

PRODUCT MONOGRAPH

**NALFENTA\***

Alfentanil Hydrochloride Injection, USP

Opioid Analgesic  
Adjunct to Anaesthesia

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## PRODUCT MONOGRAPH

**<sup>N</sup>ALFENTA\***

Alfentanil Hydrochloride Injection, USP

Opioid Analgesic  
Adjunct to Anaesthesia**CLINICAL PHARMACOLOGY**

ALFENTA alfentanil hydrochloride injection is a potent opioid analgesic/anaesthetic with a rapid onset and short duration of action. The analgesic potency of alfentanil is 1/4 to 1/3 that of fentanyl. Low to moderate doses of alfentanil in short-stay surgical procedures provide good analgesic protection against haemodynamic responses to surgical stress and rapid recovery. Haemodynamic stability and duration of action increase with increasing dosage. At high doses followed by continuous infusion in general surgery alfentanil provides haemodynamic stability, rapid recovery and a reduced need for postoperative analgesics.

Alfentanil has an immediate onset of action and plasma levels decay according to a 3-compartment model with sequential half-lives of 1 minute for the fast distribution phase, 12 minutes for the redistribution phase and 90 minutes for the terminal elimination phase. Alfentanil is extensively metabolized in the liver and small intestine. Approximately 88% of the administered dose is excreted in the urine within 48 hours with unchanged alfentanil accounting for only 0.2% - 0.5% of the recovered dose. The plasma protein binding of alfentanil is approximately 92%.

The pharmacokinetics of alfentanil are characterized by limited accumulation and extremely rapid elimination from tissue storage sites. The apparent volume of distribution is 0.59-1.0 L/kg and the plasma clearance is 5.1- 7.7 mL/kg/min. This accounts for the rapid recovery seen following IV bolus injection or continuous infusion.

At dosages of 8 µg/kg to 40 µg/kg alfentanil produces analgesia in short-stay surgery. For longer procedures, doses up to 75 µg/kg in intubated patients provide better haemodynamic stability with recovery time comparable to fentanyl. A pre-intubation loading dose of 50-75 µg/kg attenuates the response to laryngoscopy, intubation and incision. Subsequent administration of alfentanil infusion administered at a rate of 0.5-1.5 µg/kg/min with nitrous oxide/oxygen dampens sympathetic responses to surgical stress and maintains haemodynamic stability, providing smooth and rapid postoperative recovery.

At doses of 105-119 µg/kg, alfentanil produces dependable hypnosis; an anaesthetic ED<sub>90</sub> 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.

In one study of patients administered alfentanil with nitrous oxide/oxygen a narrow range of alfentanil plasma concentrations, 312-338 ng/mL, was shown to provide adequate anaesthesia for intra-abdominal surgery, while lower concentrations, approximately 250 ng/mL, blocked responses to abdominal closure. Levels from 100-200 ng/mL provide adequate anaesthesia for superficial surgery.

Attenuation of the catecholamine response with alfentanil infusion was greater than or equal to that seen with a thiopental/enflurane technique.

Patients administered doses of up to 200 µg/kg of alfentanil have shown no elevation in plasma histamine levels and no indication of histamine release.

### **INDICATIONS AND CLINICAL USE**

ALFENTA alfentanil hydrochloride is indicated:

#### **For Surgical Patients**

- As an analgesic adjunct to a barbiturate induction agent during short procedures.
- As an analgesic adjunct to barbiturate/nitrous oxide/oxygen anaesthesia when given in incremental doses for the maintenance of anaesthesia at dosages of 5-75 µg/kg in surgical procedures with an expected duration of up to one hour.
- As an analgesic adjunct given as a continuous infusion at a rate of 0.5 to 1.5 µg/kg/min with nitrous oxide/oxygen in the maintenance of general anaesthesia (see WARNINGS and PRECAUTIONS).

**For Mechanically Ventilated Patients in the Intensive Care Unit**

- As an analgesic and suppressant of respiratory drive, to aid compliance with the ventilator and to facilitate toleration of the endotracheal tube, when given as a continuous infusion.
- As an additional analgesic during brief painful procedures, when given in bolus doses to supplement continuous infusion.

**CONTRAINDICATIONS**

ALFENTA alfentanil hydrochloride is contraindicated in patients with known hypersensitivity to the drug or to other morphinomimetics.

**WARNINGS**

AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED ALFENTA ALFENTANIL HYDROCHLORIDE SHOULD HAVE APPROPRIATE SURVEILLANCE. RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

**INTENSIVE CARE PATIENTS:** ALFENTA ALFENTANIL HYDROCHLORIDE SHOULD NOT BE USED IN SPONTANEOUSLY BREATHING PATIENTS IN THE INTENSIVE CARE UNIT.

