PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[N]ALFENTANIL INJECTION USP

Alfentanil Hydrochloride

Solution for Injection, 500 mcg/mL, Intravenous

USP

Opioid Analgesic
Adjunct to Anesthesia

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RECENT MAJOR LABEL CHANGES

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TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Alfentanil Injection USP 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 anesthesia when given in incremental doses for the maintenance of anesthesia at dosages of 5-75 mcg/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 mcg/kg/min with nitrous oxide/oxygen in the maintenance of general anesthesia. (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.

1.1 Pediatrics

Pediatrics : The safety and efficacy of Alfentanil Injection has not been studied in the pediatric population. Therefore the use of Alfentanil Injection is not recommended in patients under 18 years of age (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics).

1.2 Geriatrics

Geriatrics : In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

2 CONTRAINDICATIONS

Patients who are hypersensitive to the active substance alfentanil or other opioid analgesics or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

Alfentanil Injection USP is contraindicated as analgesic in:

- Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).

- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus.
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale.
- Patients with acute alcoholism, delirium tremens, and convulsive disorders.
- Patients with severe central nervous system (CNS) depression, increased cerebrospinal or intracranial pressure, and head injury.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breast-feeding, and during pregnancy, or during labour and delivery (see Serious Warnings and Precautions and WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the risks of overdose and death with parenteral opioid formulations, Alfentanil Injection USP should only be used in patients for whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

Alfentanil Injection USP poses risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing Alfentanil Injection USP, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). Alfentanil Injection USP should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of Alfentanil Injection USP. Infants exposed in-utero or through breast milk are at risk of a life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of Alfentanil Injection USP or following a dose increase.

Serious Warnings and Precautions

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of Alfentanil Injection USP during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol
The co-ingestion of alcohol with Alfentanil Injection USP should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- **Reserve concomitant prescribing of Alfentanil Injection USP and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Adults
The dosage of Alfentanil Injection USP should be individualized according to age, body weight, physical status, underlying pathological condition, concomitant medication including human cytochrome P450 3A4 inhibitors (see DRUG INTERACTIONS), and type and duration of surgical procedure and anesthesia.

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.

4.2 Recommended Dose and Dosage Adjustment

Surgical Use - Dosage Chart

Indication	Approximate Duration of Anesthesia	Initial Dose	Increments/Infusion	Total Dose	Effects
Incremental Injection	≤30 min	5-20 mcg/kg (ventilated or spontaneously breathing)	2.5 mcg/kg	5-40 mcg/kg	Minimal hemodynamic change with some attenuation of sympathetic response to surgical stress. More rapid recovery than fentanyl. At doses >11 mcg/kg transient apnea may occur which may require assisted ventilation.
Incremental Injection	30-60 min	20-50 mcg/kg (ventilated)	5-15 mcg/kg	up to 75 mcg/kg	Minimal hemodynamic changes with attenuation of response to laryngoscopy and intubation. Recovery times better than or equal to fentanyl.
Continuous Infusion	>45 min	50-75 mcg/kg (ventilated)	0.5-1.5 mcg/kg/min	dependent on duration of procedure	Attenuation of cardiovascular response to intubation and incision, intraoperative stability and faster recovery than thiopental inhalation.

Continuous infusion: 0.5-1.5 mcg/kg/min administered with nitrous oxide/oxygen in patients undergoing general anesthesia. When the infusion is started at 0.5 mcg/kg/min and there are changes in vital signs that indicate surgical stress or lightening of anesthesia, these may be controlled by increasing the rate up to 1.5 mcg/kg/min or administering up to 3 bolus doses of 7 mcg/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 mcg/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.

Intensive Care Use - Dosage Chart

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.

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

Continuous Infusion: The recommended initial infusion rate of alfentanil in mechanically ventilated adult patients is 0.5 mcg/kg/min. The rate of infusion should be reassessed regularly and individualised 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 mcg/kg/min effectively prevent pain and aid compliance with mechanical ventilation.

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

Supplemental Bolus Doses: Supplemental bolus doses of 10-20 mcg/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.

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

Pediatrics : The safety and efficacy of Alfentanil Injection has not been studied in the pediatric population. Therefore the use of Alfentanil Injection is not recommended in patients under 18 years of age (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics).

Geriatrics: Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. Alfentanil Injection USP should be initiated at a low dose and slowly titrated to effect (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).

Premedication
The selection of pre-anesthetic medication should be based upon the needs of the individual patient.

