**Package leaflet: Information for the user**

**Fentanyl 50 micrograms/ml solution for injection**

fentanyl

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

1. What Fentanyl is and what it is used for
2. What you need to know before you are given Fentanyl
3. How Fentanyl is given
4. Possible side effects
5. How to store Fentanyl
6. Contents of the pack and other information


## 1. What Fentanyl is and what it is used for

Fentanyl 50 micrograms/ml solution for injection is a fluid that is injected. Fentanyl is a substance that reduces pain and is responsible for the action of this medicine. Fentanyl belongs to a group of strong, narcotic painkillers, which are also called opioid painkillers.

You will be given this medicine during surgery to ensure that you feel no pain.

## 2. What you need to know before you are given Fentanyl

**You should not be given Fentanyl**
- If you are allergic to fentanyl or any of the other ingredients of this medicine (listed in section 6). Also, if you are hypersensitive to other strong (narcotic) painkillers, you must not be given this medicine.
- Your lungs are not working properly (without mechanical ventilation of the lungs).

**Warnings and precautions**
After administration of this medicine, your breathing may become abnormally slow or weak. It is important that you tell your doctor about this immediately. As this may also occur some time after surgery, you will be observed for some time after the operation.

Talk to your doctor or nurse before Fentanyl is given:
- if you have poor liver, kidney or thyroid gland function;
- if you have lung or airway disease;
- if you use alcohol or drugs;
- if you have a certain muscle disorder (myasthenia gravis);
- if you are using certain medicines for depression (see ‘Other medicines and Fentanyl’);
- in elderly, debilitated patients and children (see section 3);
- if you or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs (“addiction”);
- if you are a smoker;

- if you have ever had problems with your mood (depression, anxiety or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.

Tell your doctor if one of these warnings applies to you. Close medical surveillance may be necessary when you are given this medicine. The dosage may also need to be adjusted.
Repeated use of opioid painkillers may result in the drug being less effective (you become accustomed to it). It may also lead to dependence and abuse which may result in life-threatening overdose. If you have concern that you may become dependent on Fentanyl, it is important that you consult your doctor.

If your treatment is stopped withdrawal symptoms may occur. Please tell your doctor or nurse if you think this is happening to you (see also section 4. Possible side effects).

**Children**
There is no experience with the use of this medicine in children under 2 years of age. Therefore, it is not advised to administer this medicine to children under 2 years of age.

**Other medicines and Fentanyl**
Tell your doctor or nurse if you are using, have recently used or might use any other medicines. This also applies to medicines obtained without a prescription.

It is especially important for medicines listed below as the dosage of this medicine or the other medicines may need to be adjusted, or you may need to be monitored more closely.

Tell your doctor if you are using or have recently used:
- certain medicines for depression:
  - selective serotonin reuptake inhibitors (SSRIs);
  - serotonin noradrenaline reuptake inhibitors (SNRIs);
  - monoamine oxidase inhibitors (MAO inhibitors).

  If used together, changes in mood (e.g. agitation, hallucinations [perceiving things that are not there], coma), body temperature above 38 °C, more rapid heartbeat, unstable blood pressure and hyperactive reflexes, muscle stiffness, lack of coordination and/or symptoms of the gastrointestinal tract (e.g. nausea, vomiting, diarrhoea) may occur. Your doctor will determine whether this medicine is suitable for you.
  If you are using so-called MAO inhibitors, your doctor, whenever feasible, will stop treatment with these medicines at least 2 weeks before you are given this medicine.
- strong painkillers for a long time;
- some painkillers for nerve pain (gabapentin and pregabalin);
- medicines for psychosis or Parkinson's disease;
- sleeping pills;
- tranquilisers;
- antiepileptic medicines (e. g. carbamazepine, phenytoin);
- medicines to reduce anxiety;
- medicines for certain mental illnesses;
- medicines for fungal infections (e.g. fluconazole or voriconazole);
- ritonavir (a medicine for HIV infections). If you are given a single dose of fentanyl, your doctor will be particularly vigilant. In prolonged use, you may be prescribed a lower dosage of this medicine.