ALFENTA alfentanil hydrochloride, even at the low doses used in the Intensive Care Unit, may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscular rigidity is related to dose and speed of administration of alfentanil, and may involve all skeletal muscles including those of the head and neck. A neuromuscular blocking agent may be necessary to allow intubation and mechanical ventilation. The onset of muscular rigidity occurs earlier with alfentanil than with other opioids.

The incidence may be reduced by 1) routine administration of neuromuscular blocking agents for balanced narcotic 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 75 µg/kg, 3) premedication with benzodiazepines (see PRECAUTIONS, Drug Interactions, Benzodiazepines). The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status.

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early postoperative or postinfusion period. IF ALFENTA ALFENTANIL HYDROCHLORIDE HAS BEEN USED FOR PROLONGED SEDATION IN THE INTENSIVE CARE UNIT, CLOSE OBSERVATION OF RESPIRATION SHOULD CONTINUE FOR AT LEAST 12 HOURS AFTER DISCONTINUATION OF THE INFUSION. CARE SHOULD BE TAKEN AFTER INFUSIONS AND AFTER LARGE BOLUS DOSES OF ALFENTANIL TO ENSURE THAT ADEQUATE SPONTANEOUS BREATHING HAS BEEN ESTABLISHED AND MAINTAINED IN THE ABSENCE OF VENTILATORY SUPPORT OR STIMULATION BEFORE CLOSE MONITORING OF THE PATIENT IS DISCONTINUED. THE ADJUNCTIVE USE OF SEDATIVE HYPNOTICS OR OTHER ANAESTHETIC AGENTS MAY RESULT IN SIGNIFICANT RESPIRATORY DEPRESSION EVEN WITH SMALL DOSES OF ALFENTANIL.

Hyperventilation during anaesthesia may alter the patient's responses to CO<sub>2</sub>, thus affecting respiration postoperatively.

Adequate facilities should be available for monitoring and ventilation of all patients receiving alfentanil. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression, including the use of neuromuscular blocking agents for tracheal intubation.

Non-epileptic (myo)clonic movements can occur.

### **PRECAUTIONS**

ALFENTA ALFENTANIL HYDROCHLORIDE SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS ANAESTHETICS. VITAL SIGNS SHOULD BE MONITORED ROUTINELY.

Skeletal muscle rigidity is related to the dose and speed of administration of alfentanil and administration of adequate doses of a muscle relaxant. At high doses, muscular rigidity will occur unless preventative measures are employed (see WARNINGS).

#### **Elderly Patients**

In geriatric patients, the dose of alfentanil required to produce anaesthesia, as determined by the appearance of delta waves in the EEG, was 40% lower than that needed in healthy young patients.

**Patients with Impaired Hepatic Function**

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

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.

**Patients with Impaired Renal Function**

Although the clearance of alfentanil does not appear to be altered in patients with renal impairment, it may be necessary to reduce dosage requirements due to an increased free fraction of the drug.

**Patients with Impaired Respiration**

Decreased respiratory drive and increased airway resistance occur with increasing doses of alfentanil. The degree and duration of respiratory depression is dose-related. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced. 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. 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.

**Patients with Compromised Cardiovascular Systems**

Rapid administration may produce loss of vascular tone and hypotension. Appropriate measures to maintain a stable arterial pressure should be taken. Management with fluid replacement should be considered in patients with compromised cardiovascular systems prior to induction.

In some patients administered alfentanil, bradycardia and possibly asystole can occur if the patient has received an insufficient amount of anticholinergic, or when alfentanil is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.

Careful titration of dosage may be required in patients with special conditions, such as uncontrolled hypothyroidism or alcoholism. (See PRECAUTIONS - Drug Interactions; alcohol can potentiate the

respiratory depression of narcotics.) In such cases, prolonged postoperative monitoring is required.

Patients on chronic opioid therapy, or with a history of narcotic abuse, may require increased amounts of alfentanil.

### **Head Injuries**

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

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

### **Use in Pregnancy**

There are no adequate well-controlled studies in pregnant women. Alfentanil should be used during pregnancy only if the potential benefits justify the potential risks.

### **Labour and Delivery**

There are insufficient data to support the use of alfentanil in labour and delivery. Alfentanil crosses the placenta and the fetal respiratory centre is particularly sensitive to opiates. Such use is not recommended. If alfentanil is administered nevertheless, an antidote for the child should always be at hand.

### **Nursing Mothers**

In one study of 9 women undergoing postpartum tubal ligation, minimal levels of alfentanil were detected in colostrum 4 hours after administration of 60 µg/kg alfentanil, with no detectable levels present after 28 hours. Caution should be exercised when alfentanil is administered to a nursing woman.

