Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alfentanil 500 micrograms/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains alfentanil hydrochloride equivalent to 500 micrograms alfentanil.
Each 2 ml ampoule contains alfentanil hydrochloride equivalent to 1 mg alfentanil.
Each 10 ml ampoule contains alfentanil hydrochloride equivalent to 5 mg alfentanil.

Excipient with known effect: sodium (see section 4.4).
Each 2 ml ampoule contains 7.1 mg of sodium.
Each 10 ml ampoule contains 35.4 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alfentanil is indicated in adults as:
- an analgesic for induction of anaesthesia and/or maintenance of general anaesthesia.

Alfentanil is indicated for use in neonates, infants, children and adolescents less than 18 years of age as:
- an opioid analgesic together with a hypnotic to induce anaesthesia;
- an opioid analgesic in connection with general anaesthesia during surgical procedures of both short and long duration.

4.2 Posology and method of administration

Posology

The dosage of alfentanil should be individualised according to age, body weight, physical status, underlying pathological conditions, use of other drugs and type of surgery and anaesthesia.

Adult patients

The usual recommended dosage regimen is given in Table 1.

Table 1The usual recommended dosage regimen

Adults	*Initial*	*Supplemental*
Spontaneous respiration	500 mcg (1 ml)	250 mcg (0.5 ml)
Assisted ventilation	30-50 mcg/kg	15 mcg/kg

- *Short procedures and outpatient surgery*

In spontaneously breathing patients, the initial bolus dose should be given slowly over about 30 seconds (dilution may be helpful).

After intravenous administration in unpremedicated adult patients, 500 mcg (1 ml) alfentanil may be expected to have a peak effect in 90 seconds and to provide analgesia for 5-10 minutes.

- *Procedures of medium and long duration*

Periods of more painful stimuli may be overcome by repeat administration of 250 mcg (0.5 ml) alfentanil. For procedures of longer duration, additional administrations will be required.

In ventilated patients, the last dose of alfentanil should not be given later than about 10 minutes before the end of surgery to avoid the continuation of respiratory depression after surgery is complete.

In ventilated patients undergoing longer procedures, alfentanil may be infused at a rate of 0.5-1 mcg/kg/minute. Adequate plasma concentrations of alfentanil will only be achieved rapidly if this infusion is preceded by a loading dose of 50-100 mcg/kg given as a bolus or fast infusion over 10 minutes.

Lower doses may be adequate, for example where anaesthesia is being supplemented by other agents.

The infusion should be discontinued up to 30 minutes before the anticipated end of surgery.

Increasing the infusion rate may prolong recovery. Supplementation of the anaesthetic, if required, for periods of painful stimuli, is best managed by extra bolus doses of alfentanil (500 mcg to 1 mg corresponding to 1-2 ml) or low concentrations of a volatile agent for brief periods.

Patients with severe burns presenting for dressing, etc., have received a loading dose of 18-28 mcg/kg/min for up to 30 minutes without requiring mechanical ventilation.

In heart surgery, when used as a sole anaesthetic, doses in the range of 12-50 mg/hour have been used.

Special populations

Paediatric population
Assisted ventilation equipment should be available for use in children of all ages, even for short procedures in spontaneously breathing children.

Data in children, particularly those aged 1 month to 1 year are limited (see section 5.2).

- Neonates (0 to 27 days): The pharmacokinetics are very variable in neonates, particularly in those born preterm. Clearance and protein binding are lower, and a lower dose of alfentanil may be required. Neonates should be closely monitored and the dose of alfentanil titrated according to the response.
- Infants and toddlers (28 days to 23 months): Clearance may be higher in infants and toddlers compared to that in adults. For maintenance of analgesia, the rate of infusion of alfentanil may need to be increased.
- Children (2 to 11 years): Clearance may be slightly higher in children and the rate of infusion may need to be increased.
- Adolescents: The pharmacokinetics of alfentanil in adolescents are similar to those in adults and no specific dosing recommendations are required. *Dosing recommendations for paediatric patients*

The wide variability in response to alfentanil makes it difficult to provide dosing recommendations for younger children. For older children a bolus dose of 10-20 mcg/kg alfentanil for induction of anaesthesia (i.e. to supplement to propofol or

inhalation anaesthesia) or as an analgesic is considered appropriate. Supplemental boluses of 5-10 mcg/kg alfentanil at appropriate intervals can be administered.

To maintain analgesia in children during surgery, alfentanil infusion rate of 0.5 to 2 mcg/kg/min may be administered. The dose must be titrated up or down according to the needs of the individual patient. When combined with an intravenous anaesthetic agent, the recommended dose is approximately 1 mcg/kg/min.

There may be a higher risk of respiratory complications and muscle rigidity when alfentanil is administered to neonates and very young children. Necessary precautions are detailed in section 4.4.

Hepatic impairment
Reduced doses may be required (see sections 4.4 'Special dosage considerations'and 5.2).

Renal impairment
Clearance of alfentanil is unaltered in renal failure. However, there is an increased free fraction and hence lower doses may be required (see sections 4.4 'Special dosage considerations'and 5.2).

