Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fentanyl 50 micrograms/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

Excipient with known effect
Each ampoule of 2 ml contains 7.08 mg (0.31 mmol) sodium.
Each ampoule of 10 ml contains 35.41 mg (1.54 mmol) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless solution for injection, free from visible particles.
The pH of the solution is 4.0 to 7.0.
Osmolality is approximately 285 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 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.

4.2 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 section 4.4).

Posology

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 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 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 section 5.2).

Method of administration

Administer slowly – over 1 to 2 minutes – intravenously.

4.3 Contraindications

-Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, or to other opioids.
- Poor lung function without mechanical ventilation. This is due to the respiratory depressant effect specific to morphinomimetic agents.

4.4 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.

Tolerance and Opioid use disorder (abuse and dependence)
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).

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

Paediatric population
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.

4.5 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 section 5.2). When midazolam is co-administered with fentanyl, the dose of midazolam might need to be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient data on the use of Fentanyl 50 micrograms/ml during human pregnancy to assess the potential to cause harm. Fentanyl can cross the placenta in early pregnancy and during delivery. Only limited evidence of reproductive toxicity has been seen in animal studies (see section 5.3). The potential risk for humans is unknown. Fentanyl must not be used during pregnancy unless strictly necessary.

Administration during childbirth (including caesarean section) is not recommended, as fentanyl crosses the placenta and possibly suppresses spontaneous breathing in the immediate postpartum period. If fentanyl is administered, assisted ventilation equipment must be immediately available for the mother and baby, in the event that it is needed. An opioid antagonist for the child should always be available.

Breast-feeding
Fentanyl is excreted in human milk. It is therefore not recommended to breast-feed within 24 hours after administration of fentanyl or to use breast milk expressed during this period. The associated risk should be weighed against the possible harmful effects.

Fertility
There are no clinical data on the effects of fentanyl on male or female fertility. In animal studies, some tests have shown reduced dam fertility at doses that were maternally toxic (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should not drive or use machines for some time (at least 24 hours) following the administration of Fentanyl 50 micrograms/ml.

4.8 Undesirable effects

The safety of fentanyl was evaluated in 376 subjects taking part in 20 clinical studies where fentanyl was evaluated as an anaesthetic. These subjects received at least 1 dose of fentanyl and provided safety data. Based on the pooled safety data from these clinical studies, the most common (≥ 5% incidence) adverse reactions are: nausea (26.1%), vomiting (18.6%), muscle rigidity (10.4%), hypotension (8.8%), hypertension (8.8%), bradycardia (6.1%) and sedation (5.3%).

Those adverse reactions (including the adverse reactions listed above) derived from clinical research and post-marketing data have been subdivided by system organ class and are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency group, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported with fentanyl

System Organ Class	**Adverse reactions**			
	Frequency category			
	Very common	**Common**	**Uncommon**	**Not known**
Immune system disorders				Hypersensitivity (including anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric disorders			Euphoria	Delirium
Nervous system disorders		Dyskinesia Sedation Dizziness	Headache	Convulsions Loss of consciousness Myoclonus
Eye disorders		Visual disturbances		
Cardiac disorders		Bradycardia Tachycardia Arrhythmias		Cardiac arrest
Vascular disorders		Hypotension Hypertension Vein pain	Phlebitis Blood pressure fluctuations	
Respiratory, thoracic and mediastinal disorders		Laryngospasm Bronchospasm Apnoea	Hyperventilation Hiccups	Respiratory depression
Gastrointestinal disorders	Nausea Vomiting			
Skin and subcutaneous tissue disorders		Allergic dermatitis		Pruritus
Musculoskeletal and connective tissue disorders	Muscle rigidity			
General disorders and administration			Chills Hypothermia	Drug withdrawal syndrome (see section 4.4)

site conditions				
Injury, poisoning and procedural complications		Postoperative confusion Anaesthetic complication neurological	Airway complications of anaesthesia Postoperative agitation Procedural complications	

Cases of serotonin syndrome have been reported when medicinal products containing fentanyl were co-administered with potent serotonergic agents (see sections 4.4 and 4.5).

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, Website: www.hpra.ie

4.9 Overdose

Signs and symptoms
Overdose of fentanyl is manifested by an extension of the pharmacologic effects. Respiratory depression may occur, which may vary from bradypnoea to apnoea.
Toxic leukoencephalopathy has been observed with fentanyl overdose.