### **Paediatric Use**

There are insufficient data on the safety, efficacy and dosage regimen in children under 12 years of age; therefore, the use of alfentanil is not recommended in this age group.

### **Drug Interactions**

#### **CNS Depressants**

Both magnitude and duration of CNS and cardiovascular effects may be enhanced when alfentanil is administered to patients receiving barbiturates, neuroleptics, tranquilizers, opioids, general anaesthetics or

other CNS depressants (e.g. alcohol). 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.

#### MAO Inhibitors

It is usually recommended to discontinue MAO inhibitors 2 weeks prior to any surgical or anaesthetic procedure.

#### Benzodiazepines

Administration of intravenous benzodiazepines 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. It is preferable not to administer benzodiazepines to outpatients as these drugs may lengthen the recovery period.

#### Hepatic Enzyme Inhibitors

Alfentanil is metabolized 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.

#### **Drug Abuse and Dependence**

Alfentanil can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

#### **Effect on Driving Ability and Use of Machinery**

Patients should be advised to allow sufficient time to elapse before operating a car or heavy machinery. Individual reactions vary. On average, the patient should wait 3-6 hours after doses of 1-3 mL and 12 to 24 hours after higher doses and infusions.

## **ADVERSE REACTIONS**

Adverse reactions reported in association with ALFENTA alfentanil hydrochloride use in clinical trials are listed below by 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 Disorders - General

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

### Heart Rate and Rhythm Disorders

Common: Bradycardia, Tachycardia

Uncommon: Arrhythmia

### Cardiovascular Disorders - General

Common: Hypertension, Hypotension

### Gastrointestinal Disorders

Very common: Nausea, Vomiting

### Central Nervous System Disorders

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

Uncommon: Headache

### Respiratory System Disorders

Common: Apnea, Respiratory depression

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

### Psychiatric Disorders

Common: Somnolence

Uncommon: Disorientation, Agitation, Euphoria

### Skin and Appendage Disorders

Uncommon: Pruritis, Sweating

### Vision Disorders

Uncommon: Blurred/double vision

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

### **Symptoms**

There has been no clinical experience of overdosage with ALFENTA alfentanil hydrochloride in clinical trials to date. As with other potent opioid analgesics, overdosage is expected to be manifested by an extension of the pharmacological actions of alfentanil. The intravenous LD<sub>50</sub> of alfentanil in male rats is 43.0-50.9 mg/kg.

An overdose of ALFENTA alfentanil hydrochloride injection is manifested as an extension of its pharmacologic actions.

### **Treatment**

In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained and an oropharyngeal airway or endotracheal tube may be indicated.

Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with alfentanil may be longer than the duration of action of the opioid antagonist; additional doses of the latter may be required. Administration of an opioid antagonist should not preclude more immediate countermeasures.

If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

## **DOSAGE AND ADMINISTRATION**

### **Adults**

The dosage of ALFENTA alfentanil hydrochloride should be individualized according to body weight, physical status, underlying pathological condition, concomitant medication, and type and duration of surgical procedure and anaesthesia. 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. The dose of alfentanil should be reduced in geriatric patients.

Vital signs should be monitored routinely.

Alfentanil may be administered:

1. By incremental injection as an analgesic adjunct with barbiturate/nitrous oxide/oxygen anaesthesia for short surgical procedures (expected duration of less than one hour).
2. As an analgesic adjunct to barbiturate induction for general surgical procedures followed by continuous infusion as a maintenance analgesic with nitrous oxide/oxygen for general surgical procedures.

See accompanying dosage chart.

## DOSAGE CHART - SURGICAL USE

INDICATION	APPROXIMATE DURATION OF ANAESTHESIA	INITIAL DOSE	INCREMENTS/ INFUSION	TOTAL DOSE	EFFECTS
Incremental Injection	≤ 30 min	5-20 µg/kg (ventilated or spontaneously breathing)	2.5 µg/kg	5-40 µg/kg	Minimal haemodynamic change with some attenuation of sympathetic response to surgical stress. More rapid recovery than fentanyl. At doses >11 µg/kg transient apnea may occur which may require assisted ventilation.
Incremental Injection	30-60 min	20-50 µg/kg (ventilated)	5-15 µg/kg	up to 75 µg/kg	Minimal haemodynamic changes with attenuation of response to laryngoscopy and intubation. Recovery times better than or equal to fentanyl.
Continuous Infusion	> 45 min	50-75 µg/kg (ventilated)	0.5-1.5 µg/kg/min	dependent on duration of procedure	Attenuation of cardiovascular response to intubation and incision, intra-operative stability and faster recovery than thiopental/inhalation.

