DISCLAIMER

All labeling reflected on this website is for informational and promotional purposes only. It is not intended to be used by healthcare professionals or patients for the purpose of prescribing or administering these products. Questions regarding the current content of product labeling should be directed to Akorn's Customer Service department at 800.932.5676.
Alfentanil HCI Injection is an opioid indicated:
- as the analgesic component for monitored anesthesia care (MAC).
- as a primary anesthetic agent for the induction of anesthesia in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.
- as a primary anesthetic agent for the induction of anesthesia in patients undergoing general surgery with barbiturate/nitrous oxide/oxygen.
- as an analgesic administered by continuous infusion with nitrous oxide/oxygen in the maintenance of general anesthesia.
- as an analgesic administered by continuous infusion with nitrous oxide/oxygen in the maintenance of general anesthesia.
- as an analgesic administered by continuous infusion with nitrous oxide/oxygen in the maintenance of general anesthesia.
- as an analgesic adjunct given in incremental doses in the maintenance of anesthesia with other drugs, type of anesthesia to be used, and the surgical procedure involved.

FDA at 1-800-FDA-1088 or www.fda.gov.medwatch.

Concomitant Use of CNS Depressants:
- Concomitant Use of CNS Depressants: May decrease pulmonary arterial pressure and may cause hypotension. See FPI for management instructions. For post-operative pain, start with the lowest effective dosage and monitor for potential depression and discontinue Alfentanil HCl Injection if depression is suspected.
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with Alfentanil HCl Injection because they may reduce analgesic effect of Alfentanil HCl Injection or precipitate withdrawal symptoms.

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taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required.

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

- Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. Therefore, vital signs must be monitored continuously, including following the termination of surgery.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- For purposes of administering small volumes of Alfentanil HCl Injection accurately, the use of a tuberculin syringe or equivalent is recommended.

As with other potent opioids, the respiratory depressant effect of alfentanil may persist longer than the measured analgesic effect. The total dose of all opioid agonists administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia.

If Alfentanil HCl injection is administered with a CNS depressant, become familiar with the properties of each drug, particularly each product’s duration of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available [see Warnings and Precautions (5.5)].

The physical and chemical compatibility of Alfentanil HCl Injection have been demonstrated in solution with normal saline, 5% dextrose in normal saline, 5% dextrose in water and Lactated Ringers. Clinical studies of Alfentanil HCl Injection infusion have been conducted with Alfentanil HCl Injection diluted to a concentration range of 25 mcg/mL to 80 mcg/mL. As an example of the preparation of Alfentanil HCl Injection for infusion, 20 mL of Alfentanil HCl Injection added to 230 mL of dextrose 4% by intravenous injection provides 40 mcg/mL solution of Alfentanil.

2.2 Dosage

The dosage of Alfentanil HCl Injection should be individualized and titrated to the desired effect in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. The dose of Alfentanil HCl Injection should be reduced in elderly or debilitated patients [see Warnings and Precautions (5.6)].

See Dosing Chart for the use of Alfentanil HCl Injection

1) by incremental injection as an analgesic adjunct to anesthesia with barbiturate/nitrous oxide/oxygen for short surgical procedures (expected duration of less than one hour);
2) by continuous infusion as a maintenance analgesic with nitrous oxide/oxygen for general surgical procedures; and
3) by intravenous injection in anesthetic doses for the induction of anesthesia for general surgical procedures with a minimum expected duration of 45 minutes; and
4) by intravenous injection as the anesthetic component for monitored anesthesia care (MAC).

When administering Alfentanil as induction doses, administer the dose slowly (over three minutes). Because administration of the induction dose may produce loss of vascular tone and hypotension, consider given to fluid replacement prior to induction.

