PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

ALFENTANIL KALCEKS SOLUTION FOR INJECTION/INFUSION 0.5 MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains alfentanil hydrochloride equivalent to 500 micrograms alfentanil.
Each 2 ml ampoule contains alfentanil hydrochloride equivalent to 1 mg alfentanil.

Excipient with known effect: sodium (see section 4.4).
Each 2 ml ampoule contains 7.1 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear, colourless solution free from visible particles.
pH of solution is 4.0 - 6.0.
Osmolality is 270 - 310 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Alfentanil is indicated for use as:
- an anesthetic induction agent.
- an opioid analgesic in general as well as an adjuvant to regional anesthesia and for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures.

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

4.2 Posology and method of administration

The dosage of alfentanil should be individualized according to age, body weight, physical status, underlying pathological condition, use of other drugs and type of surgery and anesthesia.
The initial dose should be reduced in the elderly (>65 years of age) and in debilitated patients. In children it should be increased. The effect of the initial dose should be taken into account in determining supplemental doses.
To avoid bradycardia, a small intravenous (i.v.) dose of an anti-cholinergic agent just before anesthetic induction may be administered.

Dosage

Adults

For use as an anesthetic induction agent

An i.v. bolus dose of ≥120 mcg/kg (17 ml/70 kg) alfentanil will induce unconsciousness and analgesia while maintaining good cardiovascular stability in patients with adequate muscle relaxation.

For short procedures and use in outpatients
Small doses of alfentanil are most useful for minor, short surgical procedures and for outpatients, provided cardiopulmonary monitoring equipment is available.

An i.v. bolus dose of 7 to 15 mcg/kg (1 to 2 ml/70 kg) is usually adequate for procedures lasting less than 10 minutes. Should the duration of the procedure exceed 10 minutes, further increments of 7 to 15 mcg/kg (1 to 2 ml/70 kg) should be given every 10 to 15 minutes or as required.

Although ventilatory support must be available, spontaneous breathing is maintained in most instances with a dose of 7 mcg/kg (1 ml/70 kg) or less, slowly injected; suggested increments with this technique are 3.5 mcg/kg (0.5 ml/70 kg). When postoperative nausea occurs, it is of relatively short duration and usually controlled by conventional measures.

For procedures of medium duration
The dose of initial i.v. bolus should be adapted to the expected duration of the surgical procedure as follows:

Table 1. Dosing for medium duration procedures

Duration of the procedure (min.)	Alfentanil mcg/kg	i.v. bolus dose ml/70 kg
10-30	20-40	3-6
30-60	40-80	6-12
>60	80-150	12-20

When surgery is more prolonged or more aggressive, analgesia can be maintained by:
- either increments of 15 mcg/kg (2 ml/70 kg) alfentanil when required (to avoid postoperative respiratory depression, no alfentanil should be administered during the last 10 minutes of surgery);
- or a alfentanil infusion at a rate of 1 mcg/kg/min (0.14 ml/70 kg/min) until 5 to 10 minutes before the completion of surgery.

Periods of painful stimuli can easily be managed by small dose increments or by temporarily increasing the infusion rate.

When alfentanil is used without N_2O/O_2 or another inhalation anesthetic, a higher maintenance dose of alfentanil is required.

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

Administration
Alfentanil is administered by bolus injection, or bolus supplemented by increments, or by infusion.

4.3 Contraindications

Hypersensitivity to the active substance, other opioids or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Respiratory depression

Respiratory depression is dose dependent and can be reversed with a specific opioid antagonist (naloxone). Several doses of naloxone may be necessary, as the respiratory depression may last longer than the effect of the opioid antagonist. Profound analgesia is accompanied by marked respiratory depression and loss of consciousness, which can persist or recur throughout the postoperative period. Patients must therefore be kept under adequate monitoring. Resuscitation equipment and opioid antagonists must be readily available. Hyperventilation under anaesthesia can alter the patient's response to CO_2 and thus affect respiration postoperatively.