## INFUSION DOSAGE

Continuous Infusion: 0.5-1.5 µg/kg/min administered with nitrous oxide/oxygen in patients undergoing general anaesthesia. When the infusion is started at 0.5 µg/kg/min and there are changes in vital signs that indicate surgical stress or lightening of anaesthesia, these may be controlled by increasing the rate up to 1.5 µg/kg/min or administering up to 3 bolus doses of 7 µg/kg given over a 5 to 10 minute period. Infusion rates should be adjusted downward in the absence of these signs until the minimum infusion rate is reached. An average alfentanil infusion rate of 1.5 µg/kg/min has been shown to maintain cardiovascular stability, dampen sympathetic responses to surgical stress and to provide rapid recovery with some postoperative analgesia. Administration of alfentanil should be discontinued 10-15 minutes prior to the end of surgery.

**Dosage for Mechanically Ventilated Patients in the Intensive Care Unit**

The dosage of alfentanil required in intensive care patients will depend on many factors including the underlying pathological condition, the severity of the pain, the type of mechanical ventilation, the individual patient's response to the drug, and the use of concomitant medications, especially sedative hypnotics or major tranquilizers.

**Continuous Infusion**

The recommended initial infusion rate of alfentanil in mechanically ventilated adult patients is 0.5 µg/kg/min. The rate of infusion should be reassessed regularly and individualized to ensure that it is kept at the minimum necessary to achieve the desired clinical effect. The optimal infusion rate varies considerably from patient to patient. However, in the majority of patients, infusion rates in the range of 0.2-2.0 µg/kg/min effectively prevent pain and aid compliance with mechanical ventilation.

An initial loading dose of up to 50 µg/kg may be required in some patients, depending on their status prior to initiation of the infusion, as well as previous analgesic or anaesthetic therapy.

**Supplemental Bolus Doses**

Supplemental bolus doses of 10-20 µg/kg may be given during periods of increased stimulation due to painful procedures such as physiotherapy or endotracheal suction.

Patients should be closely monitored for at least 12 hours following cessation of the infusion to detect any evidence of respiratory depression. Care should be taken to ensure that adequate spontaneous ventilation has been established and maintained in the absence of ventilatory support or stimulation.

At the recommended dosage, alfentanil provides analgesia and suppression of respiratory drive but it may not provide sedation or induce sleep. The addition of an anxiolytic such as a benzodiazepine may be required to achieve sedation. Neuromuscular blocking agents may also be necessary for intubation or to settle patients who are difficult to manage on mechanical ventilation.

DOSAGE CHART - INTENSIVE CARE USE		
Treatment	Dosage	
Alfentanil	initial loading dose	0-50 µg/kg
	infusion - initial rate	0.5 µg/kg/min
	- increment/decrement	0.25 µg/kg/min
	- maximum rate	2.0 µg/kg/min
	- minimum rate	0 µg/kg/min
	bolus dose prior to painful procedures	10-20 µg/kg
Other Supplements	sedative/hypnotic agents neuromuscular blocking agents	

There is no clinical experience with infusions of more than 5 consecutive days.

#### **Paediatric Dosage**

Not recommended. (See PRECAUTIONS.)

#### **Premedication**

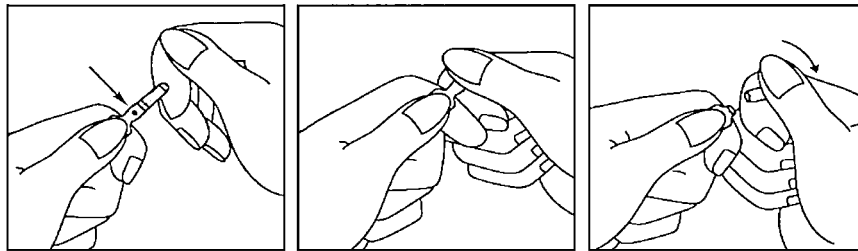
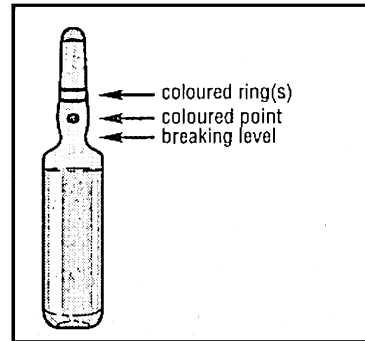
The selection of pre-anaesthetic medication should be based upon the needs of the individual patient (see PRECAUTIONS, Drug Interactions, Benzodiazepines).

#### **Neuromuscular Blocking Agents**

The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the haemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

**Instructions for Use/Handling**

1. Grasp the ampoule between thumb and index finger, leaving the tip of the ampoule free.
2. With the other hand, hold the tip of ampoule with the index finger against the neck of ampoule and the thumb on the coloured point in parallel to the identification coloured ring(s).
3. Keeping the thumb on the point, sharply break the tip of the ampoule while holding firmly the other part of the ampoule in the hand (see illustration).