**Fentanyl with alcohol**
Tell your doctor or nurse if you are using or have recently used alcohol or drugs.
Alcohol may enhance certain effects of this medicine. This medicine also influences the effect of alcohol. For these reasons, do not drink alcohol before receiving this medicine or on the day after receiving this medicine.

**Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

*Pregnancy*
There is insufficient knowledge as to whether the use of this medicine is harmful if you are pregnant. Administration of this medicine during childbirth, e.g. caesarean section, is not recommended because this medicine may cause breathing problems in the child.

*Breast-feeding*
The substance responsible for the effect of this medicine passes into breast milk. It is therefore not recommended to breast-feed for the first 24 hours after administration of this medicine. Do not use breast milk that has been expressed within 24 hours after administration of this medicine. Discuss this with your doctor.

**Driving and using machines**
Do not drive a car or any other vehicle and do not use any machines or tools for at least 24 hours after receiving this medicine, as this medicine may adversely affect your alertness and ability to drive. For this reason, your doctor will decide when you can drive again or operate hazardous machinery after you have received this medicine.

**Fentanyl contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per 2 ml ampoule, that is to say essentially 'sodium-free'.
This medicine contains 35.41 mg sodium (main component of cooking/table salt) per 10 ml ampoule. This is equivalent to 1.78% of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How to Fentanyl is given

This medicine is administered by injection into a vein.

**Dosage**
It is important that you receive the right amount of this medicine. This will vary from person to person depending on age, body weight, physical status, underlying diseases, medications used and type of surgery and anaesthesia. Your doctor will determine how much medicine you need.

**Adults**
Usually, 4-12 ml of Fentanyl is administered just before surgery. If the doctor considers it necessary, another additional dose can be administered later.

**Elderly and debilitated patients**
The dose administered to elderly (65 years and older) and debilitated patients just before surgery is lower than that prescribed for other adults. If the doctor considers it necessary, another additional dose can be administered later.

**Children aged 2 years and older**
The dose administered to children just before surgery depends on the child's body weight. If the doctor considers it necessary, another additional dose can be administered later.
Adolescents from 12 to 17 years of age are given adult doses.

**Children under 2 years of age**
There is no experience with the use of this medicine in children under 2 years of age. Therefore, it is not advised to administer this medicine in this age group.

**Patients with kidney problems**
The doctor may decide to lower the dose given to patients with kidney problems.

**Obese patients**
The dose administered to obese patients just before surgery may be lower than that prescribed for other adults. If the doctor considers it necessary, another additional dose can be administered later.

**If you are given more Fentanyl than you should**
As this medicine will be given to you by hospital staff it unlikely that you will be given too much of this medicine. However, tell your doctor or nurse immediately if you experience shallow or slow breathing or your breathing temporarily stops.
An overdose may result in a brain disorder (known as toxic leukoencephalopathy).

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects may be serious.** If you get any of the side effects listed below, your doctor must decide whether your treatment should be stopped immediately:

**Not known** (frequency cannot be estimated from the available data):
- anaphylactic shock (severe allergic reaction to certain substances, in which the following occur as a result of sudden, severe dilation of the blood vessels: sharp drop in blood pressure, paleness, restlessness, fast weak pulse, clammy skin and reduced consciousness);
- serotonin syndrome (syndrome with characteristics such as restlessness, hallucinations, coma, heart palpitations, variable blood pressure, raised body temperature, increased response to stimuli, poor coordination, stiffness, nausea, vomiting and diarrhoea).

**Other side effects.** If they get serious, tell your doctor or nurse:

**Very common** (may affect more than 1 in 10 people):
- nausea, vomiting;
- stiff muscles.

**Common** (may affect up to 1 in 10 people):
- involuntary movements, drowsiness, dizziness;
- visual disturbances;
- slowed heartbeat, more rapid heartbeat, heart rhythm disorders;
- decreased blood pressure, increased blood pressure, pain in the vein;
- spasm of the vocal cords, breathlessness due to spasms of the airway muscles, shallow or interrupted breathing;
- allergic skin inflammation;
- confusion after surgery, problems with the nervous system due to anaesthesia.