### Table: 1 Dosing Chart For Use During General Anesthesia

| Spontaneously Breathing/Assisted Ventilation | Induction of Analgesia: 8 to 20 mcg/kg
| Maintenance of Analgesia: 3 to 5 mcg/kg q 5 to 20 min or 0.5 to 1 mcg/kg/min
| Total dose: 8 to 40 mcg/kg |
| Assisted or Controlled Ventilation - Assisted or Controlled Ventilation | Induction of Analgesia: 20 to 50 mcg/kg
| Maintenance of Analgesia: 5 to 15 mcg/kg q 5 to 20 min
| Total dose: Up to 75 mcg/kg |
| Incremental Injection (To attenuate response to laryngoscopy and intubation) | Induction of Analgesia: 50 to 75 mcg/kg
| Maintenance of Analgesia: 0.5 to 3 mcg/kg/min (Average rate 1 to 1.5 mcg/kg/min)
| Infusion rates are variable and should be titrated to the desired clinical effect. See Infusion Dosage Guidelines Below
| Total dose: Dependent on duration of procedure |
| Assisted or Controlled Ventilation - Continuous Infusion (To provide attenuation of response to intubation and incision) | Induction of Analgesia: 130 to 245 mcg/kg
| Administer slowly (over 3 minutes).
| Maintenance of Analgesia: 0.5 to 1.5 mcg/kg/min or general anesthetic.
| Infusion rates are variable and should be titrated to the desired clinical effect. See Infusion Dosage Guidelines Below
| Total dose: Dependent on duration of procedure
| At these doses trunclal rigidity should be expected and a muscle relaxant should be utilized.
| In patients administered anesthetic (induction) dosages of Alfentanil HCl Injection, it is essential that qualified personnel and adequate facilities are available for the management of intraoperative and postoperative respiratory depression. |

### Infusion Dosage Guidelines For Continuous Infusion

- Induction of MAC: 3 to 8 mcg/kg
- Maintenance of MAC: 3 to 5 mcg/kg q 5 to 20 min or 0.25 to 1 mcg/kg/min

Infusion rates are variable and should be titrated to the desired clinical effect. See Infusion Dosage Guidelines Below

Total dose: 3 to 40 mcg/kg

Patients receiving monitored anesthesia care (MAC) should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure.

### Maintenance of Analgesia:

- Continuous Infusion: 0.5 to 3 mcg/kg/min administered with nitrous oxide/oxygen in patients undergoing general surgery.

Following an anesthetic induction dose of Alfentanil HCl injection, alfentanil infusion rate requirements are reduced by 30 to 50% for the first hour of maintenance. Requirements for volatile inhalation anesthetics are also reduced by 30 to 50% for the first hour of maintenance.

Changes in vital signs that indicate a response to surgical stress or lightening of anesthesia may be controlled by increasing the Alfentanil HCl injection to a maximum of 4 mcg/kg/min and/or administration of bolus doses of 7 mcg/kg. If changes are not controlled after three bolus doses given over a five-minute period, a barbiturate, vasodilator, and/or inhalation agent should be used. Infusion rates should always be adjusted downward in the absence of these signs until there is some response to surgical stimulation.

Rather than an increase in infusion rate, 7 mcg/kg bolus doses of Alfentanil HCl Injection or a potent inhalation agent should be administered in response to signs of lightening of anesthesia within the last 15 minutes of surgery. Alfentanil HCl injection infusion should be discontinued at least 10 to 15 minutes prior to the end of surgery.

In patients administered anesthetic (induction) doses of Alfentanil HCl Injection, it is essential that qualified personnel and adequate facilities are available for the management of intraoperative and postoperative respiratory depression.

### 2.3 Discontinuation of Alfentanil HCl Injection

Alfentanil HCl injection infusions should be discontinued at least 10 to 15 minutes prior to the end of surgery during general anesthesia. During administration of Alfentanil HCl injection for Monitored Anesthesia Care (MAC), infusions may be continued to the end of the procedure.

### 2.4 Dosage Modification in Elderly Patients

Reduce the initial dose of Alfentanil HCl Injection in elderly patients by up to 40% due to reduced clearance and increased sensitivity to the effects [see Specific Populations (8.5)]. The effect of the initial dose should be considered in determining supplemental doses.

### 2.5 Dosage Modifications in Obese Patients

In obese patients (more than 20% above ideal body weight) the dose of Alfentanil HCl Injection should be determined on the basis of lean body weight.