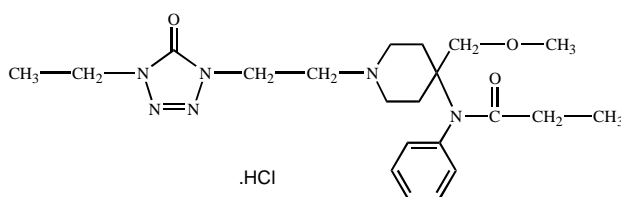


**PHARMACEUTICAL INFORMATION****Drug Substance**

Common Name: alfentanil hydrochloride

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

Structural Formula:



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

Molecular Weight: 452.98

Description: Alfentanil hydrochloride is a white to almost-white powder with a melting range of 136°-141°C and a pKa of 6.50. Alfentanil hydrochloride is freely soluble in water, methanol, ethanol and chloroform. It is soluble in polyethylene glycol, sparingly soluble in acetone, very slightly soluble in benzene and practically insoluble in diethyl ether. The log partition coefficient (n-octanol/aqueous buffer solution at pH 9.80) is 2.16.

**Composition**

ALFENTA alfentanil hydrochloride injection is a sterile, preservative-free aqueous solution. The solution contains alfentanil hydrochloride equivalent to 500 µg per mL of alfentanil base and water for injection. Sodium chloride is added to produce an isotonic solution with a pH range of 4.0-6.0.

**Stability and Storage Recommendations**

ALFENTA ampoules should be stored at room temperature (15°-25°C), protected from light.

## **AVAILABILITY OF DOSAGE FORMS**

ALFENTA alfentanil hydrochloride is a colourless, sterile, aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per mL of alfentanil base for intravenous injection. It is supplied in 2 mL ampoules. For packaging configurations, see published price list.

## **PHARMACOLOGY**

### **Analgesic Activity**

The analgesic effect of alfentanil has been studied in mice, rats and dogs.

The time to onset, potency and duration of analgesic action were examined in the mouse hot plate test. Alfentanil exhibited a rapid onset and very short duration of action (5 min) at 0.22 mg/kg. At 1.25 mg/kg the duration of action was approximately 10 minutes. The lowest observed ED<sub>50</sub> was 0.11 mg/kg. At the time of peak effect, alfentanil was approximately 60 times more potent than morphine and ¼ as potent as fentanyl. The safety margin (LD<sub>50</sub>/ED<sub>50</sub>) of alfentanil was 1.5 times that of fentanyl and 19 times that of morphine.

In the tail withdrawal test in rats, the analgesic potency of alfentanil was found to be 72 times that of morphine and ¼ that of fentanyl. The lowest ED<sub>50</sub> values were 0.044 mg/kg for alfentanil, 3.15 mg/kg for morphine and 0.011 mg/kg for fentanyl. The intravenous LD<sub>50</sub> value for alfentanil was 47.5 mg/kg with a relative safety margin of 1080. The time to peak effect was 2 minutes for alfentanil, 8 minutes for fentanyl and 30 minutes for morphine, while the durations of action were 11, 30 and 90 minutes, respectively, at twice the lowest ED<sub>50</sub>.

In dogs, the analgesic effect of alfentanil was 30 times that of morphine. When administered at a dose equianalgesic to 5 mg/kg morphine, alfentanil (0.05 mg/kg) did not cause depression of myocardial contractility or impairment of lung circulation.

### **Cardiovascular and Respiratory Effects**

The cardiovascular and respiratory effects of various doses from 2.5 to 800 µg/kg of alfentanil were studied in both anaesthetized and conscious dogs. A decrease in heart rate was observed at doses between 50 and 400 µg/kg. At 5 mg/kg (approximately 10 times the human therapeutic dose) negative inotropic properties and a decrease in aortic blood flow velocity and acceleration occurred. Sinus arrest, A-V dissociation and A-V block were seen in some dogs. These effects disappeared at higher doses.

The respiratory depressant effect of alfentanil caused a decrease in  $pO_2$  and  $pCO_2$  in conscious unventilated dogs. Convulsions occurred in four unventilated dogs at very low  $pO_2$  levels. Salivation was observed in some animals after all doses.

Bolus doses (0-32 mg/kg) of alfentanil followed by a 30-minute infusion of 0.01  $\mu\text{g}/\text{kg}/\text{min}$  in conscious dogs caused increases in aortic and pulmonary artery pressure while cardiac output was maintained. There was a significant increase in left and right arterial pressure and in systemic vascular resistance.

Rapid administration of alfentanil caused profound haemodynamic changes which may have been related to surgical trauma and the absence of other anaesthetic agents.