**Uncommon** (may affect up to 1 in 100 people):
- agitation or elated mood;
- headache;
- superficial inflammation in the veins, fluctuations in blood pressure;
- hyperventilation, hiccups;
- chills, low body temperature;
- problems with the airways due to anaesthesia, agitation after surgery, complications as a result of surgery.

**Not known** (frequency cannot be estimated from the available data):
- hypersensitivity (including: rash with severe itching and whealing (hives or urticaria); severe hypersensitivity to substances in the medicine may result in a serious reaction in which the blood vessels suddenly become very wide, causing blood pressure to fall and the heart to beat quickly but weakly, visible as paleness, restlessness and clammy skin);

- delirium (symptoms may include a combination of agitation, restlessness, disorientation, confusion, fear, seeing or hearing things that are not really there, sleep disturbance, nightmares);
- seizure/fit (convulsion), loss of consciousness, sudden muscle contraction (myoclonus);
- cardiac arrest;
- reduced force, depth and frequency of breathing;
- itching;
- symptoms of withdrawal syndrome (may manifest by the occurrence of the following side effects: nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating).

Cases of serotonin syndrome have been reported when fentanyl was used together with certain medicines for depression (see section 'Other medicines and Fentanyl').

**Reporting of side effects**
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie
By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Fentanyl

Keep this medicine out of the sight and reach of children.

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

Do not use this medicine after the expiry date which is stated on the outer carton or ampoule after "EXP". The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Fentanyl contains**
- The active substance is fentanyl (as fentanyl citrate).

Each ml of solution contains 50 micrograms of fentanyl (as fentanyl citrate).
Each ampoule of 2 ml contains 100 micrograms of fentanyl (as fentanyl citrate).
Each ampoule of 10 ml contains 500 micrograms of fentanyl (as fentanyl citrate).

- The other ingredients are sodium chloride, sodium hydroxide (for pH adjustment), water for injections. This medicine contains no preservative.

**What Fentanyl looks like and contents of the pack**
Clear, colourless solution for injection, free from visible particles.

10 glass ampoules of 2 ml
10 glass ampoules of 10 ml

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**
AS KALCEKS
Krustpils iela 71E, Rīga, LV-1057, Latvia
Tel.: +371 67083320
E-mail: kalceks@kalceks.lv

**This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:**

| | |
|---|---|
| The Netherlands | Fentanyl Kalceks 0,05 mg/ml oplossing voor injectie |
| Austria | Fentanyl Kalceks 50 Mikrogramm/ml Injektionslösung |
| Bulgaria | Fentanyl Kalceks 50 микрограма/ml инжекционен разтвор |
| Croatia | Fentanil Kalceks |
| Denmark | Fentanyl Kalceks |
| Estonia | Fentanyl Kalceks |
| Finland | Fentanyl Kalceks |
| Germany | Fentanyl Kalceks 50 Mikrogramm/ml Injektionslösung |
| Greece | FENTANYL/KALCEKS |
| Hungary | Fentanyl Kalceks 50 mikrogramm/ml oldatos injekció |
| Ireland | Fentanyl 50 micrograms/ml solution for injection |
| Italy | Fentanil Kalceks |
| Norway | Fentanyl Kalceks |
| Romania | Fentanil Kalceks 50 microgramе/ml soluţie injectabilă |
| Slovakia | Fentanyl Kalceks 50 mikrogramov/ml injekčný roztok |
| Slovenia | Fentanil Kalceks 50 mikrogramov/ml raztopina za injiciranje |
| Spain | Fentanilo Kalceks 50 microgramos/ml solución inyectable EFG |
| Sweden | Fentanyl Kalceks |
| United Kingdom (Northern Ireland) | Fentanyl 50 micrograms/ml solution for injection |

**This leaflet was last revised in 03/2023**

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The following information is intended for healthcare professionals only:

Consult the Summary of Product Characteristics (SmPC) for a complete description and other information.