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

Use with Non-Opioid Medications
If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. Alfentanil Injection USP can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration
Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including Alfentanil Injection USP. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see WARNINGS AND PRECAUTIONS). Tapering should be individualised and carried out under medical supervision.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

4.3 Administration

Strict aseptic technique must always be maintained during handling of alfentanil.

5 OVERDOSAGE

Symptoms
Overdosage is expected to lead to symptoms and signs that are an extension of the pharmacological actions of alfentanil. Depending on the individual sensitivity, the clinical presentation is determined primarily by the degree of respiratory depression, which varies from bradypnea to apnea.

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.

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 hypovolemia should be considered and, if present, it should be controlled with appropriate parenteral fluid administration.

For management of a suspected drug overdose, contact your regional poison control centre for the most recent information.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
intravenous	Sterile, preservative free aqueous solution for injection, 500 mcg/mL alfentanil (as hydrochloride)	sodium chloride for isotonicity, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection

Alfentanil Injection USP is available in 2 mL amber vials (boxes of 10).

LATEX-FREE STOPPER - Stopper contains no dry natural rubber.

7 WARNINGS AND PRECAUTIONS

General

Alfentanil Injection USP should be administered only by persons specifically trained in the use of intravenous anesthetics. Vital signs should be monitored routinely.

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.

As with other strong opioids, patients who have received alfentanil Injection USP should have appropriate surveillance. Resuscitation equipment and a opioid antagonist should be readily available.

Intensive care patients: alfentanil Injection USP should not be used in spontaneously breathing patients in the intensive care unit.

Alfentanil, 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. At high doses, muscular rigidity will occur unless a muscle relaxant is used.

The incidence may be reduced by 1) slow intravenous injection; 2) premedication with benzodiazepines; 3) routine administration of neuromuscular blocking agents for balanced intravenous anesthesia; 4) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of alfentanil at dosages up to 75 mcg/kg. 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 and loss of consciousness, which may persist into or recur in the early postoperative or postinfusion period. **If Alfentanil Injection USP 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 anesthetic agents may result in significant respiratory depression even with small doses of alfentanil.**

Alfentanil Injection USP should only be prescribed by persons knowledgeable in the continuous administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking Alfentanil Injection USP as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of Alfentanil Injection USP can occur at particularly high doses. An Alfentanil Injection USP dose reduction or change in opioid may be required.

Abuse and Misuse
Like all opioids, Alfentanil Injection USP is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, Alfentanil Injection USP should be prescribed and handled with caution.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as Alfentanil Injection USP, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Carcinogenesis and Mutagenesis
See TOXICOLOGY section.

Cardiovascular
Rapid intravenous injection of opioid analgesics increases the possibility of hypotension and respiratory depression and should be avoided (see DOSAGE AND ADMINISTRATION). Alfentanil Injection USP administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of Alfentanil Injection USP.

The use of Alfentanil Injection USP in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

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

Careful titration of dosage may be required in patients with special conditions, such as uncontrolled hypothyroidism, alcoholism, impaired hepatic or renal function.

Dependence/Tolerance
As with other opioids, tolerance and physical dependence may develop upon repeated administration of Alfentanil Injection USP and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage).

Drug and Alcohol Addiction
Alfentanil Injection USP is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to Alfentanil Injection USP; extreme caution and awareness is warranted to mitigate the risk.

Endocrine
Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal
Alfentanil Injection USP and other morphine-like opioids have been shown to decrease bowel motility. Alfentanil Injection USP may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see CONTRAINDICATIONS).

Hepatic/Biliary/Pancreatic
In patients with compromised liver function (and in geriatric patients >65 years) the plasma clearance of alfentanil may be reduced and terminal elimination half-life extended which may be prolong postoperative recovery.

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.

Neonatal Opioid Withdrawal Syndrome (NOWS)
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the

drug by the newborn.

Use of Alfentanil Injection USP is contraindicated in pregnant women (see CONTRAINDICATIONS).

Neurologic
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.

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Alfentanil Injection USP should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-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 DRUG INTERACTIONS). 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 Injection USP 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 DRUG INTERACTIONS).

Alfentanil Injection USP should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see CONTRAINDICATIONS and ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Head Injury: The respiratory depressant effects of alfentanil, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, alfentanil may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, alfentanil must be used with extreme caution and only if it is judged essential (see CONTRAINDICATIONS).

Serotonin Syndrome: Alfentanil Injection USP could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotoninergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Alfentanil Injection USP should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see DRUG INTERACTIONS).

