SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fentanyl Kalceks 0.05 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 0.0785 mg of fentanyl citrate corresponding to 0.05 mg of fentanyl.
One ampoule (2 ml) contains 0.157 mg of fentanyl citrate corresponding to 0.1 mg of fentanyl.

Excipient with known effect
Each ampoule of 2 ml contains 7.08 mg (0.31 mmol) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear colourless liquid. pH of solution 4.0 - 7.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fentanyl citrate is used:
- as a narcotic analgesic supplement in general or regional anaesthesia;
- in combination with a neuroleptic (e.g. droperidol) in the technique of neuroleptanalgesia;
- for the induction of anaesthesia, and as an adjuvant in the maintenance of general and regional anaesthesia;
- as an anaesthetic agent with oxygen in high-risk patients undergoing surgery.

4.2 Posology and 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).

Posology

The dose of medicine should be individualised according to age, body weight, physical condition, underlying pathological condition, concomitant use of other drugs, and type of surgery and anaesthesia.

Adults

- As an analgesic supplement in general anaesthesia

In low doses for minor surgical procedures: 2 mcg/kg of fentanyl.
Moderate dose: 2-20 mcg/kg of fentanyl.
In high doses during major surgery: 20-50 mcg/kg of fentanyl. The duration of the effect depends on the dose. During major surgery the administration of 20-50 mcg/kg of fentanyl with nitrous oxide/oxygen has been shown to have an attenuating effect.
When these doses were used during surgery, it is necessary to provide post-operative ventilation and to monitor the patient, due to the extended respiratory depression in the post-operative period.

Supplements of 25-250 mcg (0.5-5 ml) of fentanyl may be administered, according to patient requirements and duration of surgery.

- As an anaesthetic agent

When attenuation of the response to surgical stress is especially important, doses of 50-100 mcg/kg of fentanyl may be administered with oxygen and a muscle relaxant. This technique provides anaesthesia without use of additional anaesthetic agents. In certain cases, doses up to 150 mcg/kg of fentanyl may be necessary to produce an anaesthetic effect. In this way fentanyl is used in open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated.

Use in elderly or debilitated patients
The initial dose should be reduced in this patient group. The effect of the initial dose should be taken into account in determining supplemental doses. The administration of a small intravenous dose of an anticholinergic agent is recommended immediately before induction in order to prevent bradycardia. Droperidol may be administered to prevent nausea and vomiting.

Use in patients with hepatic impairment
Careful dose titration of fentanyl is advised in patients with hepatic impairment (see section 4.4).

Use in patients with renal impairment
Careful dose titration of fentanyl is advised in patients with renal impairment (see section 4.4).

Paediatric population

Children aged 2 to 11 years old

The usual dosage regimen in children is as follows:	Age	Initial	Supplemental
Spontaneous Respiration	2-11 years	1-3 mcg/kg	1-1.25 mcg/kg
Assisted Ventilation	2-11 years	1-3 mcg/kg	1-1.25 mcg/kg

Children aged 12 to 17 years old
Follow adult dosage.

Method of administration

This medicine can be administered intravenously either as a *bolus* or by infusion, as well as intramuscular injection.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to other morphinomimetics.

4.4 Special warnings and precautions for use

As with all potent opioids, respiratory depression is dose related and can be reversed by the administration of a narcotic antagonist (naloxone), but it may be necessary to administer additional doses of the antagonist as respiratory depression may have a longer duration of action than the opioid antagonists. Profound analgesia is accompanied by marked respiratory depression that may persist or recur in the post-operative period. Therefore, patients should remain under appropriate surveillance. Fentanyl should be administered in an environment where the airways can be controlled, and resuscitation equipment and narcotic antagonists should be available, along with personnel who can control the airways. Hyperventilation during anaesthesia may alter the patient's response to CO_2, affecting breathing, in the post-operative period.

Muscular rigidity, which may also involve the thoracic muscles, may occur, but 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 may occur.
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. Opioids may cause hypotension, especially in patients with hypovolaemia. Appropriate measures should be taken to maintain stable blood pressure. 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.
Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses.
Dose reduction is recommended in the elderly and in debilitated patients. Opioids should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism, or impaired renal or hepatic function (see section 4.2). Such patients also require prolonged post-operative monitoring.
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.

In patients with *myasthenia gravis*, careful consideration should be applied in the use of certain anticholinergic agents and neuromuscular-blocking pharmaceutical agents prior to, and during the administration of a general anaesthetic regimen which includes administering intravenous fentanyl.

Serotonin Syndrome
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 over-activity (e.g. hyperreflexia, lack of coordination, 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.

<u>Paediatric population</u>

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.

Excipients
This medicinal product contains 7.08 mg sodium per 2 ml ampoule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of other medicines on fentanyl

The use of opioid premedication, barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non-selective CNS depressants (e.g. alcohol) may enhance or prolong the respiratory depression of fentanyl. When patients have received such medicines, the dose of fentanyl required to be less than usual.

Fentanyl, a high clearance drug, 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.

Orally administered 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 as 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 and fentanyl may result in increased exposure to fentanyl.

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

Monoamine oxidase inhibitors (MAOIs)
It is usually recommended that the administration of monoamine oxidase inhibitors (MAOIs) should be discontinued two weeks prior to any surgical or anaesthetic procedure. However, several reports describe the use of fentanyl during surgical or anaesthetic procedures in patients on MAOIs without any interaction.

Serotonergic Drugs
Co-administration of fentanyl with a serotonergic agent, such as a selective serotonin re-uptake inhibitor (SSRI) or a serotonin norepinephrine re-uptake inhibitor (SNRI) or a monoamine oxidase inhibitor (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.

