pressure should be taken.

Significant respiratory depression will occur following administration of Alfentanil 500 micrograms/ml Solution for Injection in doses in excess of 1mg and is dose related. This and the other pharmacological effects of Alfentanil 500 micrograms/ml Solution for Injection are usually of short duration and can be reversed by specific opioid antagonists (e.g. Naloxone). Additional doses of the antagonists may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.

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

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

Precautions:

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

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

Alfentanil 500 micrograms/ml Solution for Injection may induce muscle rigidity during induction. Rigidity, which may also involve the thoracic muscles, can be avoided by the following measures:

- Slow iv injection (usually sufficient for lower doses);
- Pre-medication with a benzodiazepine;
- Administration of a muscle relaxant just prior to administration of Alfentanil 500 micrograms/ml Solution for Injection.

Non-epileptic myoclonic movements can occur.

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

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

Interactions with other medical products and other forms of interaction:

Alfentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. Available human pharmacokinetic data indicate that the metabolism of alfentanil may be inhibited by Rifampicin, Erythromycin, Diltiazem and Cimetidine (known cytochrome P450 3A4 enzyme inhibitors).

In vitro data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. Ketoconazole, Itraconazole, Ritonavir) may also inhibit the metabolism of alfentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of Alfentanil 500 micrograms/ml Solution for Injection.

Treatment with drugs that may depress the heart or increase vagal tone, such as beta-blockers and anaesthetic agents, may predispose to bradycardia or hypotension. Bradycardia and possibly asystole can occur when Alfentanil 500 micrograms/ml Solution for Injection is combined with non-vagolytic muscle relaxants.

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

If other narcotic or CNS depressant drugs are used concurrently with alfentanil, the effects of the drugs can be expected to be additive. When patients have received such drugs the dose of alfentanil required will be less than usual. Likewise, following the administration of alfentanil, the dose of other CNS depressant drugs should be reduced.

TECHNICAL LEAFLET (Continued)

Pregnancy and Lactation: Although no teratogenic or acute embryotoxic effects have been observed in animal experiments, insufficient data are available to evaluate any harmful effects in man.

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

Intravenous administration during childbirth (including caesarean section) is not recommended, because alfentanil crosses the placenta and because the foetal respiratory centre is particularly sensitive to opiates. If, however, Alfentanil 500 micrograms/ml Solution for Injection is administered, an antidote should always be at hand for the child.

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

Effects on the Ability to Drive and Use Machines: Where early discharge is envisaged, patients should be advised not to drive or operate machinery for 24 hours following administration.

Other Undesirable Effects: Adverse events reported in association with Alfentanil 0.5mg/ml injection use in clinical trials are listed below by decreasing frequency within each body system.

Frequency estimate: Very common >10%; Common >1% to <10%; Uncommon <0.1% to <1%.

Application Site Disorders

Uncommon: injection site pain

Body as a Whole – General Disorders

Uncommon: shivering, allergic reactions (such as anaphylaxis, bronchospasm, urticaria)

Cardiovascular Disorders, General

Common: hypotension, hypertension

Central & Peripheral Nervous System Disorders

Common: muscle rigidity (which may also involve the thoracic muscles), myoclonic movements, dizziness
Uncommon: headache

Gastro-Intestinal System Disorders

Very Common: nausea, vomiting

Heart Rate and Rhythm Disorders

Common: bradycardia, tachycardia
Uncommon: arrhythmia
Isolated reports: asystole

Psychiatric Disorders

Common: somnolence
Uncommon: disorientation, agitation, euphoria

Respiratory System Disorders

Common: apnoea, respiratory depression
Uncommon: cough, recurrence of respiratory depression, laryngospasm, hiccup

Skin and Appendages Disorders

Uncommon: pruritus, sweating

Vision Disorders

Uncommon: blurred/double vision

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

Bradycardia: Anticholinergics such as atropine or glycopyrrolate;
Hypoventilation or apnoea: Oxygen administration, assisted or controlled respiration and an opioid antagonist may be required;
Muscle rigidity: Intravenous neuromuscular blocking agent may be given.

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

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

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties: Pharmacotherapeutic group: Analgesics-Narcotics (opioid analgesic), ATC code: N01AH02 (alfentanil)

The analgesic potency of Alfentanil 0.5mg/ml Injection is one quarter that of fentanyl.

The onset of action of Alfentanil 0.5mg/ml Injection is four times more rapid than that of an equianalgesic dose of fentanyl. The peak analgesic and respiratory depressant effects occur within 90 seconds.

