

# NEW ZEALAND DATA SHEET

## 1. NAME OF THE MEDICINE

Alfentanil 500 micrograms/mL

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1mL contains alfentanil hydrochloride hydrate 543.8 micrograms, equivalent to 500 micrograms alfentanil base.

This medicine contains:

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

For a full list of excipients, see **section 6.1**.

## 3. PHARMACEUTICAL FORM

Solution for injection

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

Alfentanil is indicated in adults and children aged above one year for use as:

- an opioid analgesic in general or regional anaesthesia for both short (bolus injections) and long (bolus, supplemented by increments or by continuous infusion) surgical procedures.
- an anaesthetic induction agent.

Due to its rapid and short-lasting action, alfentanil is particularly suited as an opioid analgesic for short procedures and outpatient surgery. It is also useful as an analgesic supplement for procedures of medium and long duration, since periods of very painful stimuli can easily be overcome by small increments of alfentanil or by adapting its infusion rate.

### 4.2. Dose and method of administration

Alfentanil should be administered intravenously. Other routes of administration have not been evaluated. The dosage of alfentanil should be individualised according to age, body weight, physical status, underlying pathological condition, use of other medicines, type of anaesthesia and type and duration of the surgical procedure. As a general principle, the lowest effective dose should be used.

The initial dose should be appropriately reduced in the elderly and in debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

To avoid bradycardia, it is recommended that a small intravenous dose of an anti-cholinergic agent (e.g. atropine), be administered just before induction. Droperidol may be given to prevent nausea and vomiting. However, it is preferable not to administer droperidol to outpatients since it may lengthen their recovery period.

### Use as an induction agent

An intravenous bolus dose of  $\geq 120$  micrograms/kg (17 mL/70 kg) of alfentanil will induce hypnosis and analgesia while maintaining good cardiovascular stability in patients with adequate muscle relaxation.

### For short procedures and use in outpatients

Small doses of alfentanil are suitable for minor, short but painful surgical procedures and for outpatients, provided good monitoring equipment is available.

An intravenous bolus dose of 7 to 15 micrograms/kg (1 to 2 mL/70 kg) will suffice for procedures lasting less than 10 minutes. Should the duration of the procedure exceed 10 minutes, further increments of 7 to 15 micrograms/kg (1 to 2 mL/70 kg) should be given every 10 to 15 minutes or as required.

Spontaneous respiration may be maintained in most instances with a dose of 7 micrograms/kg (1 mL/70 kg) or less, slowly injected. Suggested increments with this technique are 3.5 micrograms/kg (0.5 mL/70 kg).

It is preferable not to administer droperidol or benzodiazepines to outpatients as these medicines may lengthen the recovery period (see section **4.5 Interactions with other medicines and other forms of interaction**). In outpatients, the use of an anticholinergic agent, a short-acting induction hypnotic, alfentanil and N<sub>2</sub>O/O<sub>2</sub> is a preferred technique.

When post-operative nausea occurs, it is of relatively short duration and easily controlled by conventional measures.

### For procedures of medium duration

The initial intravenous bolus dose should be adapted to the expected duration of the surgical procedure as follows:

Duration of the Procedure (minutes)	ALFENTANIL I.V. bolus dose	
	micrograms/kg	mL/70 kg
10-30	20-40	3-6
30-60	40-80	6-12
>60	80-150	12-20

Continuous infusion is preferred for procedures of more than 60 minutes duration.

When surgery is prolonged or more traumatic, analgesia can be maintained by either of the following:

- increments of 15 micrograms/kg (2 mL/70 kg) of alfentanil when required. To avoid postoperative respiratory depression, the last dose of alfentanil should not be administered within the last 10 minutes of surgery, or
- infusion of alfentanil at a rate of 1 micrograms/kg/minute (0.14 mL/70 kg/minute) until 5 to 10 minutes before the completion of surgery.

Periods of very painful stimuli can be easily overcome by small increments of alfentanil or by temporarily increasing the infusion rate. When alfentanil is used without N<sub>2</sub>O/O<sub>2</sub> or other inhalation anaesthetic agents, the maintenance dose of alfentanil should be increased.

