Kalcex

PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Fentanyl Kalceks solution for injection 0.05 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 0.05 mg of fentanyl (as citrate).
One ampoule (2 ml) contains 0.1 mg of fentanyl (as citrate).
One ampoule (10 ml) contains 0.5 mg of fentanyl (as citrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fentanyl Kalceks is an opioid analgesic.
It is used:
- in low doses to provide analgesia during short surgical procedures;
- in high doses as an analgesic/respiratory depressant in patients requiring assisted ventilation;
- in combination with a neuroleptic in the technique of neuroleptanalgesia

4.2 Posology and method of administration

The dosage of FENTANYL should be individualized according to age, body weight, physical status, underlying pathological condition, use of other drugs, and type of surgery and anesthesia.

To avoid bradycardia, it is recommended to administer a small intravenous dose of an anti-cholinergic just before anesthetic induction.

A neuroleptic may be given to prevent nausea and vomiting.

Adult
Use as an analgesic supplement to general anesthesia
Low dose: 2 mcg/kg
FENTANYL in small doses is most useful for minor surgery.

Moderate dose: 2-20 mcg/kg
Where surgery becomes more complicated, a larger dose will be required. The duration of activity is dependent on dosage.

High dose: 20-50 mcg/kg
During major surgical procedures, in which surgery is longer, and during which the stress response would be detrimental to the well-being of the patient, doses of 20-50 mcg/kg of FENTANYL with nitrous oxide/oxygen have been shown to have an attenuating effect. When doses in this range have been used during surgery, post-operative ventilation and observation are essential in view of the possibility of extended post-operative respiratory depression.

Supplemental doses of 25-250 mcg (0.5-5 mL) should be tailored to the needs of the patient and to the anticipated time until completion of the operation.

Use as an anesthetic agent
When attenuation of the response to surgical stress is especially important, doses of 50-100 mcg/kg may be administered with oxygen and a muscle relaxant. This technique provides anesthesia without necessitating the use of additional anesthetic agents. In certain cases, doses up to 150 mcg/kg may be required to produce this anesthetic effect. FENTANYL has been used in this fashion for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated.

Pediatrics
For induction and maintenance in children aged 2-12 years, a dose of 2-3 mcg/kg is recommended.

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

Use in patients with renal and/or hepatic impairment
The initial dose should be reduced for patients with renal and/or hepatic impairment.

Method of administration
This medicine should be given only in an environment where the airway can be controlled and by personnel who can control the airway (see section 4.4).
This medicine can be administered intravenously either as a *bolus* or by infusion, as well as intramuscular injection.

Fentanyl Kalceks may be used intravenously in adults and children.

4.3 Contraindications

Hypersensitivity to the active substance, other morphinomimetics or to any of the excipients listed in section 6.1.
Respiratory depression, obstructive airway disease.
Head injuries, raised intracranial pressure.
Concurrent administration with monoamine oxidase inhibitors (MAOI), or within 2 weeks of their discontinuation.
Hypovolemia and hypotension
Myasthenia gravis

4.4 Special warnings and precautions for use

Warnings

Tolerance and dependence may occur.
Following intravenous administration of fentanyl, a transient fall in blood pressure may occur, especially in hypovolemic patients. It is transitory. Appropriate measures to maintain a stable arterial pressure should be taken.

Significant respiratory depression will occur following the administration of fentanyl in doses in excess of 200 micrograms. This, and the other pharmacological effects of fentanyl, can be reversed by specific narcotic antagonists (e.g. naloxone). Additional doses of the narcotic antagonists may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.

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

Muscular rigidity (morphine-like effect) may occur. Rigidity, which may also involve the thoracic muscles, can be avoided by the following measures:
- slow intravenous injection (usually sufficient for lower doses);
- premedication with benzodiazepines;
- use of muscle relaxants.

Non-epileptic (myo)clonic movements can occur.