Peri-Operative Considerations
Alfentanil Injection USP is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with Alfentanil Injection USP for at least 24 hours before the operation and Alfentanil Injection USP should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated.

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Alfentanil and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

Psychomotor Impairment
Alfentanil Injection USP may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of alfentanil with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Renal
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.

Respiratory
Respiratory Depression: Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Alfentanil should be used with extreme caution in patients with substantially decreased respiratory

reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Alfentanil Injection USP, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with Alfentanil Injection USP and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

To reduce the risk of respiratory depression, proper dosing and titration of Alfentanil Injection USP are essential. Overestimating the Alfentanil Injection USP dose when converting patients from another opioid product can result in a fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and DOSAGE AND ADMINISTRATION).

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by alfentanil may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period.

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with Alfentanil Injection USP, as in these patients, even usual therapeutic doses of Alfentanil Injection USP may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of Alfentanil Injection USP is contraindicated in Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

Sexual Function/Reproduction
Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see ADVERSE REACTIONS, Post-Marketing Experience).

7.1 Special Populations

7.1.1 Special Risk Group

Alfentanil should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

7.1.2 Pregnant Women

Pregnant Women: Studies in humans have not been conducted. Alfentanil Injection USP crosses the placental barrier and is contraindicated in pregnant women.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, ADVERSE REACTIONS, Post-marketing Experience).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour and Delivery
Since opioids can cross the placental barrier and are excreted in breast milk, Alfentanil Injection USP is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Alfentanil Injection USP is used in this population

7.1.3 Breast-feeding

Since opioids can cross the placental barrier and are excreted in breast milk, Alfentanil Injection USP is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if Alfentanil Injection USP is used in this population.

7.1.4 Pediatrics

The safety and efficacy of Alfentanil Injection USP have not been studied in the pediatric population. Therefore, use of Alfentanil Injection USP is not recommended in patients under 18 years of age.

7.1.5 Geriatrics

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

8 ADVERSE REACTIONS

Adverse effects of Alfentanil Injection USP (alfentanil injection) are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The most frequently reported adverse effects (incidence ≥10%) are: nausea and vomiting. Undesirable effects listed below have been reported in clinical trials (1157 subjects) and/or from spontaneous reports from post-marketing experience. The following terms and frequencies are applied:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); and not known (cannot be estimated from the available clinical trial data).

Immune system disorders
Not known: Hypersensitivity (including anaphylactic reaction, anaphylactoid reaction and urticarial

Psychiatric disorders
Common: Euphoric mood
Rare: Agitation, crying
Not known: Disorientation

Nervous system disorders
Common: Movement disorder, dizziness, sedation, dyskinesia
Uncommon: Headache, somnolence, unresponsive to stimuli
Not known: Loss of consciousness (postoperative period), convulsion, myoclonus

Eye disorders
Common: Visual disturbance
Not known: Miosis

Cardic disorders
Common: Bradycardia, tachycardia
Uncommon: Arrhythmia, heart rate decreased
Not known: Cardiac arrest

Vascular disorders
Common: Hypertension, hypotension, blood pressure decreased, blood pressure increased
Rare: Vein pain

Respiratory, thoracic and mediastinal disorders
Common: Apnea
Uncommon: Hiccups, hypercapnia, laryngospasm, respiratory depression (including fatal outcome)
Rare: Bronchospasm, epistaxis
Not known: Respiratory arrest, cough

Gastrointestinal disorders
Very common: Nausea,vomiting

Skin and subcutaneous tissue disorders
Uncommon: Dermatitis allergic, hyperhidrosis
Rare: Pruritus
Not known: Erythema, rash

Musculoskeletal and connective tissue disorders
Common: Muscle rigidity

The incidence of chest wall rigidity can be significantly reduced by pretreatment with a nonparalyzing dose of a neuromuscular blocking agent (i.e. nondepolarizing muscle relaxant).

General disorders and administration site conditions
Common: Chills, injection site pain, fatigue
Uncommon: Pain*Not known:* Pyrexia

Injury, poisoning and procedural complications
Common: Procedural pain
Uncommon: Agitation postoperative, airway complication of anesthesia, confusion postoperative

Rare: Anesthetic complication neurological, procedural complication, endotracheal intubation complication

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

Androgen deficiency: 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. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

9 DRUG INTERACTIONS

9.1 Overview

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants
Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. 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 WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment). Alfentanil Injection USP should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

9.2 Drug-Drug Interactions

Central Nervous System (CNS) Depressants
Both magnitude and duration of CNS and cardiovascular effects may be enhanced when alfentanil is administered to patients receiving barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non-selective 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 anesthetic procedure.