### 2.6 Dosage Modifications with Concomitant Use with Other CNS Depressants

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics and general anesthetics) will have additive or potentiation effects with Alfentanil HCl Injection. When patients have received such drugs, the dose of Alfentanil HCl Injection, required will be less than usual.

Following the administration of Alfentanil HCl Injection, the dose of other CNS depressant drugs should be reduced. [see Drug Interactions (7)].

### 3 DOSAGE FORMS AND STRENGTHS

Alfentanil HCl Injection USP, for intravenous use (equivalent to 500 mcg/mL alfentanil base).

### 4 CONTRAINDICATIONS

Alfentanil HCl injection is contraindicated in patients with:

- Hypersensitivity to alfentanil (e.g., anaphylaxis) [see Adverse Reactions (6)]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Addiction, Abuse, and Misuse

Alfentanil HCl Injection contains alfentanil, a Schedule II controlled substance. As an opioid, Alfentanil HCl Injection exerts users to the risks of addiction, abuse and misuse [see Drug Abuse and Dependence (9)].

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when handling Alfentanil HCl Injection. Strategies to reduce these risks include proper product storage and control practices for a C-II drug. Contact local and state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

#### 5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Alfentanil HCl Injection should be administered only by persons specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, including respiration and cardiopulmonary resuscitation of patients in the age group being treated. Such training must include the establishment and maintenance of a patent airway and assisted ventilation. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of Alfentanil HCl Injection. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status [see Overdosage (10)]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

As with other potent opioids, the respiratory depressant effect of Alfentanil HCl Injection may persist longer than the measured analgesic effect. The total dose of all opioid agonists administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia.

Certain forms of conduction anesthesia, such as spinal anesthesia and some epidural anesthetics, can alter respiration by blocking intercostal nerves [see Clinical Pharmacology for Alfentanil HCl Injection]
particularly when an inhibitor is added after a stable dose.

Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally
are hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or

Concomitant use of Alfentanil HCl Injection with a CYP3A4 inhibitor, such as macrodilide
antibiotics (e.g., erythromycin),azole-antifungal agents (e.g., ketoconazole), and protease
inhibitors (e.g., ritonavir), may increase plasma concentrations of Alfentanil HCl Injection and
prolong opioid adverse reactions, which may exacerbate fatal respiratory depression [see
Warnings and Precautions (5.4)]. Particularly when an inhibitor is added after a stable dose
of Alfentanil HCl Injection. Similar to discontinuation of a CYP3A4 inhibitor, such as rifampin,
carbamazepine, and phenytoin, in Alfentanil HCl injection-treated patients may increase
alfentanil plasma concentrations and prolong opioid adverse reactions. When using
Alfentanil HCl Injection with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in
Alfentanil HCl injection-treated patients, monitor patients closely at frequent intervals and consider
dosage reduction of Alfentanil HCl Injection [see Dosage and Administration (2.1), Drug Interactions (7)].

Concomitant use of Alfentanil HCl Injection with CYP3A4 inducers or discontinuation of a
CYP3A4 inhibitor could result in lower than expected alfentanil plasma concentrations, and
decrease efficacy. When using Alfentanil HCl Injection with CYP3A4 inducers or discontinuing
CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing
Alfentanil HCl Injection dose [see Dosage and Administration (2.1), Drug Interactions (7)].

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

5.12 Risks due to Hypersensitivity Reactions

Alfentanil HCl Injection may cause anaphylaxis reactions. Care should be exercised when
administering to patients with known hypersensitivity to alfentanil or other opioid analgesics.

ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other
sections:

• Addiction, Abuse, and Misuse [see Warnings and Precautions (5.1)]
• Life-Threatening Respiratory Depression [see Warnings and Precautions (5.6)]
• Muscle Rigidity and Skeletal Muscle Movement [see Warnings and Precautions (5.4)]
• Interactions with Benzodiazepines and CNS Depressants [see Warnings and Precautions (5.6)]
• Serotonin Syndrome [see Warnings and Precautions (5.7)]
• Bradycardia [see Warnings and Precautions (5.8)]
• Gastrointestinal Adverse Reactions [see Warnings and Precautions (5.11)]
• Seizures [see Warnings and Precautions (5.12)]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates
observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials
of another drug and may not reflect the rates observed in practice.