Precautions

Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway

Dose reduction is recommended in the elderly and in debilitated patients.
In hypothyroidism, pulmonary disease, decreased respiratory reserve, liver or renal impairment as well as for alcohol dependent patients the dosage should be titrated with care and prolonged monitoring may be required in post-operative period.

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

If the fentanyl is administered with a neuroleptic, such as droperidol, the user should be familiar with the special properties of each medicine, particularly the difference in their duration of action. When such a combination is used, there is higher incidence of hypotension. Neuroleptics can induce extrapyramidal symptoms that may be controlled with anti-Parkinson agents.

As with other opioids, due to the anticholinergic effects, administration of fentanyl may lead to increases of bile duct pressure and, in isolated cases, spasms of the sphincter of Oddi might be observed.

Administration in labour may cause respiratory depression in the new born infant.

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early postoperative period. Care should be taken after large doses or infusions of fentanyl to ensure that adequate spontaneous breathing has been established and maintained before discharging the patient from the recovery area.

Resuscitation equipment and opioid antagonists should be readily available.
Opiate antagonist and facilities for administration of oxygen and controlled respiration should be available immediately.
Hyperventilation during anaesthesia may alter the patient's response to CO_2, thus affecting respiration postoperatively.

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

Serotonin Syndrome
Caution is advised when fentanyl is co-administered with drugs that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic medicines, such as selective serotonin re-uptake inhibitors (SSRIs) and serotonin-norepinephrine re-uptake inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]). This may occur within the recommended dose.
Serotonin syndrome may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, rapid discontinuation of fentanyl should be considered.

Drug dependence and potential for abuse
Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Risks are increased in patients with a personal history of substance abuse (including drug or alcohol abuse or addiction).

Withdrawal syndrome
Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy, which may manifest by the occurrence of the following side effects: nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating.

Paediatric population
Techniques that involve analgesia in a spontaneously breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/analgesia technique, with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of other medicines on fentanyl

The use of opioid (for premedication), barbiturates, benzodiazepines, neuroleptics, halogenic gasesand other non-selective CNS depressants (e.g. alcohol) may enhance or prolong the respiratory depression effects of fentanyl.

When patients have received CNS depressants, the dose of fentanyl required may, therefore, be less than usual. Concomitant use with fentanyl in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death.

Fentanyl is rapidly and extensively metabolised mainly by CYP3A4. Itraconazole (a potent CYP3A4 inhibitor) administered orally at 200 mg/day for 4 days had no significant effect on the pharmacokinetics of intravenous fentanyl.

Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of intravenous fentanyl by two thirds. However, peak plasma concentrations after a single dose of intravenous fentanyl were not affected. When fentanyl is used in a single dose, the concomitant administration of potent CYP3A4 inhibitors such as ritonavir requires special patient care and observation.

Concomitant administration of fluconazole or voriconazole (potent CYP3A4 inhibitors) and fentanyl may result in increased exposure to fentanyl.

With continuous treatment of fentanyl and concomitant administration of CYP3A4 inhibitors, a dose reduction of fentanyl may be required to avoid accumulation, which may increase the risk of prolonged or delayed respiratory depression.

Bradycardia and possibly cardiac arrest can occur in patients who have not received an anticholinergic drug in sufficient quantity or when fentanyl is combined with non-vagolytic muscle relaxants. Bradycardia can be prevented by atropine.

If fentanyl is administered with droperidol, there is a higher incidence of hypotension.

Grapefruit juice inhibits the metabolism of fentanyl, which reduces its effect.

Serotonergic Drugs
Co-administration of fentanyl with a serotonergic agent, such as SSRI, SNRI or MAOI may increase the risk of serotonin syndrome, a potentially life-threatening condition.

The effects of fentanyl on other medicines
Following the administration of fentanyl, the dose of other CNS depressants should be reduced.