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

Hepatic Enzyme 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, 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 drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of alfentanil

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

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.

Serotonergic Drugs
Coadministration of alfentanil with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see WARNINGS AND PRECAUTIONS).

9.3 Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see WARNINGS AND PRECAUTIONS, General).

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Alfentanil is a potent opioid analgesic/anesthetic with a rapid onset and short duration of action. The analgesic potency of alfentanil is ¼ to ⅓ that of fentanyl. Low to moderate doses of alfentanil in short-stay surgical procedures provide good analgesic protection against hemodynamic responses to surgical stress and rapid recovery. Hemodynamic stability and duration of action increase with increasing dosage. At high doses followed by continuous infusion in general surgery alfentanil provides hemodynamic 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 metabolised 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%.

10.2 Pharmacodynamics

At dosages of 8 mcg/kg to 40 mcg/kg alfentanil produces analgesia in short-stay surgery. For longer procedures, doses up to 75 mcg/kg in intubated patients provide better hemodynamic stability with recovery time comparable to fentanyl. A preintubation loading dose of 50-75 mcg/kg attenuates the response to laryngoscopy, intubation and incision. Subsequent administration of alfentanil infusion administered at a rate of 0.53 mcg/kg/min with nitrous oxide/oxygen dampens sympathetic responses to surgical stress and maintains hemodynamic stability, providing smooth and rapid postoperative recovery.

At doses of approximately 105-119 mcg/kg, alfentanil produces sedation and analgesia; an anesthetic ED_{90} of 182 mcg/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 anesthesia for intra-abdominal surgery, while lower concentrations, approximately 250 ng/mL, blocked responses to abdominal closure. Levels from 100-200 ng/mL provide adequate anesthesia 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 mcg/kg of alfentanil have shown no elevation in plasma histamine levels and no indication of histamine release.

Central Nervous System
Alfentanil produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Alfentanil depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

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 origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone overdose.

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 contractions are decreased. 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 gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System
Alfentanil may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

10.3 Pharmacokinetics

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

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

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

Elimination: Only 1% of the dose is excreted as unchanged drug; urinary excretion is the major route of elimination of metabolites. Plasma protein binding of alfentanil is approximately 92%.

Special Populations and Conditions

Pediatrics : The safety and efficacy of Alfentanil Injection has not been studied in the pediatric population. Therefore the use of Alfentanil Injection is not recommended in patients under 18 years of age (see INDICATIONS, WARNINGS AND PRECAUTIONS, Special Populations and Conditions, Pediatrics).

Geriatrics: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy (see INDICATIONS, WARNINGS AND PRECAUTIONS, Special Populations and Conditions, Geriatrics).

Hepatic Insufficiency: After administration of a single intravenous dose of 50 mcg/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 WARNINGS AND PRECAUTIONS).

Renal Insufficiency: 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 WARNINGS AND PRECAUTIONS).

11 STORAGE, STABILITY AND DISPOSAL

Store between 15 and 30°C. Protect from light. Discard unused portion. Single use vials.

12 SPECIAL HANDLING INSTRUCTIONS

Store in a secure location, and keep out of unauthorized reach. Unused portion of alfentanil should be securely discarded.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

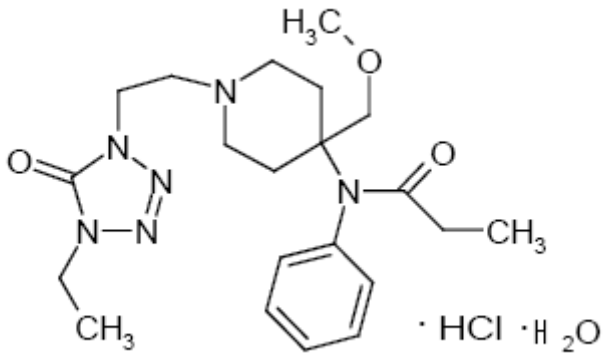
Drug Substance

Proper name: Alfentanil hydrochloride

Chemical name: *N*-[1-[2-(4-Ethyl-5-oxo-2-tetrazolin-1-yl)-ethyl]-4-methoxymethyl-4-piperidyl] propionanilide monohydrochloride monohydrate

Molecular formula and molecular mass: $C_{21}H_{32}N_6O_3 \cdot HCl \cdot H_2O$; 470.99 g/mol

Structural formula:



Physicochemical properties:

Description:	White to almost-white powder
Solubility:	Soluble in water, freely soluble in methanol, alcohol, and chloroform. Sparingly soluble in acetone.
Melting point:	138°C with decomposition
pH:	Between 4.0 and 6.0 (solution of 0.05% w/v in water)
pKa:	7.59 ± 0.40 (alfentanil base)

14 CLINICAL TIRALS

Not available.