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

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

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

Plasma protein binding of alfentanil is 92%, mainly due to a strong binding to the 'acute phase' α 1 acid-glycoprotein. It is not bound to the blood cells.

Pharmacokinetics were comparable in rats, dogs and man. In children, alfentanil has been shown to have a much shorter half-life than adults, whereas the elderly show a longer half-life for alfentanil, after IV bolus doses.

Pharmaceutical Particulars

List of Excipients: Sodium Chloride, Hydrochloric Acid 10%, Water for Injections, (* for pH adjustment only)

Incompatibilities: This medicinal product must not be mixed with other medicinal products except those mentioned below.

Shelf Life: 2 years. From a microbiological point of view, the diluted product 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 be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Special Precautions for Storage: Do not store above 25°C.

Nature and Contents of Container:

Clear Glass (Ph Eur Type 1) ampoules containing 1mg/2ml.
Clear Glass (Ph Eur Type 1) ampoules containing 5mg/10ml.
Clear Glass (Ph Eur Type 1) vials containing 25mg/50ml. The closure of the vial consists of a bromobutyl rubber stopper with an aluminium crimp seal.

The ampoules and vials are packed in a cardboard carton along with a patient information leaflet.

Pack sizes:

10 x 2ml ampoules, 10 x 10ml ampoules, 1 x 50ml vials

Instruction for Use/Handling: Alfentanil 500micrograms/ml Solution for Injection may be diluted with Sodium Chloride Injection BP, Dextrose Injection BP or Compound Lactate BP (Hartmann's Solution).

Alfentanil 500 micrograms/ml Solution for Injection is for single use only. Any unused product or contents or waste material should be disposed of in accordance with local requirements.