Plasma concentrations of etomidate increased considerably (by a factor 2-3) when combined with fentanyl. The total plasma clearance and volume of distribution of etomidate is decreased by a factor 2 to 3 without a change in half-life when administered with fentanyl.
Simultaneous administration of fentanyl and intravenous midazolam results in an increase in the terminal plasma half-life and a reduction in the plasma clearance of midazolam. When these medicines are co-administered with fentanyl their dose may need to be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the use of fentanyl in pregnant women. Fentanyl can cross the placenta in early pregnancy. Studies in animals have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Administration during childbirth (including Caesarean section) is not recommended because fentanyl crosses the placenta and the foetal respiratory centre is particularly sensitive to opioids. If fentanyl is administered, an antidote should always be available.

Breast-feeding
Fentanyl is excreted into breast milk. Therefore, breast-feeding is not recommended within 24 hours following administration of this medicine. The risk/benefit of breast-feeding following administration of fentanyl should be considered.

4.7 Effects on ability to drive and use machines

Where early discharge is envisaged, patients should be advised not to drive or operate machinery for 24 hours following administration.

4.8 Undesirable effects

The most commonly reported side effects: nausea, vomiting, muscle rigidity, hypotension, hypertension, bradycardia and sedation.

The following table displays adverse drug reactions that have been reported with the use of fentanyl intravenously from either clinical trials or post-marketing experience.

The following adverse reactions are presented according to the MedDRA system organ classes and frequency convention.

Table 1. Adverse Reactions

System Organ Class MedDRA	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to 1/100)	Rare (≥1/10 000 to 1/1000)	Very rare (<1/10 000)	Not known (cannot be estimated from the available data)
Immune system disorders						Hypersensitivity (anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric disorders		Agitation	Euphoric mood		Insomnia, sexual dysfunction (decreased libido)	Delirium
Nervous system disorders	Muscle rigidity (which may also involve the thoracic muscles)	Dyskinesia Sedation Dizziness	Headache			Convulsions Loss of consciousness Myoclonus
Eye disorders		Visual disturbances				
Cardiac disorders		Bradycardia Tachycardia Arrhythmia		Asystole		
Vascular disorders		Hypotension Hypertension Venous pain Vasodilatation	Phlebitis Blood pressure fluctuation			
Respiratory, thoracic and mediastinal disorders		Respiratory depression Laryngo-spasm Broncho-spasm Apnoea	Hyper-ventilation Hiccups	Secondary respiratory depression		
Gastrointestinal disorders	Nausea Vomiting					
Skin and subcutaneous tissue disorders		Allergic dermatitis				Pruritus
General disorders and administration site conditions			Chills Hypothermia			Drug withdrawal syndrome (see section 4.4)
Injury, poisoning and procedural complications		Postoperative confusion	Airway complication of anaesthesia			

Administration of this medicine for long periods may result tolerance and dependence (see section 4.4).
When a neuroleptic is used with fentanyl, the following adverse reactions may be observed: chills and/or shivering, restlessness, postoperative hallucinatory episodes and extrapyramidal symptoms (see section 4.4).

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 to State Agency of Medicines,
Jersikas Street 15, Rīga, LV-1003. Website: www.zva.gov.lv

4.9 Overdose

Symptoms
The manifestations of fentanyl overdosage are generally an extension of its pharmacological action. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnoea to apnoea.

Treatment
Hypoventilation or apnoea: oxygen administration assisted or controlled respiration.

Respiratory depression: specific narcotic antagonist (e.g. naloxone) should be administered. This does not preclude the use of immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of narcotic antagonist latter may therefore be required.

Muscular rigidity: intravenous neuromuscular blocking agent should be administered to facilitate assisted or controlled respiration.
The patient should be carefully observed; body warmth and adequate fluid intake should be maintained. If hypotension is severe or if it persists, the possibility of hypovolaemia should be considered. In case of hypovolaemia the parenteral solutions should be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: opioid anaesthetics, ATC code: N01AH01

Fentanyl is a synthetic opioid analgesic with similar effects of morphine. Its onset of action is rapid and its duration of action is short.
In parenteral administration it can cause pronounced analgesia, respiratory depression, bradycardia and other morphine-like effects (vomiting, constipation, physical dependence, certain vagal effects and varying degrees of sedation). The usual duration of analgesic effect is approximately 30 minutes after a single IV dose of up to 100mcg.

