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 (50 micrograms) of fentanyl.
Each ampoule (2 ml) contains 0.157 mg of fentanyl citrate corresponding to 0.1 mg (100 micrograms) of fentanyl.

For the full list of excipients, see *List of excipients*.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fentanyl is a short acting opioid used:
- as an intravenous analgesic agent in surgical procedures;
- as an adjunct in the maintenance of general anaesthesia;
- in combination with a neuroleptic agent in the technique of neuroleptanalgesia;
- as a respiratory depressant/analgesic in patients requiring prolonged assisted ventilation;
- for induction of anaesthesia.

4.2 Posology and method of administration

Fentanyl should be given only when in an environment where the airway can be controlled and by personnel who can control the airway.
The dose of fentanyl is adjusted individually according to age, body weight, physical status, pathological condition, co-medication and as well as type of surgical procedure and type of anaesthesia.
For guidance, the following dosage schedules are proposed. For other special dosage recommendations please refer to the literature.

Neuroleptanalgesia and neuroleptanaesthesia
For neuroleptanalgesia adults normally will require an initial dose of 50 to 100 micrograms (0.7 - 1.4 microgram/kg) fentanyl, slowly injected intravenously in combination with a neuroleptic (preferably droperidol). If necessary a second dosage of 50 to 100 micrograms (0.7 - 1.4 microgram/kg) fentanyl can be given 30 to 45 minutes after the initial dose.
For neuroleptanaesthesia under the condition of assisted ventilation adults in general will require an initial dose of 200 to 600 micrograms (2.8 - 8.4 micrograms/kg) fentanyl slowly injected intravenously in combination with a neuroleptic (preferably droperidol).
The dosage depends on the duration and the severity of the surgical procedure and on the medication used for general anaesthesia. For maintenance of anaesthesia, additional doses of 50 to 100 micrograms (0.7 - 1.4 microgram/kg) fentanyl can be given every 30 to 45 minutes. The time

intervals and doses of these additional administrations have to be adjusted according to the course of the surgical procedure.

Analgesic component in general anaesthesia
Adults
Premedication: 50 to 100 micrograms (1 to 2 mL) fentanyl administered intramuscularly 30 to 60 minutes prior to surgery (modified for high risk patients).
For induction: If fentanyl is used as an analgesic component in general anaesthesia with intubation and ventilation of the patient, in adults initial fentanyl doses of 70 - 600 micrograms (1 - 8.4 micrograms/kg) can be applied as adjunct to general anaesthesia.
For maintenance of analgesia during general anaesthesia, additional doses of 25 - 100 microgram (0.35 - 1.4 microgram/kg) fentanyl are to be injected subsequently. The time intervals and the dosage are to be adjusted according to the course of the surgical procedure.

Pain management in the intensive care unit
For use in pain management of ventilated patients in the intensive care unit, the dosage of fentanyl has to be adjusted individually, depending on the course of pain and on concomitant medication. Normally the initial doses are in the range of 50 to 100 micrograms i.v. (0.7 - 1.4 microgram/kg), but can be titrated higher if necessary.
The initial dose normally is followed by repeated injections, of up to a total of 25 to 125 micrograms fentanyl per hour (0.35 - 1.8 microgram/kg/h).

Dosage in paediatric population
Children aged 12 to 17 years should follow the recommended adult dose schedule.
For children aged 2 to 11 years the usual dosage regimen is recommended as follows:

Table 1 Dosage in paediatric population

	Age in years	Initial dose in micrograms/kg body weight	Supplemental dose in micrograms/kg body weight
Spontaneous respiration	2 - 11	1 - 3	1-1.25
Assisted ventilation	2 - 11	1 - 3	1-1.25

Use in children
Analgesia during operation, enhancement of anaesthesia with spontaneous respiration:
Techniques that involve analgesia in a spontaneous 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.

Dosage in elderly and weak patients
The initial dose in elderly and weak patients should be reduced. The effect of the initial dose should be taken into account for the determination of supplemental doses.