Treatment
For hypoventilation or apnoea, oxygen must be given and, if necessary, ventilation must be applied. For respiratory depression, an opioid antagonist should be administered. This does not preclude taking more direct countermeasures.
The shorter duration of action of the opioid antagonist compared to fentanyl should be taken into account. Repeated administration of the opioid antagonist may be needed. If respiratory depression is accompanied by muscle rigidity, a muscle relaxant can - if necessary - be administered to facilitate breathing.
The patient should be closely observed. Body temperature and adequate fluid intake must be maintained. If hypotension is severe or persistent, hypovolaemia must be taken into account. In this case, appropriate parenteral fluids should be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anaesthetics, opioid anaesthetics, ATC code: N01AH01

Fentanyl is a synthetic opioid with a μ-agonist pharmacological effect.
Fentanyl is a potent opioid analgesic. Fentanyl can be used as an analgesic supplement in general anaesthesia or as an anaesthetic alone. A dose of 100 micrograms (2.0 ml) has a similar analgesic effect as 10 mg morphine. Fentanyl has a rapid onset of action. The maximum analgesic effect and the depressant effect on respiration take place within a few minutes. The mean duration of action of the analgesic effect is approximately 30 minutes after a single dose up to 100 micrograms. The depth of analgesia is dose-dependent and can be adjusted to the pain level of the surgical procedure.

5.2 Pharmacokinetic properties

Distribution
Following intravenous injection, fentanyl plasma concentrations decline rapidly, with successive distribution half-lives of approximately 1 minute and approximately 15 minutes and a terminal elimination half-life of approximately 8 hours. Fentanyl has a V_c (central compartment volume of distribution) of approximately 15 l and a total V_{dss} (steady-state volume of distribution) of approximately 400 l. The binding of fentanyl to plasma proteins is approximately 84%.

Biotransformation
Fentanyl is rapidly metabolised, primarily in the liver by CYP3A4. Fentanyl has no active metabolites, the major metabolite is norfentanyl. Clearance is approximately 600 ml/min. *In vitro* studies with midazolam as a substrate revealed that fentanyl inhibited CYP3A4.

Elimination
Approximately 75% of the administered dose is excreted in the urine within 24 hours. Only 10% of the dose excreted in the urine is present as unchanged substance.

Special populations

Children
Following intravenous administration, plasma protein binding of fentanyl is lower in newborns than in adults. In preterm neonates, it is higher (about 77%) than in term neonates (about 62%). Clearance per kg body weight and total volume of distribution after intravenous administration of fentanyl is higher in infants and children than in adults. This may lead to the need for a higher fentanyl dose per kg. The terminal half-life is longer in newborn infants. CYP3A4 activity is very low at birth but increases postpartum to attain 30-40% of the adult level 1 month postpartum. Values for clearance, steady-state volume of distribution and terminal half-life for children of different ages are given in the table below.

Table 2 Clearance, steady-state volume of distribution and terminal half-life in children

	Cl (ml/kg/min)*	V_{ss} (l/kg)*	Beta T½ (hours)
Infants 1-26 days postpartum	3.4 - 58.7	1.3 - 30.3	1.3 - 15.9
Infants 48-71 days postpartum	21.9 - 32.3	6.0 - 9.5	3.1 - 15.5
Children 3.17 ± 0.68 years	11.5 ± 4.19	3.06 ± 1.02	4.1 ± 1.3
Adolescents 12 ± 1.73 years	7.05 ± 1.24	1.92 ± 1.04	3.5 ± 1.2

** Values for steady-state clearance and volume of distribution were normalised for body weight*

Renal impairment
Data obtained from a study where fentanyl was administered intravenously to patients undergoing kidney transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive Fentanyl 50 micrograms/ml, they should be carefully observed and the dose should be reduced if necessary (see section 4.2).

Adult patients with burn wounds
Following a bolus or a short-term intravenous infusion of fentanyl, clearance is increased by a maximum of 44%, together with a larger volume of distribution. This results in lower plasma concentrations of fentanyl. This may necessitate an increase in the fentanyl dose.

Obese patients
An increase in the total clearance of fentanyl has been observed with increased body weight. For patients with a BMI > 30 kg/m^2, clearance increases by approximately 10% per 10 kg increase in lean body mass.

5.3 Preclinical safety data

In vitro, fentanyl, like other opioid analgesics, showed mutagenic effects in a mammalian cell tests only at cytotoxic concentrations, together with metabolic activation. Fentanyl showed no mutagenicity in *in vivo* studies with rodents and bacterial tests.
In a two-year carcinogenicity study in rats, fentanyl was not associated with an increased incidence of tumours.

Some tests in female rats revealed reduced fertility, as well as mortality in embryos. These findings were related to toxicity in the dams and were not a direct effect of the medicinal product on the developing embryo. There was no evidence of teratogenic effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

4 years.

After first opening: the product should be used immediately.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only. If only part used, discard the remaining solution.

Use finger protection when opening an ampoule.

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

PA2165/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 2020
Date of last renewal: 19th June 2022

10 DATE OF REVISION OF THE TEXT

June 2023