15 NON-CLINICAL PHARMACOLOGY

15.1 Pharmcodynamics

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_{50} 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_{50}/ED_{50}) 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_{50} values were 0.044 mg/kg for alfentanil, 3.15 mg/kg for morphine and 0.011 mg/kg for fentanyl. The intravenous LD_{50} 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_{50}.

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 mcg/kg of alfentanil were studied in both anesthetised and conscious dogs. A decrease in heart rate was observed at doses between 50 and 400 mcg/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, AV dissociation and AV 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 mcg/kg/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 hemodynamic changes which have been related to surgical trauma and the absence of other anesthetic 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 mcg/kg and fentanyl 100 mcg/kg on spontaneous and reflex cardiovascular responses were recorded in anesthetised 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
Anesthetic 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 normalisation 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 hemodynamic parameters were evaluated in the dog following the administration of alfentanil 0.5 mg/kg with succinylcholine, pancuronium or propanolol. There were decreases in heart rate and partial AV 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. Propanolol 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 hemodynamic 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 hemodynamic 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 (≤50 mcg/mL) did not induce significant hemolysis of red blood cells or plasma fraction precipitation when incubated with whole blood.

15.2 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 feces as the secondary route (24.0%). Alfentanil was rapidly metabolised 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 feces 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.

Tissue distribution studies of ^{3}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}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 $t_{½}$ was 1.7 minutes and $t_{½\beta}$ was 11 minutes. Total plasma clearance averaged 26.9 mL/min/kg.

In the dog, plasma levels of ^{3}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 feces. Only 1% of the recovered dose was unchanged alfentanil.

In a comparative pharmacokinetic study, plasma levels of alfentanil decayed biphasically in the rat ($t_{½\beta}$ = 12 min) and triphasically in the dog ($t_{½\beta}$ = 104 min) and in man ($t_{½\beta}$ = 88 min). In dogs, the pharmacokinetic behaviour was not significantly different at analgesic (50 mcg/kg) or anesthetic (300 mcg/kg) doses.

16 NON-CLINICAL TOXICOLOGY

16.1 Acute Toxicity

LD_{50} values were determined in the following species:

Species/Observation Period	No. Animals/Dose	LD_{50} mg/kg
Albino Mice	10 F	72.2 (47.4-110)
7 days	10 M	73.8 (44.8-121)
Wistar Rats	10 F	43.0 (23.7-78.0)
7 days	10 M	50.9 (30.7-84.2)
Albino Guinea Pigs	10 F	81.9 (54.7-123)
14 days	10 M	71.8 (54.9-93.9)
Mongrel Dogs	4 F	87.5 (67.0-114)
14 days	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_{50} of alfentanil infusion was 400 mg/kg in the rat; approximately 8 times the acute LD_{50} for the injection.

16.2 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, hematology, 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.

16.3 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 Wister 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.

16.4 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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[N]ALFENTANIL INJECTION USP
Alfentanil Injection

Read this carefully before you are given **Alfentanil Injection USP**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Alfentanil Injection USP**.

Serious Warnings and Precautions

- **Even if you take Alfentanil Injection USP as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **You may get life-threatening breathing problems while taking Alfentanil Injection USP. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **If you took Alfentanil Injection USP while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
  - **has changes in their breathing (such as weak, difficult or fast breathing)**
  - **is unusually difficult to comfort**
  - **has tremors (shakiness)**
  - **has increased stools, sneezing, yawning, vomiting, or fever**

  Seek immediate medical help for your baby.
- **Taking Alfentanil Injection USP with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is Alfentanil Injection USP used for?
Alfentanil Injection USP is a pain medication. It is given along with other drugs used for anesthesia by your doctor. It may be given:
• to you before and/or during surgery;
• if you are undergoing painful medical procedures;
• to patients on a ventilator who are in the intensive care unit.

How does Alfentanil Injection USP work?
Alfentanil Injection USP is a fast acting pain relief medication and belongs to a class of

medicines known as opioids. It provides pain relief for a short period of time. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in Alfentanil Injection USP?
Medicinal ingredients: Alfentanil (as alfentanil hydrochloride)
Non-medicinal ingredients: Hydrochloric acid and/or sodium hydroxide, sodium chloride, water for injection.