The following adverse reaction information is derived from controlled and open clinical trials
in 785 patients who received intravenous Alfentanil HCl Injection during induction and
maintenance of general anesthesia. The controlled trials included treatment comparisons with
fentanyl, thioental sodium, enflurane, saline placebo and halothane. The incidence of certain
side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported
incidence in the clinical trials of Alfentanil HCl Injection induction, and by the type of surgery, e.g.,
nausea and vomiting have a higher reported incidence in patients undergoing gynecologic
surgery. The overall reports of nausea and vomiting with alfentanil were comparable to fentanyl.

Incidence Greater than 1% - Probably Causally Related (Derived from clinical trials)

Gastrointestinal: Nausea (28%), vomiting (18%)

Cardiovascular: Arrhythmia, bradycardia (14%), hypertension (18%), hypotension (10%),
tachycardia (12%)

Musculoskeletal: Chest wall rigidity (17%), skeletal muscle movements*

Respiratory: Apnea*, postoperative respiratory depression

Central Nervous System: Blurred vision, dizziness*, sleepiness/postoperative sedation

*Incidence 3% to 9%; all others 1% to 3%

Incidence Less than 1% - Probably Causally Related (Derived from clinical trials)

Body as a whole: Anaphylaxis

Central Nervous System: Headache*, myoclonic movements, postoperative confusion*,
postoperative euphoria*, shivering*

Dermatological: Itching*, urticaria*

Injection Site: Pain*

Musculoskeletal: Skeletal muscle rigidity of neck and extremities

Respiratory: Bronchospasm, hypercarbia*, laryngospasm*

*Incidence 0.3% to 1%

Postmarketing Experience

The following adverse reactions have been identified during post-marketing surveillance, not seen in clinical trials, are italicized.

Body as a whole: Anaphylaxis

Central Nervous System: Headache*, myoclonic movements, postoperative confusion*,
postoperative euphoria*, shivering*

Dermatological: Itching*, urticaria*

Injection Site: Pain*

Musculoskeletal: Skeletal muscle rigidity of neck and extremities

Respiratory: Bronchospasm, hypercarbia*, laryngospasm*
The concomitant use of alfentanil HCl injection and CYP3A4 inhibitors can increase the plasma concentration of alfentanil, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of alfentanil HCl injection and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of alfentanil HCl injection is achieved [see Warnings and Precautions (5.4)].

After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the alfentanil plasma concentration will decrease [see Clinical Pharmacology (12.2)], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to alfentanil.

Table 2 includes clinically significant drug interactions with alfentanil HCl injection.