Dosage in patients with chronic opioid medication
In patients with chronic opioid medication or with a known history of opioid abuse, a higher dosage of fentanyl may be necessary.

Dosage in patients with additional diseases
In patients with one of the following diseases the intended dosage of fentanyl should be titrated very carefully:
- uncompensated hypothyreosis;
- lung diseases, especially those with reduced vital capacity;
- alcohol abuse;
- impaired hepatic function;

- impaired renal function.

Caution is also required if fentanyl is to be administered to patients with adrenal insufficiency, prostatic hypertrophy, porphyria and bradyarrhythmia.

In all these conditions, except alcohol abuse, the dose may have to be reduced. In alcohol abuse, the dose may have to be either reduced or increased.

In these patients a prolonged postoperative monitoring period is recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Known intolerance to fentanyl or other morphino-mimetics.
Respiratory depression.
Obstructive airways disease.
In patients after operative interventions in the biliary tract.

4.4 Special warnings and precautions for use

Fentanyl must only be given where the airway can be controlled and only by professionals who can control the airways.

Warnings:

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

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.

Respiratory Depression
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.

Significant respiratory depression will occur following the administration of fentanyl in doses in excess of 200 mcg. This, and the other pharmacological effects of fentanyl, can be reversed by specific narcotic antagonists (e.g. naloxone). Additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist. Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patients response to CO_2, thus affecting respiration postoperatively.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of fentanyl and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe fentanyl concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section *Interaction with other medicinal products and other forms of interaction*).

Risks from Concomitant Use with Benzodiazepines
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Fentanyl Kalceks with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, 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 Fentanyl Kalceks is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine 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 benzodiazepines (see section *Interaction with other medicinal products and other forms of interaction*).

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

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

Non-epileptic (myo)clonic movement can occur.

Special dosing conditions
The use of rapid bolus injections of opioids should be avoided in patients with compromised intracerebral compliance; in such patients the transient decrease in the mean arterial pressure has occasionally been accompanied by a transient reduction of the cerebral perfusion pressure.

It is wise to reduce dosage in the elderly and debilitated patients.

In uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism and liver or renal impairment the dosage should be titrated with care and prolonged post-operative monitoring may be required.

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

Precautions:

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

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

Bile duct
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.

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 drugs 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.

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of Fentanyl Kalceks with serotonergic drugs (see section *Interaction with other medicinal products and other forms of interaction*). This may occur within the recommended dosage range.
Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (see section *Interaction with other medicinal products and other forms of interaction*). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue Fentanyl Kalceks if serotonin syndrome is suspected.

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, decreased appetite, 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 dosing 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.

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 section *Undesirable effects, Postmarketing Experience*).

Paediatric population
Techniques that involve analgesia in a spontaneous 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

Effect of other drugs on fentanyl

Drugs such as barbiturates, benzodiazepines, neuroleptics, halogenic gases, and other non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depression of narcotics.

When patients have received such drugs, the dose of fentanyl required will be less than usual.

Fentanyl, a high clearance drug, is rapidly and extensively metabolized mainly by CYP3A4. Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of i.v. fentanyl.

Co-administration of fluconazole or voriconazole and fentanyl may result in an increased exposure to 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 use of potent CYP3A4 inhibitors such as ritonavir requires special patient care and observation.

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

It is usually recommended to discontinue MAO-inhibitors 2 weeks prior to any surgical or anesthetic procedure. However, several reports describe the uneventful use of fentanyl during surgical or anaesthetic procedures in patients on MAO inhibitors.

When fentanyl is used in combination with non-vagolytic muscle relaxants, bardycardia and possibly asystole may occur.

Concomitant use of fentanyl and droperidol can result in higher incidence of hypotension.

Pretreatment with, or concurrent administration of, cimetidine may increase plasma levels of fentanyl, when repeated doses of both drugs are used.