Risk from concomitant use of central nervous system (CNS) depressants, especially benzodiazepines or related drugs
Concomitant use of alfentanil and CNS depressants especially benzodiazepines or related drugs in spontaneous breathing patients, may increase the risk of profound sedation, respiratory depression, coma and death. If a decision is made to administer alfentanil concomitantly with a CNS depressant, especially a benzodiazepine or a related drug, the lowest effective dose of both drugs should be administered, for the shortest period of concomitant use. Patients should be carefully monitored for signs and symptoms of respiratory depression and profound sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Muscular rigidity
Muscular rigidity, which may also involve thoracic muscles, can occur and may lead to respiratory depression. This can be avoided by slow i.v. injection (normally sufficient in small doses), premedication with benzodiazepines and the use of muscle relaxants. Non-epileptic (myo)clonic movements may occur.

Myasthenia gravis
Alfentanil can cause muscular rigidity following i.v. administration, indicating the use of muscle relaxants. Alfentanil should not, therefore, be used for patients with myasthenia gravis, as the use of muscular relaxants is unsuitable in these subjects.

Heart disease
Bradycardia and possibly cardiac arrest can occur if the patient has been given too low dose of anticholinergic, or if alfentanil is combined with non-vagolytic muscular relaxants. Bradycardia can be treated with atropine.

Special dosage considerations
Opioids can induce hypotension, particularly in hypovolemic patients and patients with heart failure. Induction doses must be adjusted and administered slowly so as to avoid cardiovascular depression. Suitable measures must be taken to maintain stable arterial pressure.

Caution is required in patients with craniocerebral traumas and raised intracranial pressure. Fast bolus injections of opioids must be avoided in the case of compromised cerebral blood flow, as the brief drop in arterial pressure may be accompanied by a short-lived reduction in cerebral perfusion pressure.

Alfentanil must be titrated with care in patients with the following conditions:
- uncontrolled hypothyroidism;
- lung disease, particularly in the case of impaired respiratory capacity;
- alcoholism or impaired liver or kidney function.

These patients also require prolonged post-operative monitoring.

Particular caution should be observed in patients with obstructive airways disease or respiratory depression (if not being ventilated).

Patients should be advised to discontinue monoamine oxidase (MAO) inhibitors 2 weeks before surgery (see section 4.5).

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

Tolerance and opioid use disorder (abuse and dependence)
Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids. Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).
Alfentanil can produce dependence because of its chemical structure and morphinomimetic characteristics. When alfentanil will be given only intraoperatively (as intended) as anaesthetic agent addiction is not to be expected.

Neonatal withdrawal syndrome
If women take opioids chronically during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome. Neonates exposed to opioids chronically may also experience neonatal withdrawal syndrome (see section 4.6).

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

Elderly
The dosage should be reduced in elderly and debilitated patients (see section 4.2).

Excipients
If large amounts of the solution are administered (e.g. more than 6.5 ml, equivalent to more than 1 mmol sodium) the following should be taken into account: This medicinal product contains 3.54 mg sodium per ml of solution, equivalent to 0.18% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs modifying the effect of alfentanil

Other central nervous system (CNS) depressants
Barbiturates, benzodiazepines, antipsychotics (neuroleptics), general anaesthetics and other non-selective CNS depressants (e.g. alcohol) may enhance the respiratory depressant effect of opioids. Once the patient has received such drugs, a lower dose of alfentanil than usual will be required. Similarly, the dose of CNS depressants will be lower after the administration of alfentanil.
Concomitant use of alfentanil in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression and death.

CYP3A4 inhibitors (cytochrome P450 3A4)
Alfentanil is metabolized mainly by cytochrome P450 3A4. *In vitro* data suggest that potent cytochrome P450 3A4 enzyme inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may inhibit the metabolism of alfentanil. Human pharmacokinetic data indicate that the metabolism of alfentanil is inhibited by fluconazole, voriconazole, erythromycin, diltiazem and cimetidine (known cytochrome P450 3A4 enzyme inhibitors). This can also increase the risk of prolonged or delayed respiratory depression. If concomitant use is necessary, particularly careful monitoring will be required for the patient. It may be necessary to reduce the dose of alfentanil.

