SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fentanyl 100 micrograms in 2 ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml ampoule contains 100 micrograms of fentanyl as Fentanyl Citrate (50 micrograms of fentanyl per ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection
Clear, colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. As the sole intravenous analgesic agent in surgical procedures.
2. As an adjunct in the maintenance of general anaesthesia and analgesia.
3. In conjunction with a neuroleptic agent in the technique of neuroleptanalgesia.
4. As a respiratory depressant/analgesic in patients requiring prolonged assisted ventilation.

4.2 Posology and method of administration

Posology
Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway (see section 4.4).

Recommended Dosage:

1. As sole I.V. analgesic agent in surgical procedures
Adults: The usual dose is 100 to 800 micrograms (0.1 to 0.8mg) initially, depending on response, with maintenance doses of 50 micrograms (0.05mg) as necessary, in conjunction with controlled ventilation.

2. As an adjunct in the maintenance of general anaesthesia and analgesia *Adults:* 50 micrograms (0.05mg) supplements as necessary.

3. In conjunction with a neuroleptic agent in the technique of neuroleptanalgesia
Adults: The usual dose is 100 micrograms (0.1mg) initially, with maintenance doses of 50 micrograms (0.05mg) as necessary.

4. In patients requiring prolonged assisted ventilation
Adults: Up to 600 micrograms (0.6mg) initially, with supplemental doses of 50 to 200 micrograms (0.05mg to 0.2mg).

Paediatric population
Children aged 12 to 17 years old- Follow adult dosage

Children aged 2 to 11 years old:
The usual dosage regimen in children is as follows:

	Age	Initial	Supplemental
Spontaneous Respiration	2-11 yrs	1-3 micrograms/kg	1-1.25 micrograms/kg
Assisted Ventilation	2-11 yrs	1-3 micrograms/kg	1-1.25 micrograms/kg

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 (see section 4.4).

Elderly
Elderly patients will require reduced doses.

Obese patients
Obese patients should have dosage calculated according to their lean body mass.

Method of administration
Intravenous.

4.3 Contraindications

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

Known intolerance to fentanyl or other morphino-mimetics.

Use in patients with respiratory depression, cyanosis, excessive bronchial exudation, bronchoconstriction (reversible or irreversible), or chronic pulmonary disease.

Use in patients after operative interventions in the biliary tract.

Use in patients who are receiving, or have within two weeks received, monoamine oxidase inhibitors.

Use in the presence of acute alcoholism, increased intracranial pressure or coma.

4.4 Special warnings and precautions for use

Fentanyl is intended for use in hospitals only by those trained in anaesthesia and familiar with the use of potent opioids when given intravenously. As with all potent opioids, respiratory depression is dose-related and can be reversed by a specific opioid antagonist such as naloxone, but additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist. Profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the post-operative period. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and

opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's responses to CO2, thus affecting respiration postoperatively.

Induction of muscle rigidity, which may also involve the thoracic muscles, can occur, but can be avoided by the following measures: slow i.v. injection (ordinarily sufficient for lower doses), premedication with benzodiazepines and the use of muscle relaxants.

Non-epileptic myoclonic movements can occur.

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 relaxants. Bradycardia can be treated with atropine.

Opioids may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Repeated use will result in the development of tolerance requiring increases in dosage to achieve the required effects.

Generally, it is preferable to vary opioid analgesics at intervals in patients requiring prolonged periods of analgesia.

Dependence on fentanyl, when given as a single dose or finite number of intra-operative doses has not been reported.

However, repeated administration at short term intervals for prolonged periods may result in the development of dependence, with a withdrawal syndrome on cessation of therapy.

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

This product should only be used with great caution in patients who are dependent on drugs in view of the severe respiratory depression which may ensue. Patients on chronic opioid therapy or with history of opioid abuse may require higher doses.

Opioid should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism; pulmonary disease, decreased respiratory reserve; alcoholism; impaired hepatic or renal function. Such patients also require prolonged post-operative monitoring.

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.

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

<u>Serotonin Syndrome</u>

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.

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.

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 4.5).

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.

Excipient

This medicine contains less than 1mmol sodium (23mg) per dose, that is to say essentially ‘sodium-free’.

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, gabapentinoids (gabapentin and pregabalin), and other, non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depression of opioids. 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 metabolised 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 IV fentanyl.

Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of IV fentanyl by two thirds; however, peak plasma concentrations after a single dose of IV 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.

Diltiazem is another CYP3A4 inhibitor which can cause accumulation of Fentanyl.

Co-administration of fluconazole or voriconazole and fentanyl may result in an increased exposure to fentanyl.

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.

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
Co-administration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

<u>Sedative medicines such as benzodiazepines or related drugs:</u>

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

<u>Effect of fentanyl on other drugs</u>

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

The total plasma clearance and volume of distribution of etomidate is 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.