Global ventricular function was studied in adult dogs. Alfentanil (0.2 mg/kg) produced a significant increase in the slope of the pressure-length relationship, in left ventricular peak pressure and in  $dP/dt$ . There was no change in  $dL/dt$ . The inotropic stimulation in response to alfentanil administration shifted the end-systolic pressure-volume relationship to the left and upward.

The effects of alfentanil 500  $\mu\text{g}/\text{kg}$  and fentanyl 100  $\mu\text{g}/\text{kg}$  on spontaneous and reflex cardiovascular responses were recorded in anaesthetized dogs. A similar decrease in resting heart rate was observed after both drugs, which had returned to baseline after 180 minutes in the alfentanil group but not after the fentanyl. Alfentanil decreased somato-cardiovascular reflexes by 54% and 55% compared with 73% and 82% for fentanyl. Mean arterial pressure recovered in 15 minutes and heart rate in 70 minutes following alfentanil compared to 70 and 90 minutes following fentanyl.

Single injections of alfentanil and fentanyl produced dose-dependent changes in respiratory frequency and minute volume, with peak effects at 3 and 5 minutes, respectively. Repeat injections of alfentanil produced more distinct and regular changes in respiratory frequency and tidal volume than fentanyl. Alfentanil had an earlier peak effect and shorter duration than fentanyl. All other respiratory effects were similar.

### **Effect on Cerebral Circulation and Vasculature**

Anaesthetic doses of alfentanil did not alter the cerebral blood flow (CBF) response to hypoxia or hypercarbia in the dog. The lower limit of autoregulation was not affected while the upper limit was significantly increased. Bolus injections of 0.16-0.64 mg/kg alfentanil had no effect on CBF, mean arterial blood pressure or cerebral vascular resistance.

**EEG**

The effect of alfentanil (0.04, 0.16 and 0.63 mg/kg) on EEG patterns was compared with fentanyl 0.004 mg/kg, sufentanil 0.0004 mg/kg and morphine 1.6 mg/kg in dogs. Spindle-like bursts of biphasic waves were more frequent and of higher amplitude after alfentanil than after the other compounds. All compounds increased power in delta and theta bands; the effect was dose-related with alfentanil.

Only the highest dose of alfentanil produced an increased power in the alpha band similar to that seen with morphine, fentanyl and sufentanil. Alfentanil had no significant effect on sleep cycles.

A bolus injection of alfentanil 0.16 mg/kg followed by a 60-minute infusion of 0.01 mg/kg/min in the dog resulted in a total decrease of power in the frontal cortex within 30 minutes. The total power in the occipital cortex was unaffected. There was a rapid normalization of the EEG and spontaneous breathing at the end of the infusion.

There was a dose-related effect of alfentanil (0.04, 0.16 and 0.63 mg/kg) on the somatosensory evoked potential (SEP) in the S1 cortex, medial lemniscus and ventral posterolateral thalamus. There was a decrease in amplitude and extension in latency of the late components of the SEP evoked by parostimulation. Earlier waves were unaffected. The cortical SEP elicited by direct brain stimulation of the lemniscus or thalamus was resistant to the suppressant effects of alfentanil.

**Drug Interaction Studies**

Cardiac and haemodynamic parameters were evaluated in the dog following the administration of alfentanil 0.5 mg/kg with succinylcholine, pancuronium or propranolol. There were decreases in heart rate and partial A-V block after the loading dose of alfentanil. There were no significant changes after the addition of succinylcholine; however, pancuronium 0.1 mg/kg had a pronounced stimulating effect on aortic blood pressure, heart rate, cardiac output, LV dp/dt maximum and rate pressure product. Propranolol 0.16 mg/kg in alfentanil-treated dogs produced a significant decrease in cardiac performance in the absence of pronounced changes in heart rate and LV end diastolic pressure.

Alfentanil was studied in combination with parasympatholytic, sympatholytic and sympathomimetic drugs to assess their effect on the autonomic stimulation seen with all morphinomimetic compounds.

Parasympatholytic agents reinforced alfentanil's stimulation of the autonomic nervous system, sympatholytics and central vasomotor depressors partially blocked the stimulation while sympathomimetics reinforced and prolonged it.

The haemodynamic effects of alfentanil and verapamil were assessed in the dog. Alfentanil alone significantly decreased mean arterial pressure, heart rate and pulmonary capillary wedge pressure and

increased stroke volume. The addition of verapamil caused no significant change in haemodynamic parameters other than a slower heart rate at 15 and 30 minutes.

### **Miscellaneous Studies**

The antagonistic effects of naloxone were examined in rabbits and in rats treated with alfentanil. Pretreatment with naloxone was more effective in minimizing the effect of alfentanil on respiration than when the order of administration was reversed.