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Clinical Impact</th>
<th>Intervention</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>May reduce the analgesic effect of alfentanil HCl injection and precipitate withdrawal symptoms.</td>
<td>Avoid concomitant use.</td>
<td>Urethane, intravenous methylene blue.</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.</td>
<td>Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.</td>
<td>Furosemide, ethacrynic acid, triamterene</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Diazepam may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.</td>
<td>Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of alfentanil HCl injection and/or the muscle relaxant as necessary.</td>
<td>Intravenous diazepam, oral diazepam, oral clonazepam</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Clinical impact: Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.</td>
<td>Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.</td>
<td>Urea, ethacrynic acid, furosemide, indapamide</td>
</tr>
<tr>
<td>Anticholinergic Drugs</td>
<td>Clinical impact: The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.</td>
<td>Monitor patients for signs of urinary retention or reduced gastric motility when alfentanil HCl injection is used concomitantly with anticholinergic drugs.</td>
<td>Atropine, scopolamine, hyoscine, benzatropine</td>
</tr>
<tr>
<td>CYP3A4 Inducers</td>
<td>The concomitant use of alfentanil HCl injection and CYP3A4 inducers can decrease the plasma concentration of alfentanil [see Clinical Pharmacology (12.3)], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to alfentanil [see Warnings and Precautions (5.13)].</td>
<td>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the alfentanil plasma concentration will decrease [see Clinical Pharmacology (12.3)], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.</td>
<td>Rifampin, carbamazepine, phenytoin</td>
</tr>
<tr>
<td>Benzodiazepines and Other Central Nervous System (CNS) Depressants</td>
<td>Diazepam administered immediately prior to or in conjunction with high doses of alfentanil HCl injection may produce vasodilation and hypotension, and may result in delayed recovery. Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when alfentanil HCl injection is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents.</td>
<td>Monitor patients receiving alfentanil HCl injection and benzodiazepines or other CNS depressants for hypotension patients and prolonged respiratory depression and sedation. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following alfentanil induction. [see Warnings and Precautions (5.2)].</td>
<td>Alprazolam, lorazepam, diazepam, midazolam, triazolam, clonazepam, oxazepam, temazepam</td>
</tr>
<tr>
<td>Serotonergic Drugs</td>
<td>The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome [see Warnings and Precautions (5.7)].</td>
<td>If concomitant use is necessary, consider increasing the alfentanil plasma concentration will increase [see Clinical Pharmacology (12.3) and Precautions (5.1)].</td>
<td>Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazadone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and others, such as linezolid and intravenous methylene blue).</td>
</tr>
<tr>
<td>Monoamine Oxidase Inhibitors</td>
<td>Severe and unpredictable potentiation of monoamine oxidase (MAO) inhibitors has been reported rarely with alfentanil. MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see Warnings and Precautions (5.2)].</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.25 mg/kg/day (4.6, 18, or 72.6 times the human total dose of 335 mcg/kg based on body surface area, respectively). Decreased free fetuses per litter and decreased litter size in the high dose group were noted in the presence of maternal toxicity (decreased body weight gain and mortality in the high-dose group). No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered 8 mg/kg/day alfentanil (232 times the human dose of 335 mcg/kg/day based on body surface area) continuously from Gestation Day 5 through Gestation Day 20 via subcutaneous infusions using osmotic minipumps.

Pregnant rats were treated intravenously with alfentanil 0.08, 0.31, or 1.25 mg/kg/day (2.3, 9, or 36.6 times the human total dose of 335 mcg/day based on body surface area, respectively) during gestation and throughout lactation. Reduced birth weights and decreased pup survival were noted in the mid- and high-dose groups in the presence of maternal toxicity (increased mortality in the mid- and high-dose groups).

8.2 Lactation

Risk Summary

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Alfentanil HCl Injection and any potential adverse effects on the breastfed infant from Alfentanil HCl Injection or from the underlying maternal condition. Clinical Considerations

Infants exposed to Alfentanil HCl Injection through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2)].

8.4 Pediatric Use

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

8.5 Geriatric Use

In one clinical trial, the dose of alfentanil required to produce anaesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. The initial dose of Alfentanil HCl Injection should be appropriately reduced in elderly. Patients over the age of 65 have been found to have reduced plasma clearance and extended terminal elimination which may prolong postoperative recovery. Elderly patients (aged 65 years or older) may have increased sensitivity to alfentanil. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Alfentanil HCl Injection slowly in geriatric patients [see Warnings and Precautions (5.6)].

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Alfentanil HCl Injection should be administered with caution patients with liver dysfunction because of the extensive hepatic metabolism. Reduce the dosage as needed and monitor closely for signs of respiratory depression, sedation, and hypotension.

8.7 Renal Impairment

Alfentanil HCl Injection should be administered with caution patients with kidney dysfunction because of the renal excretion of alfentanil HCl and its metabolites. Reduce the dosage as needed and monitor for signs of respiratory depression, sedation, and hypotension.

8.8 Respiratory Impairment

Alfentanil HCl Injection 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 anesthesia, this can be managed by assisted or controlled respiration.

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Alfentanil HCl Injection contains alfentanil, a Schedule II controlled substance.

9.2 Abuse

Alfentanil HCl Injection contains alfentanil, a substance with a high potential for abuse similar to other opioids including morphine, sufentanil etc. Alfentanil HCl Injection can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.1)]. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal. Alfentanil HCl Injection, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

8.9 Overdose

Acute overdose with Alfentanil HCl Injection can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and hypotension. If necessary, auffed intravenous catheter should be inserted for the maintenance of venous access. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Use in Specific Populations (8.1)].