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 (see Section 5.3). The potential risk for humans is unknown.

IV administration during childbirth (including Caesarean section) is not recommended because fentanyl crosses the placenta and because the foetal respiratory centre is particularly sensitive to opioids. If fentanyl is nevertheless administered, an antidote for the child should always be at hand.

Breast-feeding

Fentanyl is excreted into human milk. Therefore, breast feeding is not recommended for 24 hours following the administration of the drug. The risk/benefit of breastfeeding following fentanyl administration should be considered.

Fertility

There are no clinical data on the effects of fentanyl on male or female fertility. In animal studies, some tests on rats showed reduced female fertility at maternal toxic doses (see section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Fentanyl has a moderate influence on the ability to drive and use machines. Where early discharge is envisaged, patients should be advised not to drive or to operate machinery.

4.8 Undesirable effects

The following table displays ADRs that have been reported with the use of fentanyl IV from either clinical trials or postmarketing experiences.

The displayed frequency categories use the following convention: 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); and not known (cannot be estimated from the available clinical trial data).

System Organ Class	**Adverse Drug Reactions**			
	Frequency Category			
	Very Common (≥1/10)	**Common (≥1/100 to < 1/10)**	**Uncommon (≥1/1,000 to < 1/100)**	**Not Known (cannot be estimated from the available clinical trial data)**
Immune System Disorders	- -	- -	- -	Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric Disorders	- -	- -	Euphoric Mood	Delirium
Nervous System Disorders	- -	Dyskinesia; Sedation; Dizziness	Headache	Convulsions (including clonic convulsions and

				grand mal convulsion); Stupor; Loss of consciousness/ Coma; Myoclonus; Hyperaesthesia/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 Disorders	Muscle Rigidity (which may also involve the thoracic muscles)	-	-	-
General Disorders and Administration Site Conditions	-	-	Chills; Hypothermia	Drug withdrawal syndrome (see section 4.4)
Injury, Poisoning and Procedural Complications	-	Confusion postoperative; Anaesthetic complication neurological	Airway complication of anaesthesia: Agitation postoperative; Procedural complication	-

When a neuroleptic is used with fentanyl, the following adverse reactions may be observed: chills and/or shivering, restlessness, post-operative hallucinatory episodes and extrapyramidal symptoms (see Section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Symptoms
An overdose of fentanyl manifests itself as an extension of its pharmacologic actions. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnoea to apnoea.

Toxic leukoencephalopathy has been observed with fentanyl overdose.

Management
In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific opioid antagonist, such as naloxone, should be used as indicated to control respiratory depression. This does not preclude the use of more immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.
If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration.
The patient should be carefully observed; body warmth and adequate fluid intake should be maintained. If hypotension is severe or if it persists, the possibility of hypovolaemia should be considered and, if present, it should be controlled with appropriate parenteral fluid administration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid 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 the sole anaesthetic. Fentanyl preserves cardiac stability, and obtunds stress-related hormonal changes at higher doses. A dose of 100 μg (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 IV dose of up to 100 μg. 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 LD50/ED50 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.

Histamine assays and skin-wheal testing in man, as well as in vivo testing in dogs, have indicated that clinically significant histamine release is rare with fentanyl.

All actions of fentanyl are immediately and completely reversed by a specific opioid antagonist, such as naloxone.

5.2 Pharmacokinetic properties

Distribution
Secondary peak plasma levels may occur. Protein binding at physiological pH is approximately 90% and decreases as the pH becomes acidic. Increased plasma levels may occur in patients with hepatic disease, in elderly or obese patients and after repeated doses.

Biotransformation and Elimination
Metabolism takes place in the liver and excretion is mainly through urine, with a limited amount through faeces.

The half-life varies from two to seven hours and may be prolonged to fifteen hours in elderly patients or after repeated administration.

5.3 Preclinical safety data

In vitro fentanyl showed mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in in-vivo rodent studies and bacterial assays. In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumours at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females, which were the maximum tolerated doses for males and females. Some tests on female rats showed reduced fertility as well as embryo mortality. These findings were related to maternal toxicity and not a direct effect of the drug 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

Fentanyl Citrate is incompatible with thiopental and methohexital.

6.3 Shelf life

5 years.
If only part of an ampoule is used, discard the remaining solution.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

2 ml, clear glass one-point-cut (OPC) ampoules, glass type I Ph. Eur. borosilicate glass, packed in cardboard cartons to contain 10 x 2 ml ampoules.

6.6 Special precautions for disposal and other handling

For single use only. Discard any
remaining contents. C.D. (2).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd.
4045 Kingswood Road
Citywest Business Park
Co. Dublin Ireland

8 MARKETING AUTHORISATION NUMBER

MA079/00401

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 17 November 2011

10 DATE OF REVISION OF THE TEXT

August 2023