Alfentanil Injection USP comes in the following dosage forms:
Solution for injection: 500 mcg/mL.

Do not use Alfentanil Injection USP if:
- your doctor did not prescribe it for you
- you are allergic to alfentanil or to any of the other ingredients in **Alfentanil Injection USP**
- you are allergic to other drugs in the same family
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are pregnant or planning to become pregnant or you are in labour
- your are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you are given Alfentanil Injection USP. Talk about any health conditions or problems you may have, including if you:
- have a history of illicit or prescription drug abuse or alcohol abuse
- have trouble breathing or other breathing problems
- have severe kidney, liver or lung disease
- have heart disease
- have low blood pressure
- have past or current ~~or had~~ depression
- suffer from chronic or severe constipation
- have problems with your adrenal or prostate gland
- have, or had in the past, hallucinations or other severe mental problems
- suffer from migraines
- are pregnant or planning to become pregnant
- are breastfeeding

Other warnings you should know about:

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, Nursing, Labour and Delivery:
Do not use **Alfentanil Injection USP** while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. **Alfentanil Injection USP** can then cause life-threatening breathing problems in your unborn baby or nursing infant.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to **Alfentanil Injection USP**. **Alfentanil Injection USP** can cause:

- drowsiness
- dizziness or
- light headedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting
- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off **Alfentanil Injection USP**.

Serotonin Syndrome: Alfentanil Injection USP can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take **Alfentanil Injection USP** with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Alfentanil Injection USP:

- alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are being given **Alfentanil Injection USP**. It can lead to:
    - drowsiness
    - unusually slow or weak breathing
    - serious side effects or
    - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by **Alfentanil Injection USP**
- other opioids analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders)
- drugs used to treat serious mental or emotional disorders (such as bipolar disorder and schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- some heart medications (such as beta blockers)
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

Your doctor should tell you what medication you may or may not take after your surgery.

How Alfentanil Injection USP is given: [section kept as is since product is injection and not oral product]
Afentanil Injection USP is givenvia an injection.

You should be given it:

- only in a hospital or clinic that has the proper monitoring and support equipment in place.
- by a healthcare professional that has been specifically trained in the use of intravenous anesthetics.

Usual dose: Your doctor will decide the best dose for you. It will depend on your age, weight, your health, medications you are currently taking and the type of surgery you are having.

Overdose:

If you think you have been given too much Alfentanil Injection USP, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from being given Alfentanil Injection USP?

You may experience some of these side effects during your procedure or after it. These are not all the possible side effects you may feel. If you experience any side effects not listed here, talk to your healthcare professional.

- nausea

- vomiting
- poor appetite
- drowsiness
- insomnia
- dizziness
- fainting
- dry mouth
- weakness, uncoordinated muscle movement
- itching
- constipation
- high or low blood pressure
- excessive sweating
- feeling of intense happiness or excitement (euphoria)
- feeling agitated
- crying
- headache
- trouble with your vision
- sleep apnea (a sleep disorder where your breathing is interrupted during sleep)
- pain at the injection site
- feeling tired
- chills
- low sex drive, impotence (erectile dysfunction), infertility

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing		x	
Drowsiness, dizziness.		x	
Fast, slow, or uneven heartbeat.		x	
Severe nausea or vomiting.		x	
Stiffness in the muscles of your neck, chest, hands, or legs.		x	
Trouble breathing, or chest tightness.		x	
UNCOMMON Mild skin rash or itching.	x		
Twitching or muscle movements you cannot control.	x		
Pain, itching, burning, swelling, or lump under your skin where the needle is placed.	x		

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Twitching or muscle movements you cannot control.	x		
RARE Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone cold and clammy skin.			x
Respiratory Depression: Slow, shallow or weak breathing.			x
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			x
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			x
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		x	
Fast, Slow or Irregular Heartbeat: heart palpitations.		x	
Low Blood Pressure: dizziness, fainting, light-headedness.	x		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			x

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- **Keep unused or expired Alfentanil Injection USP in a secure place to prevent theft, misuse or accidental exposure.**
- Store sterile solution for injection between 15 and 30°C. Protect from light. Discard unused portion. Single use vials.
- Keep out of reach and sight of children.

If you want more information about Alfentanil Injection USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.sandoz.ca, or by calling 1-800-361-3062.

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