Bradycardia may be intensified by pretreatment with, or concurrent use of, drugs such as beta-blockers, suxamethonium, halothane, vecuronium, which may themselves cause bradycardia.

Serotonergic Drugs
The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Fentanyl Kalceks if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (see section *Special warnings and precautions for use*).

Effect of fentanyl on other drugs

Following the administration of fentanyl, the dose of other CNS depressant drugs should be reduced.

Plasma concentration of etomidate increased considerably (by a factor 2 to 3) when combined with fentanyl. The total plasma clearance and volume of distribution of etomidate are 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 drugs are co-administered with fentanyl their dose may need to be reduced.

Benzodiazepines

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see section *Special warnings and precautions for use*).
Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of fentanyl in pregnant women. Fentanyl can cross the placenta in early pregnancy. Studies in animals have shown some reproductive toxicity. 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 nevertheless administered, assisted ventilation equipment must be immediately available for the mother and infant if required. An antidote for the child should always be at hand.

Breast-feeding
Fentanyl is excreted into human milk. It is therefore recommended that breast feeding is not initiated within 24 hours of treatment. The risk/benefit of breast feeding following fentanyl administration should be considered.

Fertility
There are no human data on fertility available. In animal studies, male fertility was impaired.

4.7 Effects on ability to drive and use machines

Fentanyl has a moderate influence on the ability to drive and use machines. Patients should only drive or operate a machine if sufficient time has elapsed after the administration of fentanyl.
This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely.

4.8 Undesirable effects

The safety of fentanyl was evaluated using fentanyl i.v. as an anaesthetic. Safety data are provided after at least 1 dose of fentanyl i.v. Based on pooled safety data, the most commonly reported Adverse Drug Reactions (ADRs) were: nausea, vomiting, muscle rigidity, hypotension, hypertension, bradycardia and sedation. Including the above-mentioned ADRs, the following table displays ADRs that have been reported with the use of fentanyl i.v.

Table 2 Adverse Drug Reactions

System Organ Class	**Adverse Drug Reactions**			
	Frequency Category			
	Very common	**Common**	**Uncommon**	**Not known**
Immune system disorders				Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric disorders			Euphoric mood	Delirium Drug dependence (see section *Special warnings and precautions for use*)
Nervous system disorders		Dyskinesia Sedation Dizziness	Headache	Convulsions Loss of consciousness Myoclonus Hyperalgesia
Eye disorders		Visual disturbance		
Cardiac disorders		Bradycardia Tachycardia Arrhythmia		Cardiac arrest

Vascular disorders		Hypotension Hypertension Vein pain	Phlebitis Blood pressure fluctuation	
Respiratory, thoracic and mediastinal disorders		Laryngospasm Bronchospasm Apnoea	Hyperventilation Hiccups	Respiratory depression Cough
Gastrointestinal disorders	Nausea Vomiting			Constipation
Skin and subcutaneous tissue disorders		Dermatitis allergic		Pruritus
Musculoskeletal and connective tissue disorder	Muscle rigidity (which may also involve thoracic muscles)			
General disorders and administration site conditions			Chills Hypothermia Drug withdrawal syndrome (see section *Special warnings and precautions for use*)	
Injury, poisoning and procedural complications		Confusion postoperative	Airway complication of anaesthesia Agitation postoperative	

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 *Special warnings and precautions for use*).

Postmarketing Experience
Serotonin syndrome (see section *Special warnings and precautions for use*).
Adrenal insufficiency (see section *Special warnings and precautions for use*).
Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. 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.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

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 Centre for Adverse Drug Reaction Monitoring by visiting the website portal.npra.gov.my

4.9 Overdose

Symptoms and signs

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

Treatment

Hypoventilation or apnoea:	O_2 administration, assisted or controlled respiration.
Respiratory depression:	Specific narcotic antagonist (e.g. naloxone). 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.

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 analgesic, ATC code: N01AH01.