Elderly and debilitated patients
The initial dose must be reduced in elderly (>65 years) and debilitated patients. The effect of the initial dose must be borne in mind when determining such supplementary doses.

Patients with concurrent comorbidity
Alfentanil must be titrated with care in patients with the following conditions:

- uncontrolled hypothyroidism;
- lung disease, particularly in the case of reduced respiratory capacity;
- alcoholism or impaired liver and kidney function.These patients also require prolonged postoperative monitoring.

Method of administration

For intravenous use. Alfentanil should be given as bolus injections (short procedures) or bolus supplemented by repeat administration of alfentanil, or by infusion (long painful procedures).
Alfentanil should only be given by individuals trained in the administration of general anaesthetics and the management of the respiratory effects of potent opioids.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

Myasthenia gravis

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

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

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

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

Alfentanil must be titrated with care in patients with the following conditions:

- uncontrolled hypothyroidism;
- lung disease, particularly in the case of impaired respiratory capacity;
- alcoholism or impaired liver or kidney function.

These patients also require prolonged post-operative monitoring.

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

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

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids. Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Alfentanil can produce dependence because of its chemical structure and morphinomimetic characteristics. When alfentanil will be given only intraoperatively (as intended) as anaesthetic agent addiction is not to be expected.

Elderly

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

Paediatric population
When administering alfentanil to neonates and very young children, there may be an increased risk of respiratory complications as compared to use in older children and adults. Younger children should therefore be monitored immediately after the start of alfentanil administration. Assisted ventilation equipment should be available for use on children, regardless of age, even during short-duration procedures in children with spontaneous breathing.

Owing to the risk of muscular rigidity in neonates and infants being given alfentanil, the concurrent use of a muscle relaxant should be considered. All children should be monitored for a sufficient period of time after cessation of treatment with alfentanil to ensure that there is spontaneous respiration again.

Owing to varying pharmacokinetics in neonates, it may be necessary to give a lower dose of alfentanil. Neonates should be carefully monitored, and the alfentanil dosage must be titrated in keeping with the child's response (see section 4.2).

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Drugs modifying the effect of alfentanil

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

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

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

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

Effect of alfentanil on other drugs

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

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

4.6 Fertility, pregnancy and lactation

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

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

Breast-feeding

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

Fertility
There are limited human data available on the effects of alfentanil on male or female fertility. Animal studies do not indicate direct harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

Table 2 Undesirable effects

Immune system disorders Not known (cannot be estimated from available data)	Allergic reactions such as anaphylaxis, anaphylactoid reaction, urticaria).
Psychiatric disorders Common (≥1/100 to <1/10) Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from available data)	Euphoria. Agitation, crying. Disorientation.
Nervous system disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to >1/100) Not known (cannot be estimated from available data)	Movement disorders, dizziness,drowsiness, dyskinesia. Headache, somnolence, unresponsive to stimuli. Loss of consciousness (during postoperative period), convulsions, myoclonus.
Eye disorders Common (≥1/100 to <1/10) Not known (cannot be estimated from available data)	Visual disturbances. Miosis.
Cardiac disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Not known (cannot be estimated from available data)	Bradycardia, tachycardia. Arrhythmia, decreased heart rate. Cardiac arrest.
Vascular disorders Common (≥1/100 to <1/10) Rare (≥1/10,000 to <1/1,000)	Hypotension, hypertension. Vein pain.
Respiratory, thoracic and mediastinal disorders	

Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from available data)	Apnoea. Hiccups, hypercapnia, laryngospasm, respiratory depression (including fatal outcome) Bronchospasm, epistaxis. Respiratory arrest, coughing.
Gastrointestinal disorders Very common (≥1/10)	Nausea, vomiting.
Skin and subcutaneous tissue disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from available data)	Allergic dermatitis, hyperhidrosis. Pruritus. Erythema, rash.
Musculoskeletal and connective tissue disorders Common (≥1/100 to <1/10)	Muscular rigidity.
General disorders and administration site conditions Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Not known (cannot be estimated from available data)	Chills, injection site pain, fatigue. Pain. Fever.
Injury, poisoning and procedural complications Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Procedural pain. Postoperative agitation, airway complications from anaesthesia, postoperative confusion. Neurological anaesthesia complications, procedural complications, endotracheal intubation complications.

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

4.9 Overdose

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

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

If the respiratory depression is associated with muscular rigidity, it may be necessary to administer a neuromuscular blocker intravenously in order to facilitate respiration.
The patient must be kept under close observation: Body heat and adequate fluid intake must be kept up. In the event of severe or persistent hypotension, hypovolaemia must be considered, and this can be corrected by administering parenteral fluid.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid anaesthetics, ATC code: N01AH02

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

5.2 Pharmacokinetic properties

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

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

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

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

Elimination
Alfentanil is eliminated quickly after intravenous administration. Terminal half-lives of 83-223 min have been reported. Plasma clearance in people under 40 averages 356 ml/min and drops about 8% per decade after the age of 40. Excretion takes place rapidly: sequential distribution half-lives are 1 and 14 min, and the total half-life is 90-111 min (interval 50-150 min), which is several times shorter than that of fentanyl and sufentanil. Once steady-state has been reached by infusion, the half-life remains unchanged.
When administration is ceased, the patient wakes quickly with no opioid after-effects.