Alfentanil may be administered as an infusion for more prolonged procedures with the following infusion solutions:

- 0.9% sodium chloride injection
- 5.0% glucose injection
- compound sodium lactate intravenous injection (Ringer Lactate Injection)

**WARNING:** The prepared infusion should commence as soon as possible after its preparation and within 24 hours of preparation. Any storage of the prepared solution should be at 2 - 8°C. Alfentanil must not be mixed with any products other than those listed above.

#### **For long procedures**

Alfentanil may be used as the analgesic component of anaesthesia for long lasting surgical procedures, especially when rapid extubation is indicated. Optimum analgesia and stable autonomic condition are maintained through an individually adapted initial intravenous dose, and by adjusting the infusion rate to the severity of the surgical stimuli and the reactions of patients.

#### **Special populations**

##### ***Paediatric Use***

The safety of alfentanil in children younger than one year has not been established. The usual children's dose of alfentanil is identical to that used in adults, however, some cases may require a higher or more frequent dosing due to alfentanil having a shorter half-life in children.

##### ***Elderly and debilitated patients***

The initial dose should be appropriately reduced in the elderly (>65 years of age) and in debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

#### **4.3. Contraindications**

Alfentanil is contraindicated in those with a known intolerance or sensitivity to alfentanil, or to other opioid analgesics.

#### **4.4. Special warnings and precautions for use**

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

An opioid antagonist, oxygen, and resuscitative and intubation equipment should be readily available. Due to the possibility of delayed respiratory depression, monitoring of the patient must continue until well after surgery in an approved recovery facility.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Alfentanil 500 micrograms/mL, with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see Section 4.5 **Interactions with other medicines and other forms of interaction**].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Alfentanil 500 micrograms/mL is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see Section 4.5 **Interactions with other medicines and other forms of interaction**].

### **Respiratory Depression**

As with other potent opioids, profound analgesia is accompanied by marked respiratory depression and loss of consciousness, which can persist or recur in the post-operative period. Respiratory depression is dose related, and can be reversed by specific opioid antagonists such as naloxone. Naloxone administration may need to be repeated because the respiratory depression may last longer than the duration of action of the opioid antagonist. Recovery room staff should be aware that marked respiratory depression has been reported as occurring after periods of up to several hours after the patient has been perceived to be alert, conversing coherently, and with normal respiration. For this reason patients should remain under appropriate surveillance. Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's responses to CO<sub>2</sub>, thus affecting respiration postoperatively.

### **Tolerance and Opioid Use Disorder (abuse and dependence)**

Tolerance, physical, and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids. Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

### **Neonatal Withdrawal Syndrome**

If women take opioids chronically during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome. Neonates exposed to opioids chronically may also experience neonatal withdrawal syndrome (see **Pregnancy**).

### **Muscle Rigidity**

Induction of muscle rigidity, which may also involve the thoracic muscles can occur, but can be avoided by the following measures:

- slow intravenous injection, especially when higher doses are indicated
- premedication with benzodiazepines
- administration of muscle relaxants prior to a dose of alfentanil.

Non-epileptic (myo)clonic movements can occur.

### **Cardiac Effects**

Bradycardia and possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic agent, or when alfentanil is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.

Opioids may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

### **Use in Patients with Compromised Intracerebral Compliance**

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

### **Use in the Elderly**

It is recommended that the dose of alfentanil be reduced in the elderly, because of reduced clearance. The dosage should be individualised based on clinical response.

### **Use in Hepatic or Renal Impairment**

It is recommended that the dose of alfentanil be reduced in those patients with chronic liver or kidney disease, because of decreased plasma protein concentrations and reduced clearance. Due to the variable pharmacokinetics and pharmacodynamics, the dosage should be titrated individually and adjusted on the basis of the clinical response.

### **Use in Hypothyroidism**

It is recommended that the dose of alfentanil be reduced in those patients with hypothyroidism, because of reduced clearance. The dosage should be individualised based on clinical response.