**Therapeutic indications**
Fentanyl 50 micrograms/ml is an anaesthesia analgesic:
- for use as an opioid analgesic supplement in general or local anaesthesia;
- for administration with a neuroleptic.

**Posology and method of administration**
Fentanyl 50 micrograms/ml may only be administered in an environment where the airways can be monitored and by personnel able to monitor the airways (see SmPC section 4.4).

The dosage of Fentanyl 50 micrograms/ml must be determined individually based on age, body weight, physical status, underlying pathological condition, medication use and type of surgery and anaesthesia.

*Adults*
At induction, 200 to 600 micrograms (2.8 to 8.5 micrograms/kg) corresponding to 4-12 ml is usually injected intravenously. Doses above 200 micrograms should only be administered together with ventilation. For maintenance of analgesia, additional intravenous doses of 50 to 200 micrograms (0.7 to 2.8 micrograms/kg) corresponding to 1-4 ml can be administered after 30 to 45 minutes.

*Paediatric population*
*Adolescents 12 to 17 years of age*
Follow adult dosage.

*Children 2 to 11 years of age*

A dose of 1.25-2.5 micrograms/kg or 0.25-0.5 ml per 10 kg body weight is generally recommended for induction in children. For maintenance of analgesia, additional intravenous doses of 0.25 ml per 10 kg can be administered every 30-45 minutes.

*Children under 2 years of age*
There is no experience with fentanyl in children under 2 years of age.

*Use in children*
In spontaneously breathing children, analgesia techniques may only be used as part of an anaesthesia technique or as part of a sedation/analgesia technique by experienced personnel in an environment where sudden muscle rigidity (requiring intubation) or apnoea (requiring ventilation) can be treated (see SmPC section 4.4).

*Use in the elderly*
As with other opioids, the starting dose for elderly (> 65 years) and debilitated patients should be reduced. The effect of the initial dosage must be taken into account when determining additional doses.

*Use in patients with renal impairment*
In patients with renal impairment, a reduction in the Fentanyl 50 micrograms/ml dose should be considered and these patients should be carefully observed for signs of fentanyl toxicity (see SmPC section 5.2).

*Use in obese patients*
In obese patients, there is a risk of overdose if the dose is calculated on the basis of body weight. The dose for obese patients (BMI > 30 $kg/m^2$) should be determined based on estimated lean body mass instead of body weight alone. Further titration should proceed with caution, based on effect (see SmPC section 5.2).

Method of administration
Administer slowly – over 1 to 2 minutes – intravenously.

**Contraindications**
- Hypersensitivity to the active substance or to any of the excipients listed in section 6, or to other opioids.
- Poor lung function without mechanical ventilation. This is due to the respiratory depressant effect specific to morphinomimetic agents.

**Special warnings and precautions for use**
- Fentanyl may only be administered in an environment where the airways can be monitored and by personnel able to monitor the airways.
- Like all potent opioids, fentanyl can produce respiratory depression, which is dose-related. Significant respiratory depression will occur when administered at doses above 200 micrograms fentanyl (4 ml). Administration of naloxone, a specific opioid antagonist, can counteract this effect. It may be necessary to repeat the opioid antagonist dose because respiratory depression may last longer than the duration of action of the opioid antagonist. Deep analgesia is accompanied by manifest respiratory depression, which may persist or recur in the postoperative period. It is therefore important that patients remain under proper surveillance. Resuscitation equipment and opioid antagonists should be immediately available. Hyperventilation during anaesthesia may change the patient's response to $CO_2$ and can therefore also affect breathing after surgery.
- Muscle rigidity can develop, as a result of which respiratory depression may also occur. The incidence may be reduced by slow intravenous injection (normally sufficient for low dosages). The reaction can be treated by artificial ventilation, premedication with benzodiazepines and, if necessary, administration of a muscle relaxant.
- The occurrence of anaphylactic reactions should be taken into account when administering fentanyl.
- Non-epileptic myoclonic reactions may occur.