Special populations

Paediatric population
Only limited paediatric data are available. The values for the pharmacokinetic parameters are shown in the table below.

Table 3Pharmacokinetic parameters for alfentanil in paediatric subjects

Pharmacokinetic parameters for alfentanil in paediatric subjects			

	$t_{1/2\beta}$ (hours)	CL (ml/kg/min)	Vd_{ss} (l/kg)
Pre-term neonates (0-27 days) Gestational age 25-40 weeks; ***n = 68***	0.7-8.8	0.9-8.4	0.3-1.2
Term neonates (0-27 days) Gestational age: 35-41 weeks; ***n = 18***	4.1-5.5	1.7-3.2	0.5-0.8
Infants and young children aged 28 days – 23 months; ***n = 34***	0.9-1.2	7.7-13.1	0.4-1.1
Children aged 2-11 years; ***n = 32***	0.7-1.3	4.7-10.2	0.2-1.0
Adolescents aged 12-14 years; ***n = 3***	1.1-1.9	5.5-7.4	0.3-0.6

NB! Data for neonates, infants and young children, and older children are given as a range of mean values.
CL = clearance. Vd_{ss} = volume of distribution at steady state. $t_{1/2\beta}$ = half-life in the elimination phase.

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

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

Hepatic impairment
After administration of a single intravenous dose of 50 mcg/kg, the terminal half-life is significantly longer in cirrhotic patients than in controls. The volume of distribution remains unchanged. The free fraction of alfentanil in cirrhotic patients increased to 18.5%, as compared with 11.5% in controls. This increase in the free fraction, together with a reduction in clearance from 3.06 ml/min/kg in controls to 1.60 ml/min/kg in cirrhotic patients will result in an increased clinical effect of alfentanil (see sections 4.2 and 4.4).

Renal impairment
The volume of distribution and clearance of the free fraction is the same in renal failure patients and healthy controls. The free fraction of alfentanil in renal patients increased to between 12.4 and 19%, as compared with between 10.3 and 11% in controls. This can result in an increased clinical effect of alfentanil (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, mutagenicity or toxicity to reproduction and development. With regard to a possible carcinogenic potential of alfentanil, long-term animal studies are not available.

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

4 years.

Shelf life after dilution

Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C and 2 to 8°C (see section 6.6).
From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

2 ml and 10 ml type I hydrolytic class colourless borosilicate glass ampoules with one point cut.
Ampoules are packed in polyvinylchloride film liner. Liners are packed into a cardboard box.

Pack sizes:
5 or 10 ampoules of 2 ml
5 or 10 ampoules of 10 ml

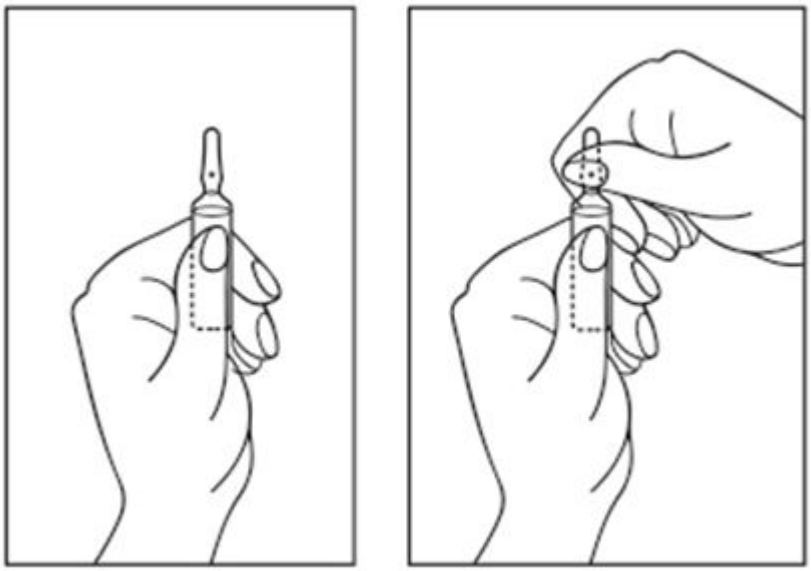
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

Instructions on preparation of diluted solution:
- Inspect the ampoule visually prior to use. Only clear solutions free from particles should be used.
- Wear gloves while opening the ampoule.
- Open the ampoule:

1. Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2. Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).



- Use medicinal product immediately after opening the ampoule.
- Dilute the content of ampoule to a concentration of 25-80 mcg/ml with:
  - 0.9% sodium chloride solution or
  - 5% glucose solution or
  - Ringer lactate solution.

- Discard any unused portion.
- If the skin is accidentally exposed, treat by flushing the affected area with water. Avoid using soap, alcohol and other detergents, which may cause chemical or physical damage to the skin.

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

For shelf life of diluted solution, see section 6.3.

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

7 MARKETING AUTHORISATION HOLDER

AS Kalceks
Krustpils Iela 71e
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

PA2165/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th September 2019

10 DATE OF REVISION OF THE TEXT

July 2023