Product licence number: PL 0156/0101

Prepared: August 2006

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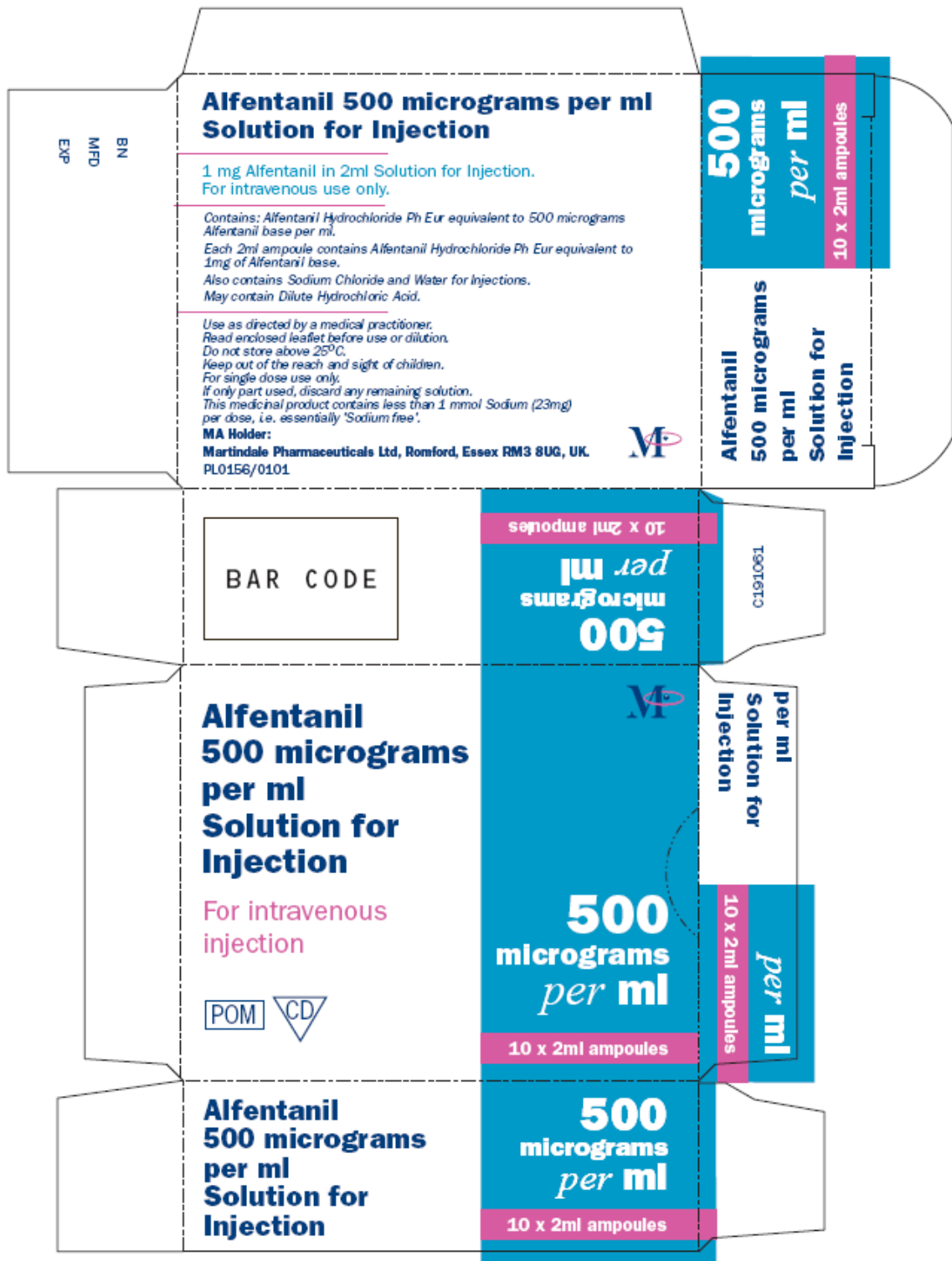
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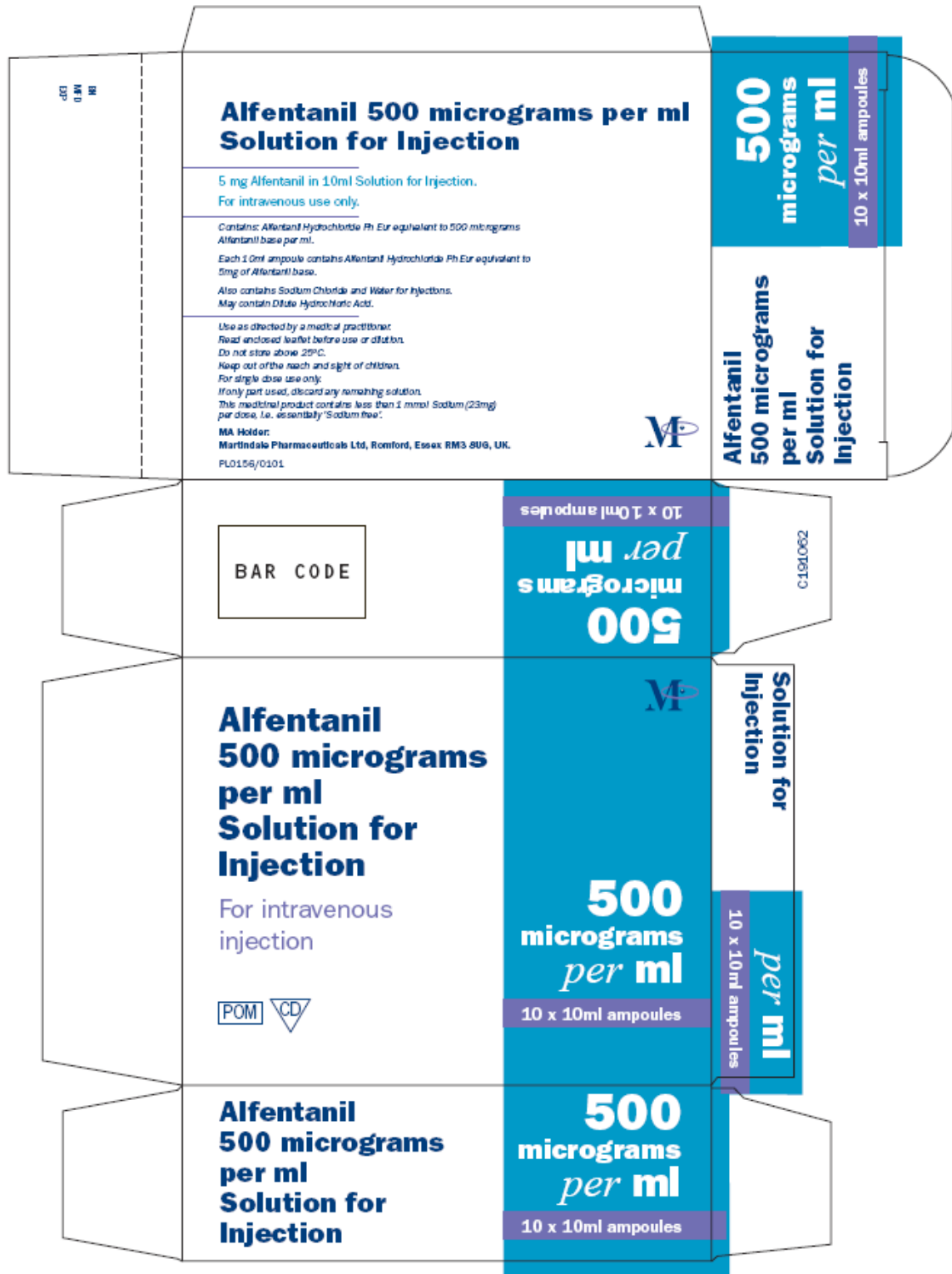
Bampton Road, Harold Hill, Romford,
Essex RM3 8JG, UK.