Effect of alfentanil on other drugs

After administration of alfentanil, the dose of other CNS depressants should be reduced. This is particularly important after surgery, since profound analgesia is accompanied by marked respiratory depression, which can persist or recur during the postoperative period. Administering a CNS depressant, e.g. benzodiazepine, during this period can disproportionally increase the risk of respiratory depression.

Monoamine oxidase inhibitors (MAO inhibitors)
MAO inhibitors should be discontinued two weeks prior to any surgical or anaesthetic procedure (see section 4.4).

Serotonergic drugs
Co-administration of alfentanil and a serotonergic drug such as an selective serotonin reuptake inhibitor (SSRI), serotonin and noradrenaline reuptake inhibitor (SNRI) or monoamine oxidase (MAO) inhibitor may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Effect of alfentanil on the metabolism of other drugs
In combination with alfentanil, the blood concentration of propofol is 17% higher than in the absence of alfentanil. The concomitant use of alfentanil and propofol may require a lower dose of alfentanil.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although no teratogenic or acute embryotoxic effect has been observed in animal studies, insufficient data are available to evaluate any harmful effect in man. Consequently, it is necessary to consider possible risks and advantages before administering alfentanil to pregnant patients.

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

Intravenous administration during childbirth (including Caesarean section) is not advisable because alfentanil crosses the placenta and may suppress spontaneous respiration after the birth. If alfentanil is administered nevertheless, assisted ventilation equipment must be immediately available in the event of the need arising for mother and infant. An opioid antagonist for the child must always be available. The half-life of the opioid antagonist may be shorter than the half-life of alfentanil, and repeated administration of the opioid antagonist may be necessary (see section 4.4.)

Breast-feeding
Alfentanil is excreted in breast milk. Therefore, breast-feeding or the use of expressed breast milk is not recommended for the first 24 hours following the administration of alfentanil.

4.7 Effects on ability to drive and use machines

Alfentanil has major influence on the ability to drive and use machines.
The patient is recommended not to drive or operate machinery for at least 24 hours following administration of alfentanil.

4.8 Undesirable effects

The safety of alfentanil was evaluated in 1,157 subjects, who participated in 18 clinical studies. Alfentanil was administered to induce anaesthesia or as an analgesic/anaesthetic adjuvant to local or general anaesthesia during short, medium-length and long surgical procedures. These people were given at least one dose of alfentanil and generated safety data.

Based on safety data collected from these clinical studies, the most commonly reported undesirable effects (≥5% incidence) (with % incidence) were: nausea (17.0%), vomiting (14.0%), apnoea (8.6%), abnormal voluntary movements (7.9%) and bradycardia (5.4%).

The following table shows undesirable effects from the use of alfentanil reported either in clinical studies or from post-marketing experience.

Table 2 Undesirable effects

Immune system disorders Very rare (<10,000, including isolated reports)	Allergic reactions such as anaphylaxis, anaphylactoid reaction, urticaria).
Psychiatric disorders Common (≥1/100 to <1/10) Rare (≥1/10,000 to <1/1,000) Very rare (<10,000, including isolated reports)	Euphoria. Agitation, crying. Disorientation.
Nervous system disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Very rare (<10,000, including isolated reports)	Movement disorders, dizziness, drowsiness, dyskinesia. Headache, somnolence, unresponsive to stimuli. Loss of consciousness (during postoperative period), convulsions, myoclonus.
Eye disorders Common (≥1/100 to <1/10) Very rare (<10,000, including isolated reports)	Visual disturbances. Miosis.
Cardiac disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Very rare (<10,000, including isolated reports)	Bradycardia, tachycardia. Arrhythmia, decreased heart rate. Cardiac arrest.
Vascular disorders Common (≥1/100 to <1/10) Rare (≥1/10,000 to <1/1,000)	Hypotension, hypertension. Vein pain.
Respiratory, thoracic and mediastinal disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Very rare (<10,000, including isolated reports)	Apnoea. Hiccups, hypercapnia, laryngospasm, respiratory depression (including fatal outcome) Bronchospasm, epistaxis. Respiratory arrest, coughing.