### **Others**

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

Opioids should be titrated with caution in those with any of the following conditions: pulmonary disease, decreased respiratory reserve and alcoholism. Such patients also require prolonged post-operative monitoring.

**As is the case with any opioid analgesic, alfentanil should not be used in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have head injury or brain tumour.**

### **Opioid Induced Hyperalgesia**

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid, particularly at high doses or with chronic use, in which there is an increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. OIH may manifest as increased levels of pain, more generalized pain (i.e., less focal), or pain from ordinary (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. When OIH is suspected, the dose of opioids should be reduced or tapered off, if possible.

#### 4.5. Interactions with other medicines and other forms of interaction

##### Anaesthetic Agents

As with other opioids, the respiratory depressant and cardiovascular depressant effects of alfentanil may be potentiated by halogenated inhalation agents such as propofol. When patients have received such agents, the dose of alfentanil required will be less than usual.

##### Central Nervous System (CNS) depressants

Medicines such as barbiturates, benzodiazepines or related drugs, phenothiazine derivatives, neuroleptics, general anaesthetics, and other non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depressant and cardiovascular depressant effects of opioids. When patients have received such CNS depressants, the dose of alfentanil required will be less than usual. Concomitant use with alfentanil in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death (see **Special warnings and precautions for use**). The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

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

##### Cytochrome P450 3A4 (CYP3A4) inhibitors

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

##### Monoamine Oxidase Inhibitors (MAOI)

As monoamine oxidase inhibitors have been reported to potentiate the effects of opioid analgesics, the use of alfentanil in patients who have received MAO inhibitors within two weeks should be avoided.

##### Effect of Alfentanil on the Metabolism of Other Medicines

In combination with alfentanil, the blood concentrations of propofol are 17% higher than in the absence of alfentanil. The concomitant use of alfentanil and propofol may require a lower dose of alfentanil.

<b>Benzodiazepines and other Central Nervous System (CNS) Depressants</b>	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see <b>Section 4.4 Warnings and Precautions</b> ].

Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, drugs with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol.
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#### 4.6. Fertility, pregnancy and lactation

##### Pregnancy

The intravenous use of opioid analgesics during labour (including caesarean section) can cause respiratory depression in the newborn infant since alfentanil crosses the placenta. Therefore, alfentanil should only be used during labour after weighing the needs of the mother against the risk to the foetus. If alfentanil is administered, assisted ventilation equipment must be immediately available for use if required for the mother and infant. An opioid antagonist for the child must always be available. The half-life of the opioid antagonist may be shorter than the half-life of alfentanil, therefore, repeated administration of the opioid antagonist may be necessary.

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 the possible risks and potential advantages before administering this medicine to pregnant patients.

Chronic use of an opioid during pregnancy may cause drug dependence in the neonate, leading to neonatal withdrawal syndrome. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome.

##### Breastfeeding

Alfentanil may be excreted in human milk. Therefore, breastfeeding or use of expressed breast milk is not recommended during the 24 hours following the administration of alfentanil.

#### 4.7. Effects on ability to drive and use of machines

Driving and the operation of machines can be resumed when sufficient time has elapsed following administration of alfentanil. Individual reactions vary greatly. It is recommended that patients not drive or use machines for at least 24 hours after administration of alfentanil.

#### 4.8. Undesirable effects

##### Clinical Trial Data

The safety of alfentanil was evaluated in 1157 subjects who participated in 18 clinical trials. Alfentanil was administered as an anaesthetic induction agent or as an analgesic/anaesthesia adjuvant to regional and general anaesthesia, in short, medium, and long surgical procedures. These subjects took at least one dose of alfentanil and provided safety data. Adverse Drug Reactions (ADRs) that were reported for  $\geq 1\%$  of alfentanil-treated subjects in these trials are shown in Table 1.