- Bradycardia and cardiac arrest may occur if the patient has been given too low an amount of anticholinergic agent or if Fentanyl 50 micrograms/ml is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.
- Opioids can cause hypotension, especially in hypovolaemic patients. Appropriate measures must be taken to maintain stable arterial pressure.
- The use of rapid bolus opioid injections must be avoided. In patients with impaired intracerebral compliance, the temporary reduction in mean arterial pressure is sometimes accompanied by a short-term reduction in perfusion pressure.
- Patients receiving chronic treatment with opioids, or who are addicted to opioids, may require higher doses.
- Dose reduction is recommended in elderly and debilitated patients. Opioids must be carefully titrated in patients with one or more of the following underlying conditions: uncontrolled hypothyroidism, pulmonary disease, impaired lung function or alcoholism. Patients with liver dysfunction should be dosed with caution due to possible impaired metabolism. Patients with renal impairment should be carefully monitored for symptoms of fentanyl toxicity. As a result of dialysis, the volume of distribution of fentanyl may change, which may affect serum concentrations. These patients should be observed for a longer period postoperatively.
- If Fentanyl 50 micrograms/ml is administered together with neuroleptics, the practitioner must be familiar with the specific properties of both agents, particularly the differences in duration of action. The risk of hypotension is greater when this combination is administered. Neuroleptics may give rise to extrapyramidal symptoms that can be countered with antiparkinson agents. Combination with antiparkinson agents may increase the risk of tardive dyskinesia.
- As with other opioids, due to anticholinergic effects, administration of fentanyl may lead to increased pressure in the bile duct and spasms of the sphincter of Oddi may occasionally be seen.
- In patients with myasthenia gravis, the use of certain anticholinergic agents and neuromuscular blockers should be carefully considered before and during administration of a general anaesthesia regimen in which fentanyl is administered intravenously.
- Caution is advised if Fentanyl 50 micrograms/ml is co-administered with medicinal products that affect serotonergic neurotransmitter systems.
  A potentially life-threatening serotonin syndrome may develop with concomitant use of serotonergic medicinal products such as selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) and with medicinal products that inhibit the degradation of serotonin (including monoamine oxidase inhibitors [MAO inhibitors]). This may occur within the recommended dose.
  Serotonin syndrome may include changes in the psychological state (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular disorders (e.g. hyperreflexia, poor coordination, rigidity) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).
  If serotonin syndrome is suspected, rapid discontinuation of Fentanyl 50 micrograms/ml should be considered.

<u>Tolerance and Opioid use disorder (abuse and dependence)</u>
Tolerance, physical dependence and psychological dependence may develop upon repeated administration of opioids.
Repeated use of opioids may lead to Opioid use disorder (OUD). 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).

<u>Withdrawal syndrome</u>
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>

In spontaneously breathing children, analgesia techniques may only be used as part of an anaesthesia technique or as part of a sedation/analgesia technique by experienced personnel in an environment where sudden muscle rigidity (requiring intubation) or apnoea (requiring ventilation) can be treated.

*Excipients*
This medicinal product contains:
7.08 mg sodium per 2 ml ampoule, that is to say essentially 'sodium-free'.
35.41 mg sodium per 10 ml ampoule, equivalent to 1.78% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

**Interaction with other medicinal products and other forms of interaction**
*Effects of other agents on fentanyl*
*MAO inhibitors and other serotonergic medicinal products*
Co-administration of fentanyl and MAO inhibitors may lead to paroxysmal CNS stimulation and hypertension. Co-administration should be avoided and whenever feasible treatment with MAO inhibitors must be discontinued for at least 2 weeks before initiation of treatment with Fentanyl 50 micrograms/ml.
Co-administration of fentanyl with a serotonergic agent, such as an SSRI or an SNRI, or a MAO inhibitor may increase the risk of serotonin syndrome, a potentially life-threatening condition.
If concomitant use of Fentanyl 50 micrograms/ml with SSRIs, SNRIs or MAO inhibitors is unavoidable, the patient should be monitored for symptoms of serotonin syndrome during concomitant use.