Gastrointestinal disorders Very common (≥1/10)	Nausea, vomiting.
Skin and subcutaneous tissue disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Very rare (<10,000, including isolated reports)	Allergic dermatitis, hyperhidrosis. Pruritus. Erythema, rash.
Musculoskeletal and connective tissue disorders Common (≥1/100 to <1/10)	Muscular rigidity.
General disorders and administration site conditions Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Very rare (<10,000, including isolated reports)	Chills, injection site pain, fatigue. Pain. Fever.
Injury, poisoning and procedural complications Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Procedural pain. Postoperative agitation, airway complications from anaesthesia, postoperative confusion. Neurological anaesthesia complications, procedural complications, endotracheal intubation complications.

Paediatric population
The frequency, type and severity of adverse reactions in children are expected to be as in adults, with the exception of the following:

Mild to moderate muscle rigidity has frequently been seen in neonates, although the number of neonates included in clinical studies was small. Severe rigidity and jerking can occur less commonly and may be accompanied by transient impaired ventilation, especially with high doses of alfentanil or with a rapid rate of intravenous injection.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms
Overdose manifests itself as an extension of alfentanil pharmacological action. Different degrees of respiratory depression can occur, varying from bradypnoea to apnoea.

Treatment
In the event of hypoventilation or apnoea, oxygen must be given and respiration assisted or controlled, as required. A specific opioid antagonist, like naloxone, must be administered in order to control respiratory depression. This does not preclude more instant countermeasures. The respiratory depression may last longer than the effect of the antagonist. Multiple doses of the antagonist may therefore be needed.

If the respiratory depression is associated with muscular rigidity, it may be necessary to administer a neuromuscular blocker intravenously in order to facilitate respiration.

The patient must be kept under close observation: Body heat and adequate fluid intake must be kept up. In the event of severe or persistent hypotension, hypovolaemia must be considered, and this can be corrected by administering parenteral fluid.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid anaesthetics, ATC code: N01AH02

Alfentanil is a potent, fast-acting and short-duration opioid analgesic related chemically to fentanyl. Following intravenous administration of alfentanil, the onset of action is almost immediate; the incipient effect is only one quarter that of an equivalent analgesic dose of fentanyl. The maximum analgesic and respiratory depressant effect sets in within 1-2 minutes.
The period of action for alfentanil is only one third of the equivalent analgesic dose of fentanyl, and it is clearly dose-dependent. For analgesia lasting longer than 60 minutes, infusion is preferred. The depressant effect of alfentanil on respiratory rate and alveolar ventilation is also shorter than that of fentanyl, and in most instances the analgesic effect lasts longer than the respiratory depression. The duration and severity of the respiratory depression are dose-dependent.
Together with other opioid analgesics and depending on the dose and the rate of administration, alfentanil can cause muscular rigidity as well as euphoria, miosis and bradycardia.
At doses of up to 200 mcg/kg alfentanil, there was no significant increase in histamine concentration or clinical signs of histamine release.
Recuperation following the administration of alfentanil is typically fast and steady, with a low incidence of postoperative nausea and vomiting.
The action of alfentanil is reversed by a specific opioid antagonist, such as naloxone.

5.2 Pharmacokinetic properties

Alfentanil is a synthetic opioid with μ-agonist pharmacological effect. Alfentanil is only used intravenously.

Distribution
The low ionization (11% at pH 7.4) contributes significantly to speedy distribution. Distribution in the tissues is limited: the total volume of distribution varies from 0.4 to 1.0 l/kg, roughly one quarter to one tenth that of fentanyl.

Alfentanil's limited lipid solubility and strong plasma protein binding (92%) contribute to its limited volume of distribution.

Biotransformation
Alfentanil is metabolized mainly in the liver. Only 1% of the active substance is found unchanged in the urine. The metabolites are inert and 70 to 80% of them are excreted with the urine.