**Table 1. Adverse Drug Reactions Reported by  $\geq 1\%$  of alfentanil -treated Subjects in 18 Clinical Trials**

System / Organ Class Adverse Reaction	Alfentanil (n=1157) %
Psychiatric Disorders Euphoric mood	1.8
Nervous System Disorders Movement disorder	7.9

Dizziness	2.4
Sedation	1.5
Dyskinesia	1.4
<b>Eye Disorders</b>	
Visual disturbance	1.1
<b>Cardiac Disorders</b>	
Bradycardia	5.4
Tachycardia	1.0
<b>Vascular Disorders</b>	
Hypotension	4.1
Hypertension	2.2
Blood pressure decreased	1.3
Blood pressure increased	1.0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	
Apnoea	8.6
<b>Gastrointestinal Disorders</b>	
Nausea	17.0
Vomiting	14.0
<b>Musculoskeletal and Connective Tissue Disorders</b>	
Muscle rigidity	3.1
<b>General Disorders and Administration Site Conditions</b>	
Fatigue	2.0
Chills	1.8
Injection site pain	1.6
<b>Injury, Poisoning, and Procedural Complications</b>	
Procedural pain	1.1

Additional ADRs that occurred in <1% of alfentanil -treated subjects in the 18 clinical trials are listed below in Table 2.

**Table 2. Adverse Drug Reactions Reported by <1% of alfentanil -treated Subjects in 18 Clinical Trials**

<b>System / Organ Class</b>
Adverse Reaction
<b>Psychiatric Disorders</b>
Agitation
Crying
<b>Nervous System Disorders</b>
Headache
Somnolence
Unresponsive to stimuli
<b>Cardiac Disorders</b>
Arrhythmia
Heart rate decreased
<b>Vascular Disorders</b>

Vein pain
<b>Respiratory, Thoracic and Mediastinal Disorders</b> Bronchospasm Hiccups Hypercapnia Laryngospasm Epistaxis Respiratory depression
<b>Skin and Subcutaneous Tissue Disorders</b> Dermatitis allergic Hyperhidrosis Pruritus
<b>General Disorders and Administration Site Conditions</b> Pain
<b>Injury, Poisoning, and Procedural Complications</b> Confusion postoperative Agitation postoperative Airway complication of anaesthesia Anaesthetic complication neurological Procedural complication Endotracheal intubation complication

**Post-marketing Data**

Adverse drug reactions first identified during post-marketing experience with alfentanil are included in Table 3. The frequencies are provided according to the following convention:

- Very common  $\geq 1/10$
- Common  $\geq 1/100$  and  $< 1/10$
- Uncommon  $\geq 1/1,000$  and  $< 1/100$
- Rare  $\geq 1/10,000$ ,  $< 1/1,000$
- Very rare  $< 1/10,000$ , including isolated reports

In Table 3, ADRs are presented by frequency category based on spontaneous reporting rates.

**Table 3. Adverse Drug Reactions Identified During Post-Marketing Experience with alfentanil by Frequency Category Estimated from Spontaneous Reporting Rates**

<b>Immune System Disorders</b>	
<i>Very rare</i>	Hypersensitivity (including anaphylactic reaction, anaphylactoid reaction, and urticaria)
<b>Psychiatric Disorders</b>	
<i>Very rare</i>	Disorientation
<b>Nervous System Disorders</b>	
<i>Very rare</i>	Loss of consciousness <sup>a</sup> , Convulsion, Myoclonus
<b>Eye Disorders</b>	
<i>Very rare</i>	Miosis
<b>Cardiac Disorders</b>	
<i>Very rare</i>	Cardiac arrest

<b>Respiratory, Thoracic and Mediastinal Disorders</b>	
<i>Very rare</i>	Respiratory arrest, Respiratory depression <sup>b</sup> , Cough
<b>Skin and Subcutaneous Tissue Disorders</b>	
<i>Very rare</i>	Erythema, Rash
<b>General Disorders and Administration Site Conditions</b>	
<i>Very rare</i>	Pyrexia

<sup>a</sup> Postoperative period.

<sup>b</sup> Including fatal outcome.