Fentanyl is a well established chemical entity. It is an opioid analgesic with a high affinity for the μ-opioid receptor.
Fentanyl can be used as an analgesic supplement to general anaesthesia or as a sole anaesthetic. Fentanyl preserves cardiac stability, and obtunds 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 noted for several minutes. The usual duration of action of the analgesic effect is approximately 30 minutes after a single i.v. dose of up to 100 micrograms. Depth of analgesia is dose-related and can be adjusted to the pain level of the surgical procedure. Fentanyl has a broad safety margin. In rats, the ratio LD_{50}/ED_{50} for the lowest level of analgesia is 277, as compared with 69.5 and 4.6 for morphine and pethidine, respectively.
Like other opioid analgesics, fentanyl, depending upon the dose and speed of administration, can cause muscle rigidity, as well as euphoria, miosis and bradycardia.
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
Fentanyl is a lipid-soluble drug and its pharmacokinetics can be described in terms of a three-compartment model. Following intravenous injection, there is a short distribution phase during which high concentrations of fentanyl are achieved quickly in well-perfused tissues such as the lungs, kidneys and brain.

Distribution

The drug is redistributed to other tissues; it accumulates more slowly in skeletal muscle and yet more slowly in fat, from which it is gradually released into the blood. Up to 80% of fentanyl is bound to plasma proteins.

Elimination
Fentanyl is primarily metabolised in the liver, probably by N-dealkylation, and it is excreted mainly in the urine with less than 10% representing the unchanged drug. The terminal half-life of fentanyl is 3.7 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid, concentrated (for pH adjustment)
Water for injections

6.2 Incompatibilities

Fentanyl citrate is incompatible with alkaline solutions (due to reduced solubility) and some drugs.
Fentanyl Kalceks is incompatible with alkaline injections including methohexital and thiopental.
Compatibility must be checked before administration.
This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 5 years.

After opening the ampoule
Once opened, the product should be used immediately.

After dilution
Chemical and physical in-use stability has been demonstrated for 24 hours at 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

Store below 30 ºC. Store in the original package in order to protect from light.
Do not freeze.

For storage conditions after dilution or opening the ampoule, see section *Shelf life*.

6.5 Nature and contents of container

Type I colourless glass ampoules of 2 ml.
5 ampoules are packed in a liner. Two liners are packed into an outer carton.

Pack size: 10 ampoules.

6.6 Special precautions for disposal and other handling

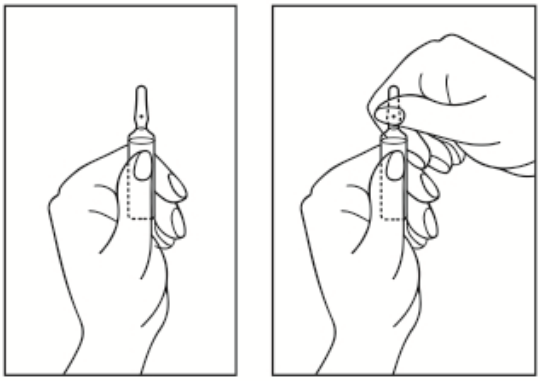
For single use only. Discard any unused contents.
The solution is to be visually inspected prior to use. Only clear solutions free from particles should be used.

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.

After dilution with sodium chloride (0.9%) or glucose (5%) for intravenous infusion, the diluted solutions are clear, colourless and free from particles.

Instruction of ampoule opening:
Wear gloves while opening 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).



Accidental dermal exposure should be treated by rinsing the affected area with water. Avoid use of soap, alcohol, and other cleaning materials that may cause chemical or physical abrasions to the skin.

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

7. PRODUCT REGISTRATION HOLDER AND MANUFACTURER

Product Registration Holder:
Eucogen Sdn Bhd
6A, Jalan Sungai Burung U
32/U, Bukit Rimau, 40460 Shah
Alam, Selangor, Malaysia

Brunei Darussalam Product Licence Holder:
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Manufacturer:
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Slovakia

8. DATE OF REVISION OF THE TEXT

02/2022