5.2 Pharmacokinetic properties

Distribution
After intravenous injection, fentanyl plasma concentrations fall rapidly, with sequential distribution half-lives of about 1 minute and 18 minutes and a terminal elimination half-life of 475 minutes. Fentanyl has a Vc (volume of distribution of the central compartment) of 13L, and a total Vdss (distribution volume at steady-state) of 339L. The plasma protein binding of Fentanyl is about 84%.

Metabolism
Fentanyl is rapidly metabolized, mainly in the liver by CYP3A4.The major metabolite is norfentanyl. Fentanyl clearance is 574 mL/min.

Excretion
Approximately 75% of the administered dose is excreted in the urine within 24 hours and only 10% of the dose eliminated in urine is present as unchanged drug.

Special Populations
Pediatrics
The plasma protein binding of fentanyl in newborns is approximately 62% and lower than in adults. The clearance and the volume of distribution are higher in infants and children.

Renal impairment
Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive FENTANYL, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary.

Adult patients with burns
An increase in clearance up to 44% together with a larger volume of distribution results in lower fentanyl plasma concentrations.

Obese patients
An increase in clearance of fentanyl is observed with increased body weight. In patients with a BMI>30, clearance of fentanyl increases by approximately 10% per 10kg increase of the fat free mass (lean body mass).

5.3 Preclinical safety data

In vitro fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in *in vitro* rodent studies and bacterial assays. Long term carcinogenicity studies with fentanyl have not been performed.
Some tests on female rats showed reduced fertility as well as embryo mortality. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. There was no evidence of teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

The product is chemically incompatible with the induction agents thiopentone and methohexitone because of the wide differences in pH. Fentanyl citrate is also reportedly physically incompatible with pentobarbital sodium and nafcilline.

6.3 Shelf life

4 years.

6.4 Shelf life after reconstitution

FENTANYL can be diluted with 0.9% sodium chloride or 5% glucose solution for infusion. The shelf-life after dilution is 24 hours at both 30ºC and at 2-8ºC.

6.5 Special precautions for storage

Do not store above 30 °C.
Store in the original package in order to protect from light. Do not freeze.

6.6 Nature and contents of container

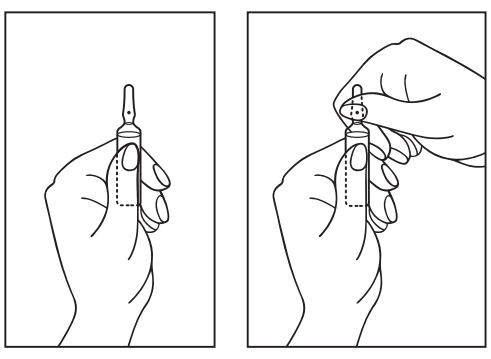
2 ml or 10 ml of solution in colourless I hydrolytic class borosilicate glass ampoule with break line or open point cut. Ampoules are marked with colour ring codes: upper ring – red, lower ring – green.
5 ampoules in polyvinyl chloride (PVC) liner.
2 liners in a cardboard box.

Pack sizes:
10 ampoules of 2 ml.
10 ampoules of 10 ml.

Not all pack sizes may be marketed.

6.7 Special precautions for disposal and other handling

Instructions for ampoule opening:
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 finger protection when opening an ampoule.
The injection is for single patient use and should be used immediately after opening.
The injection should not be used if particles are present. Any unused portion should be discarded.

7. PRODUCT OWNER

AS KALCEKS
71E, Krustpils St., Riga, LV-1057, Latvia

8. MARKETING AUTHORISATION NUMBER(S)

SIN15802P

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of authorisation: 10.09.2019.

10. DATE OF REVISION OF THE TEXT

N.A.

Place for AS Kalceks internal code
Place for manufacturer internal code