Although it is unlikely, alfentanil could cause opioid dependence, and has the potential for being abused. See also **Section 4.4 Special warnings and precautions for use**.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://pophealth.my.site.com/carmreportnz/s/>

## **4.9. Overdose**

### **Signs and Symptoms**

The manifestations of alfentanil overdose are an extension of its pharmacological actions. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnoea to apnoea.

### **Treatment**

In the presence of hypoventilation or apnoea, oxygen should be administered, and respiration should be assisted or controlled as indicated. A specific opioid antagonist, such as naloxone, should be used as indicated to control respiratory depression. This does not preclude the use of more immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist, therefore, additional doses of the latter may be required.

If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent may be required to facilitate assisted or controlled respiration.

The patient should be carefully observed, body warmth and adequate fluid intake should be maintained. If hypotension is severe or if it persists, the possibility of hypovolaemia should be considered, and if present, it should be controlled with appropriate parenteral fluid administration.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: opioid anaesthetics, ATC Code: N01AH02

## **Mechanism of action**

Alfentanil is a potent, short acting, opioid analgesic chemically related to fentanyl.

The onset of action of alfentanil is more rapid than that of an equianalgesic dose of fentanyl and the maximal analgesic and respiratory depressant effect occurs within 1 to 2 minutes.

The duration of action of alfentanil is shorter than that of an equianalgesic dose of fentanyl, and is dose-related. For analgesia lasting longer than 60 minutes, an infusion is preferable.

The depressant effect of alfentanil on respiratory rate and alveolar ventilation lasts for a shorter time than that of fentanyl. In most cases, the duration of analgesia exceeds that of the respiratory depression. The duration and degree of respiratory depression tend to be dose-related.

At higher doses (>120 micrograms/kg), alfentanil can be used as an anaesthetic induction agent. The induction is smooth, pain-free and devoid of cardiovascular and hormonal stress responses to intubation.

The safety margin of alfentanil is comparatively better than that of other opioid analgesics. In rats, the ratio of LD<sub>50</sub>/ED<sub>50</sub> for the lowest level of analgesia for alfentanil is 1080 compared with 4.6, 69.5 and 277 for pethidine, morphine and fentanyl, respectively.

Depending upon the dose and speed of administration, alfentanil can cause muscle rigidity, as well as euphoria, miosis and bradycardia, which is common with other opioid analgesics.

At doses up to 200 micrograms/kg, alfentanil failed to produce a significant increase in histamine levels or any clinical evidence of histamine release.

Recovery after alfentanil administration is rapid and smooth, with a low incidence of post-operative nausea and vomiting.

A specific opioid antagonist, such as naloxone immediately and completely reverses all actions of alfentanil.

## **5.2. Pharmacokinetic properties**

Alfentanil is a synthetic opioid with  $\mu$ -agonist pharmacologic effects, used only intravenously.

### **Distribution**

The sequential distribution half-lives of alfentanil are 0.4 - 2.2 minutes and 8 - 32 minutes, Plasma protein binding of alfentanil is about 92%. This and the low degree of ionisation (11% at pH = 7.4), contributes to a rapid but limited tissue distribution. Reported volumes of distribution are 1.27 - 4.81 L (volume of distribution of the central compartment) and 12.1 - 98.2 L (volume of distribution at steady state).

### **Metabolism**

Alfentanil is metabolised mainly by the liver with only 1% of the active substance found unaltered in the urine. The metabolites are inactive and 70% to 80% of the metabolites are eliminated via the urine.

### **Elimination**

Alfentanil is rapidly eliminated after intravenous administration. Terminal elimination half-lives of 83-223 min have been reported. The plasma clearance in young subjects averages 356 mL/min, and decreases with age. Only 1% of unchanged alfentanil is found in urine. Once steady state has been reached after infusion, the elimination half-life remains unaltered.

Patient recovery (i.e. return to consciousness) generally occurs rapidly on discontinuation of alfentanil.