Elimination
Alfentanil is eliminated quickly after intravenous administration. Terminal half-lives of 83-223 min have been reported. Plasma clearance in people under 40 averages 356 ml/min and drops about 8% per decade after the age of 40. Once steady-state has been reached by infusion, the half-life remains unchanged.
When administration is ceased, the patient wakes quickly with no opioid after-effects.

Special populations

Paediatric population
Protein binding in neonates is 75%, increasing to 85% in children.

Only limited pharmacokinetic data are available on the use of alfentanil in children. Alfentanil is metabolized by CYP3A4. CYP3A4 activity is low in neonates and increases after birth to reach 30-40% of adult levels when the child is one month old. CYP3A4 activity increases further to 45% when the child is 6 months, 80% when the child is 12 months and reaches adult level when the child is 6 years old.

Hepatic impairment
After administration of a single intravenous dose of 50 mcg/kg, the terminal half-life is significantly longer in cirrhotic patients than in controls. The volume of distribution remains unchanged. The free fraction of alfentanil in cirrhotic patients increased to 18.5%, as compared with 11.5% in controls. This increase in the 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 an increased clinical effect of alfentanil (see section 4.4).

Renal impairment
The volume of distribution and clearance of the free fraction is the same in renal failure patients and healthy controls. The free fraction of alfentanil in renal patients increased to between 12.4 and 19%, as compared with between 10.3 and 11% in controls. This can result in an increased clinical effect of alfentanil (see section 4.4).

5.3 Preclinical safety data

Preclinical effects observed were only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Alfentanil has a wide safety margin. In rats the ratio of LD_{50}/ED_{50} for the lowest level of analgesia, for alfentanil is 1080 compared with 4.6, 69.5 and 277 for pethidine, morphine and fentanyl respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.7.

6.3 Shelf life

5 years.

6.4 Shelf life after dilution

Chemical and physical in-use stability has been demonstrated for 48 hours at 25 °C and 2 to 8 °C (see section 6.7).

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

6.5 Special precautions for storage

Store at or below 30 °C.
For storage conditions after dilution of the medicinal product, see section 6.4.

6.6 Nature and contents of container

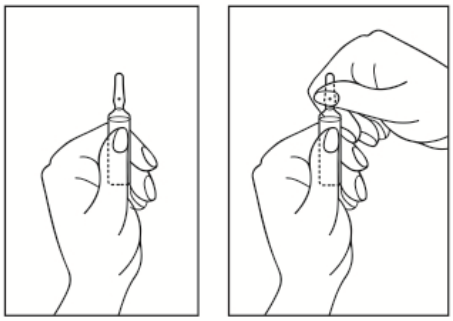
2 ml type I hydrolytic class colourless borosilicate glass ampoules with one point cut.
Ampoules are packed in liner. Liners are packed into a cardboard box.

Pack size: 10 ampoules

6.7 Special precautions for disposal and other handling

For single use only.

Instructions on preparation of diluted solution:
- Inspect the ampoule visually prior to use. Only clear solutions free from particles should be used.
- Wear gloves while opening the ampoule.
- Open the ampoule:
  1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
  2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



- Use medicinal product immediately after opening the ampoule.
- Dilute the content of ampoule to a concentration of 25-80 mcg/ml with:
  - 0.9% sodium chloride solution or
  - 5% glucose solution or
  - Ringer lactate solution.
- Discard any unused portion.
- If the skin is accidentally exposed, treat by flushing the affected area with water. Avoid using soap, alcohol and other detergents, which may cause chemical or physical damage to the skin.

Such diluted solutions are chemically and physically stable when in contact with widely used intravenous administration devices.

For shelf life of diluted solution, see section 6.4.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER AND MANUFACTURER

Product Owner:
AS KALCEKS

Krustpils iela 71E, Rīga, LV-1057, Latvia

Manufacturer:
HBM Pharma s.r.o.
Sklabinska 30, 036 80 Martin, Slovakia

8. REGISTRATION NUMBER

SINXXXXXX

9. DATE OF APPROVAL

Date of approval:

10. DATE OF REVISION OF THE TEXT

07/2024