10. OVERDOSAGE

Clinical Management

Acute overdose with Alfentanil HCl Injection can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and hypotension. If necessary, auffed intravenous catheter should be inserted for the maintenance of venous access. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Use in Specific Populations (8.1)].

11. DESCRIPTION

Alfentanil HCl Injection, contains alfentanil, an opioid agonist, chemically designated as N-[2-(4-ethyl-4-5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl-N-phenylpropanamide monohydrochloride (1:1) with a molecular weight of 452.98 and an n-octanol: water partition coefficient of 128:1 at pH 7.4. The structural formula of Alfentanil HCl is:

![Structural formula of Alfentanil HCl](image)

Alfentanil HCl Injection is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 mcg per mL of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0 to 6.0. Each mL contains:

Active: Alfentanil base 500 mcg.

Inactive: Sodium Chloride 9 mg and Water for Injection q.s.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alfentanil HCl Injection is an opioid agonist. The principal actions of therapeutic value are analgesia and sedation.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Alfentanil produces respiratory depression by direct action on brain stem respiratory centers.
The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation. Alfentanil causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

**Effects on the Gastrointestinal Tract and Other Smooth Muscle**

Alfentanil causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

**Effects on the Cardiovascular System**

Alfentanil produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

**Effects on the Endocrine System**

Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon [see Adverse Reactions (6.2)].

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see Adverse Reactions (6.2)].

**Effects on the Immune System**

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

**Concentration–Efficacy Relationships**

In one study involving 15 patients administered alfentanil with nitrous oxide/oxygen, a narrow range of plasma alfentanil concentrations, approximately 310 to 340 ng/mL was shown to provide adequate anesthesia for intra-abdominal surgery, while lower concentrations, approximately 190 ng/mL blocked responses to skin closure. Plasma concentrations between 100 to 200 ng/mL provided adequate anesthesia for superficial surgery.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids [see Dosage and Administration (2.1)]. The minimum effective analgesic concentration of alfentanil for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

**Concentration–Adverse Reaction Relationships**

There is a relationship between increasing alfentanil plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see Dosage and Administration (2.1, 2.2)].

**12.3 Pharmacokinetics**

Alfentanil HCl Injection is administered intravenously for the induction of analgesia and anesthesia.

**Absorption**

The onset of the anesthetic action is immediate when Alfentanil HCl Injection is administered intravenously.

**Distribution**

The pharmacokinetics of alfentanil can be described as a three-compartment model with sequential distribution half-lives of 1 and 14 minutes. Alfentanil has an apparent volume of distribution of 0.4 to 1 L/kg, with an average plasma clearance of 5 mL/kg/min. Plasma protein binding of alfentanil is approximately 92%.

**Elimination**

Alfentanil has a terminal elimination half-life of 90 to 111 minutes.

**Metabolism**

The liver is the major site of biotransformation.

**Excretion**

Only 1% of the dose is excreted as unchanged drug; urinary excretion is the major route of elimination of metabolites.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis**

Long-term studies in animals to evaluate the carcinogenic potential of alfentanil have not been conducted.

**Mutagenesis**

Alfentanil was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) or clastogenic in the *in vivo* micronucleus assay.

**Impairment of Fertility**

Female rats were treated with intravenous alfentanil beginning 14 days prior to mating and throughout gestation with doses of 0.08, 0.31, or 1.25 mg/kg (2.3, 9, or 36.3 times the human daily dose of 335 mcg/day based on body surface area, respectively) beginning 56 days prior to mating with non-dosed females. There was reduced pregnancy rate in the untreated females mated to the high dose males; however, there was also paternal toxicity was noted in all animals (decreased weight gain in all groups and mortality in the two highest dose groups).

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**HOW SUPPLIED**

Alfentanil HCl Injection, USP is supplied in individually sealed dosage forms which pose no known risk to health care providers having incidental contact. Accidental dermal exposure to alfentanil should be treated by rinsing the affected area with water.

Store at 20° to 25°C (68 to 77°F). [See USP Controlled Room Temperature]. Protect from light.