## Special Populations

### *Paediatrics*

Protein binding in newborns is 75% and increases in children to 85%. The plasma clearance in newborns is approximately  $7.2 \pm 3.2$  mL/kg/min and  $4.7 \pm 1.7$  mL/kg/min in children between 4.5 to 7.75 years. The volume of distribution at steady state was  $1230 \pm 520$  mL/kg in newborns and  $163.5 \pm 110$  mL/kg in children. The half-life is  $146 \pm 57$  minutes in newborns and  $40.2 \pm 8.9$  minutes in children.

### *Hepatic Impairment*

After administration of a single intravenous dose of 50 µg/kg, the terminal half-life in cirrhotic patients is significantly longer than in controls. The volume of distribution remains unchanged. The free fraction of alfentanil increases in cirrhotic patients to 18.5% compared with 11.5% in controls. This increase in free fraction together with a reduction in clearance from 3.06 mL/min/kg in controls to 1.60 mL/min/kg in cirrhotic patients will result in a more prolonged and pronounced effect (see **Section 4.4 Special warnings and precautions for use**).

### *Renal Impairment*

The volume of distribution and clearance of the free fraction is similar in renal failure patients and healthy controls. The free fraction of alfentanil in patients with renal failure is increased to 12.4 to 19 % compared with 10.3 to 11% in controls. This may result in an increase in clinical effect of alfentanil (see **Section 4.4 Special warnings and precautions for use**).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Sodium chloride  
Hydrochloric acid  
Water for injection

### 6.2. Incompatibilities

Alfentanil must not be mixed with products other than those listed under **Section 4.2 Dose and method of administration**.

### 6.3. Shelf Life

Shelf life before first opening:

3 years.

#### Shelf-life after dilution:

Chemical and physical in-use stability of the dilutions has been demonstrated for 48 hours.

From a microbiological point of view, the dilutions should be used immediately.

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

Shelf-life after first opening:

The product should be used immediately after opening.

**6.4. Special precautions for storage**

Stored below 25°C.

Any storage of the prepared solution should be at 2 - 8°C.

**6.5. Nature and contents of container**

Colourless glass ampoules.

Alfentanil 500 micrograms/mL, 1 mg in 2 ml: Packs of 10 ampoules.

Alfentanil 500 micrograms/mL, 5 mg in 10ml: Packs of 5 ampoules.

Not all pack sizes may be marketed.

**6.6. Special precautions for disposal and other handling**

Wear gloves while opening ampoule.

Accidental dermal exposure should be treated by rinsing the affected area with water. Avoid usage of soap, alcohol, and other cleaning materials that may cause chemical or physical abrasions to the skin.

**7. MEDICINE SCHEDULE**

Class B3 Controlled Drug

**8. SPONSOR**

Max Health Ltd  
PO Box 44452  
Pt Chevalier, Auckland 1246  
Telephone: (09) 815 2664

**9. DATE OF FIRST APPROVAL**

03 April 2014

**10. DATE OF REVISION OF THE TEXT**

10 September 2025

**SUMMARY TABLE OF CHANGES**

Section changed	Summary of new information
2	<ul style="list-style-type: none"><li>Relocation of sodium content from section 4.4</li></ul>
4.4	<ul style="list-style-type: none"><li>Addition of Tolerance and Opioid Use Disorder</li><li>Addition of Neonatal Withdrawal</li></ul>

	<ul style="list-style-type: none"> <li>• Addition of Opioid Induced Hyperalgesia</li> <li>• Addition of wording about non-epileptic (myo)clonic movements.</li> </ul>
4.5	<ul style="list-style-type: none"> <li>• Addition of statement about concomitant use of gabapentinoids.</li> </ul>
4.6	<ul style="list-style-type: none"> <li>• Addition of statement about chronic use of opioid during pregnancy.</li> </ul>
4.7	<ul style="list-style-type: none"> <li>• Revised wording.</li> </ul>
4.8	<ul style="list-style-type: none"> <li>• Addition of 'Reporting of suspected adverse reactions' statement.</li> </ul>
4.9	<ul style="list-style-type: none"> <li>• Additional wording 'risk assessment'.</li> </ul>