LABELLING

Carton for 2ml ampoules



Carton for 10ml ampoules



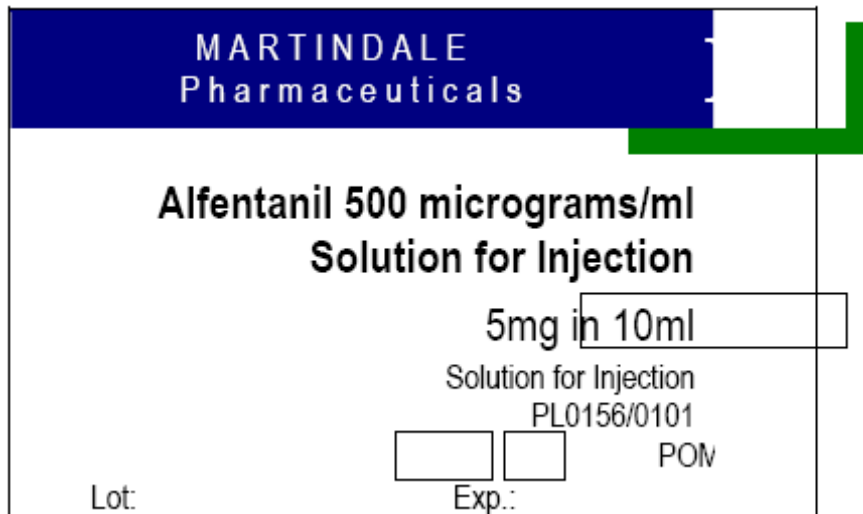
Carton for 50ml vial

<p style="writing-mode: vertical-rl; transform: rotate(180deg);">1x50ml vial</p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);">500 micrograms per ml</p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);">Alfentanil 500 micrograms per ml Solution for Injection</p>	<p>Alfentanil 500 micrograms per ml Solution for Injection</p> <p>25mg Alfentanil in 50ml Solution for Injection. For intravenous use only.</p> <p><i>Use as directed by a medical practitioner. Read enclosed leaflet before use or dilution. Do not store above 25°C. Keep out of the reach and sight of children. For single dose use only. If only part used, discard any remaining solution.</i></p> <p>MA Holder: Martindale Pharmaceuticals Ltd Romford, Essex RM3 8UG, UK. PL0156/0101</p> 	<p>Alfentanil 500 micrograms per ml Solution for Injection</p> <p>POM </p> <p>500 micrograms per ml</p> <p>1x50ml vial</p> 	<p>Alfentanil 500 micrograms per ml Solution for Injection</p> <p>For intravenous injection</p> <p>500 micrograms per ml</p> <p>1x50ml vial</p> 	<p>Alfentanil 500 micrograms per ml Solution for Injection</p> <p><i>Contains: Alfentanil Hydrochloride Ph Eur equivalent to 500 micrograms Alfentanil base per ml.</i></p> <p><i>This 50ml vial contains Alfentanil Hydrochloride Ph Eur equivalent to 25mg of Alfentanil base.</i></p> <p><i>Also contains Sodium Chloride and Water for Injections. May contain Dilute Hydrochloric Acid. This medicinal product contains less than 1 mmol Sodium (23mg) per dose, i.e. essentially 'Sodium free'.</i></p> <div style="border: 1px solid black; padding: 5px; text-align: center;"> <p>BAR CODE</p> </div> <p>C191063</p>
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2ml ampoule label



10ml ampoule label



50ml vial label