The dose of naloxone required to antagonize 0.16 mg/kg alfentanil in the rat was 0.01 mg/kg. The time to onset of antagonism was 1 minute. A single dose of naloxone 0.02 mg/kg completely reversed the narcotic effects of alfentanil 0.16 mg/kg.

Plasma levels of histamine were determined in the dog following 0.63 mg/kg alfentanil and 0-15 mg/kg sufentanil. There was no significant change in plasma histamine levels following administration of either alfentanil or sufentanil.

In vitro alfentanil ( $\leq 50 \mu\text{g/mL}$ ) did not induce significant haemolysis of red blood cells or plasma fraction precipitation when incubated with whole blood.

### **Pharmacokinetics**

The excretion of tritium-labelled alfentanil in rats was rapid and complete; 88.3% within 24 hours and 95.1% within 48 hours. The principal route of excretion was the urine (72.8%) with the faeces as the secondary route (24.0%). Alfentanil was rapidly metabolized into a large number of metabolites with oxidative O - demethylation and oxidative N - dealkylation at the piperidine nitrogen as the major metabolic pathways. Only 0.2% of the administered dose was excreted in the urine and faeces as the parent drug.

In the rat, biliary excretion of radioactive alfentanil was 11.2% at 1 hour, 16.9% at 2 hours, 20.1% at 4 hours and 23.9% at 24 hours after dosing. No unchanged alfentanil could be detected in the bile.

The in vitro plasma protein binding was 92.1% in human plasma, 83.6% in the rat and 72.9% in dogs.

Tissue distribution studies of  $^3\text{H}$ -alfentanil in the rat demonstrated a high uptake of radioactivity 8 minutes after administration, with the highest concentration in the liver. Within the first hour there was extensive distribution to the muscle mass of the body. The lowest concentration was seen in the brain.

Radioactivity levels decreased markedly by 30 minutes to 1 hour except in the liver, kidney, small intestine and bladder contents, intestinal tissues, glands and bone marrow. High radioactivity was observed in the gastric contents. At 2 hours postdosing, radioactivity had been redistributed from the muscles but

persisted in the liver, lungs, gallbladder, gastrointestinal tract and some glandular tissue. Levels of unchanged alfentanil in all tissues were lower than corresponding plasma levels except in the stomach walls (15 minutes after dosing).

Placental concentrations resembled those of skeletal muscle and accounted for less than 0.8% of the administered dose. Fetal levels were lower than those in the placenta.

The distribution phase of  $^3\text{H}$ -alfentanil 0.16 mg/kg lasted up to 2 hours (plasma level 27 ng/mL) in the rat and was followed by a terminal elimination half-life of 7.12 hours. For the unchanged drug the  $t_{1/2\alpha}$  was 1.7 minutes and  $t_{1/2\beta}$  was 11 minutes. Total plasma clearance averaged 26.9 mL/min/kg.

In the dog, plasma levels of  $^3\text{H}$ -alfentanil decreased rapidly with unchanged drug accounting for 80% of total plasma radioactivity at 10 minutes, 15-20% at 60 minutes and 1.1-1.4% at 6 hours after dosing. Approximately half the administered radioactivity was excreted during the first 24 hours after dosing and another 20% during the second 24 hours. At 96 hours after dosing, 97% of the administered dose had been excreted in the urine and 8% in the faeces. Only 1% of the recovered dose was unchanged alfentanil.

In a comparative pharmacokinetic study, plasma levels of alfentanil decayed biphasically in the rat ( $t_{1/2\beta} = 12$  min) and triphasically in the dog ( $t_{1/2\beta} = 104$  min) and in man ( $t_{1/2\beta} = 88$  min). In dogs, the pharmacokinetic behaviour was not significantly different at analgesic (50  $\mu\text{g}/\text{kg}$ ) or anaesthetic (300  $\mu\text{g}/\text{kg}$ ) doses.

## TOXICOLOGY

### Acute Toxicity

LD<sub>50</sub> values were determined in the following species:

Species/Observation Period	No. Animals/Dose	LD <sub>50</sub> mg/kg
Albino Mice 7 days	10 F	72.2 (47.4 - 110)
	10 M	73.6 (44.8 - 121)
Wistar Rats 7 days	10 F	43.0 (23.7 - 78.0)
	10 M	50.9 (30.7 - 84.2)
Albino Guinea Pigs 14 days	10 F	81.9 (54.7 - 123)
	10 M	71.8 (54.9 - 93.9)
Mongrel Dogs 14 days	4 F	87.5 (67.0 - 114)
	4 M	59.5 (22.7 - 156)

Signs of toxicity: excitation; hunching; loss of righting reflex; convulsions; muscular rigidity; blockage of the pinna and corneal reflex; tremors; dyspnea; hypotonia; exophthalmos; sedation; cyanosis; hypoventilation; ataxia and salivation.