The total plasma clearance and volume of distribution of etomidate are decreased (by a factor 2-3), with no change in half-life, when combined with fentanyl, which results in a considerable increase in the plasma concentration of etomidate. 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 (intramuscular or intravenous) during childbirth (including caesarean section) is not recommended because fentanyl crosses the placenta and affects the foetal respiratory centre that is particularly sensitive to opioids. However, if fentanyl is administered, an antidote for the newborn should always be available.

Breast-feeding
Fentanyl is excreted into human 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

Patients should only drive or operate machinery if sufficient time has elapsed after the administration of fentanyl.

4.8 Undesirable effects

Table 1 displays adverse drug reactions that have been reported with the use of fentanyl from either clinical trials or postmarketing experience.

The following adverse reactions are presented according to the MedDRA system organ classes and MedDRA frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), not known (cannot be estimated from the available data).

Table 1. Adverse Reactions

System Organ Class MedDRA	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Not known (cannot be estimated from the available data)
Immune system disorders				Hypersensitivity (anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric disorders			Euphoric mood	Delirium
Nervous system disorders		Dyskinesia Sedation Dizziness	Headache	Convulsions Loss of consciousness Myoclonus
Eye disorders		Visual disturbances		
Cardiac disorders		Bradycardia Tachycardia Arrhythmia		Cardiac arrest

Vascular disorders		Hypotension Hypertension Venous pain	Phlebitis Blood pressure fluctuation	
Respiratory, thoracic and mediastinal disorders		Laryngospasm Bronchospasm Apnoea	Hyper-ventilation Hiccups	Respiratory depression
Gastrointestinal disorders	Nausea Vomiting			
Skin and subcutaneous tissue disorders		Allergic dermatitis		Pruritus
Musculo-skeletal and connective tissue disorder	Muscle rigidity			
General disorders and administration site conditions			Chills Hypothermia	Drug withdrawal syndrome (see section 4.4)
Injury, poisoning and procedural complications		Post-operative confusion	Airway complication of anaesthesia Post-operative agitation	

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 via the national reporting system.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: opioid anesthetics, ATC code: N01AH01

Fentanyl is a potent narcotic analgesic, synthetic opioid with μ-agonist pharmacological effects. It can be used as an analgesic supplement to general anaesthesia or as a sole anaesthetic. Fentanyl preserves cardiac stability and counteracts stress-related hormonal changes at higher doses. A dose of 100 micrograms (2.0 ml) is approximately equivalent in analgesic activity to 10 mg of morphine. The onset of action is rapid. However, the maximum analgesic and respiratory depressant effect may not be noticed for several minutes. The usual duration of action of the analgesic effect is approximately 30 minutes after a single intravenous dose of up to 100 micrograms. The degree of anaesthesia is dose related and can be adjusted to the level of pain of the surgical procedure.
Fentanyl has a wide therapeutic index. In rats, the ratio LD50/ED50 for the lowest level of analgesia is 277, compared with 69.5 and 4.6 for morphine and pethidine, respectively.
Like other narcotic analgesics, fentanyl can cause muscle rigidity, as well as euphoric mood, miosis and bradycardia, depending on the dose and rate of administration.
Histamine assays and skin-wheal testing in humans, as well as *in vivo* testing in dogs, have shown that clinically significant histamine release is rare with fentanyl.
All actions of fentanyl are completely reversed by the administration of a narcotic antagonist such as naloxone.

5.2 Pharmacokinetic properties

Absorption and distribution
Plasma concentrations of fentanyl fall rapidly after intravenous injection, with plasma profiles characterised by biphasic distribution with half-lifes of 1 min, and 18 min, respectively, and terminal elimination half-life of 475 min. Fentanyl has a V_c (central compartment volume of distribution) of 13 L and a total V_{dss} (volume of distribution at steady state) of 339 L.
The plasma-protein binding of fentanyl is approximately 84 %.

Biotransformation
Fentanyl is metabolised rapidly, mainly in the liver by CYP3A4. The main metabolite is norfentanyl. Fentanyl clearance is 574 ml/minute.

Elimination
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.

Special populations
Paediatric population
The plasma-protein binding of fentanyl in newborns is approximately 62%, which is lower than in adults. The clearance and the volume of distribution are higher in infants and children. This may result in a need to increase the dose of fentanyl.

5.3 Preclinical safety data

The preclinical data show no special hazard for humans, based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity.

In a two-year carcinogenicity study in rats, fentanyl was not associated with any increased incidence of tumours at subcutaneous doses up to 33 mcg/kg/day in males and 100 mcg/kg/day in females, which were the maximum doses tolerated by males and females.
Some tests on female rats showed reduced fertility and increased embryo mortality. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. In a pre- and post-natal development study, the survival rate of offspring was significantly reduced at doses that slightly reduced maternal weight. This effect may have been due either to a change in maternal care or to a direct effect of fentanyl on the pups. No effects were observed on the somatic development and behaviour of the offspring. There was no evidence of teratogenic effects.

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 6.6.

6.3 Shelf life

5 years.

Once ampoule has been opened, the product should be used immediately.

Chemical and physical in-use stability has been demonstrated for 48 hours at room temperature or 2-8 °C.
From a microbiological point of view, the medicine 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 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

For storage conditions after dilution or first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I colourless glass ampoules of 2 ml.
Pack size: 10 ampoules.

6.6 Special precautions for disposal and other handling

If necessary, fentanyl may be mixed with sodium chloride (0.9%) or glucose (5%) for intravenous infusion. These dilutions are compatible with the plastic material used for infusions.

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

05/2022