Agents such as barbiturates, benzodiazepines, neuroleptics, halogenated gases, gabapentinoids (gabapentin and pregabalin) or other agents that exert a non-selective depressant effect on the central nervous system (including alcohol) may enhance respiratory depression caused by opioids. If patients have been given such agents, the required fentanyl dose may be lower than usual.

Fentanyl, a high clearance agent, is rapidly and extensively metabolised by CYP3A4. Oral administration of 200 mg itraconazole (a potent CYP3A4 inhibitor) daily for 4 days had no significant effect on the pharmacokinetics of intravenously administered fentanyl. Oral administration of ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of intravenously administered fentanyl by two-thirds; however, peak plasma concentrations were not affected after a single dose of intravenously administered fentanyl.

Co-administration of fluconazole or voriconazole and fentanyl may increase exposure to fentanyl by approximately 25 to 40%. During concomitant use of fluconazole or voriconazole and fentanyl, patients should be closely monitored, with adjustment of the fentanyl dose as necessary.

When fentanyl is administered in a single dose, special care and patient observation is required when concomitantly using potent CYP3A4 inhibitors such as ritonavir. With continuous administration, a reduction in the fentanyl dose may be necessary to prevent accumulation of fentanyl, which may lead to an increased risk of prolonged or delayed respiratory depression.

*Cytochrome P450 3A4 (CYP3A4) inducers*
Fentanyl injection along with strong CYP3A4 inducers (e.g. carbamazepine, phenytoin), may decrease the plasma concentrations of fentanyl, thus decreasing its efficacy. Patient should be closely monitored for evidence of reduced analgesic effects if fentanyl is used together with a strong CYP3A4 inducer. The increase of fentanyl dose should also be considered, if necessary.

*Effects of fentanyl on other agents*
Concomitant use of other medicinal products with a depressant effect on the central nervous system, including opioids, sedatives, hypnotics, agents for general anaesthesia, phenothiazines, tranquillisers, muscle relaxants, sedating antihistamines and alcoholic beverages, can have an additive depressant effect; hypoventilation, hypotension and deep sedation or coma may occur in such cases. Therefore, concomitant use of fentanyl with one of the above-mentioned agents requires special care and patient observation.

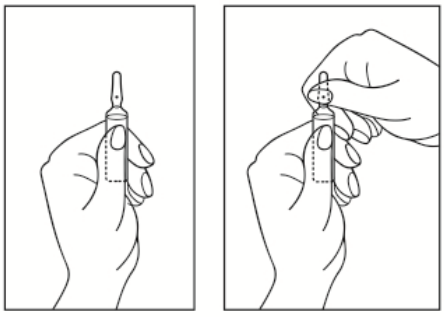
Upon concomitant use with fentanyl, plasma concentrations of etomidate increased considerably (by a factor of 2-3). During concomitant use, the total plasma clearance and volume of distribution of etomidate decrease by a factor of 2 to 3 without any change in the half-life.

Co-administration of fentanyl and intravenous midazolam results in an increase in the terminal plasma half-life and a decrease in the plasma clearance of midazolam. Exposure to midazolam is increased by approximately 50%. The mechanism of interaction is competitive inhibition of CYP3A4 (see SmPC section 5.2). When midazolam is co-administered with fentanyl, the dose of midazolam might need to be reduced.

**Incompatibilities**
This medicinal product must not be mixed with other medicinal products.

**Special precautions for disposal and other handling**
For single use only. If only part used, discard the remaining solution.
Use finger protection when opening an ampoule.
After first opening: the product should be used immediately.
Instruction of 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).



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