Observations were mainly of CNS effects characteristic of opioid analgesics. Animals died from suffocation due to respiratory centre depression. Acute toxicity in rats was not affected by speed of injection. The LD<sub>50</sub> of alfentanil infusion was 400 mg/kg in the rat; approximately 8 times the acute LD<sub>50</sub> for the injection.

### Subacute Toxicity

#### Four-Week Intravenous Toxicity Study in Wistar Rats

Alfentanil was administered daily to 20 male and 20 female rats in doses of 0, 0.08, 0.31 and 1.25 mg/kg IV for 4 weeks. There were no deaths at 0 or 0.08 mg/kg. Those that occurred in the other 2 groups usually occurred within 2 hours of alfentanil administration and were attributed to suffocation. Transient muscle rigidity, exophthalmos and loss of righting reflex were observed in all groups. These effects lasted approximately 8 minutes at 0.08 mg/kg, 15 minutes at 0.31 mg/kg and 45 minutes at 1.25 mg/kg. Transient diarrhea was also seen in most animals but was not dose dependent. There was a slight decrease in food consumption in the high-dose group although there was no significant difference in body weight after 4 weeks. Alfentanil had no effect on behaviour or physical appearance of the rats. Male rats exhibited an increase in non-segmented heterophils at 0.31 mg/kg and in thrombocytes at 1.25 mg/kg. Females exhibited an increase in segmented heterophils at 0.31 mg/kg and a decrease in lymphocytes at 0.31 mg/kg. Urinalysis and serum analysis revealed comparable values between groups.

At autopsy, there were no significant macroscopic or histological differences between groups.

#### Four-Week Intravenous Toxicity Study in Beagle Dogs

Twelve male and 12 female Beagle dogs were administered 0, 0.08, 0.31 or 1.25 mg/kg IV alfentanil daily for 4 weeks. There were no deaths. There was a dose-related incidence of ataxia, catatonia, and apnea during the first few days. Dogs in the high-dose group experienced sporadic apnea, convulsions and dyskinesia throughout the study. All groups exhibited decreased food consumption and weight loss which was dose-related and significantly different from controls in the 0.08 and 1.25 mg/kg groups. There were no significant differences in EKG, haematology, urinalysis, biochemistry and histology other than elevated SGPT at all dosages throughout the study. A trend toward thymic involution and vaginal changes was considered to be related to poor general physical condition.

#### **Reproduction and Teratology**

##### Fertility Studies in Male and Female Wistar Rats

Groups of 20 female rats were administered IV alfentanil 0, 0.08, 0.31 and 1.25 mg/kg for 14 days prior to mating with untreated males and throughout pregnancy. Another 4 groups of 20 untreated females were mated with groups of 20 males which had received the above doses for 56 days prior to mating. Mortality was significantly increased in the 0.31 mg/kg and the 1.25 mg/kg groups. In surviving animals, there was no evidence of impaired fertility, embryotoxicity or teratogenicity.

##### Intravenous Embryotoxicity and Teratogenicity Study in Wistar Rats

Groups of 20 female rats were administered IV alfentanil 0, 0.08, 0.31 or 1.25 mg/kg from day 6 to 15 of pregnancy. Body weight gain and food consumption were normal in all groups. There were no adverse effects on pregnancy, delivery or litter parameters. No teratogenic effects were observed.

##### Intravenous Embryotoxicity and Teratogenicity Study in New England White Rabbits

Groups of 20 female rabbits received IV alfentanil 0, 0.08, 0.31 or 1.25 mg/kg from day 6 to day 15 of pregnancy. Body weight gain was significantly lower in high-dose animals. There were no significant differences in pregnancy rate or mortality among dams. There was a significantly lower 24-hour survival rate in the offspring of the 1.25 mg/kg group attributed to poor maternal health. No teratogenic effects were observed.

##### Intravenous Embryotoxicity and Teratogenicity Study in Wistar Rats: Peri and Postnatal Toxicity

Groups of 20 female rats were administered IV alfentanil 0, 0.08, 0.31 or 1.25 mg/kg from day 16 of pregnancy through a 3-week lactation period. There were no differences between groups in body weight gain, pregnancy rates or mortality. Cannibalism occurred in 2 of 19 high-dose litters. Birth weight was lower in the 0.31 mg/kg group. Survival rates were lower in the offspring of the 0.31 and 1.25 mg/kg groups; probably due to maternal toxicity. No teratogenic effects were observed.

**Mutagenicity**

The mutagenicity potential of alfentanil was assessed in the Ames test, micronucleus test and the mouse dominant lethal test. There was no evidence of mutagenicity in any test.

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