FENTANYL PANPHARMA

Fentanyl Panpharma 0.05 mg/ml

1. PRODUCT NAME

FENTANYL PANPHARMA 100 mcg/2 ml

FENTANYL PANPHARMA 500 mcg/10 ml

Solution for injection for I.V. and epidural administration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 50 mcg fentanyl (as fentanyl citrate) – ampoules of 2 ml and 10 ml

3. PHARMACEUTICAL FORM

Solution for injection for I.V. and epidural administration

4. CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see section 4.5., Interactions).
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4.1. Therapeutic indications

Fentanyl Panpharma is indicated:

- For analgesic action of short duration during anaesthetic periods (premedication, induction and maintenance) and in the immediate postoperative period, as need arises.
- As a narcotic analgesic supplement in general or regional anaesthesia.
- For administration with a neuroleptic (such as droperidol) as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia.
- For use as an anaesthetic agent with oxygen in selected high-risk patients (open-heart surgery or certain neurological or orthopaedic procedures).
- By the epidural route for the postoperative management of pains following surgical procedures and Caesarean sections, and as adjunct to general anesthesia.

4.2. Posology and method of administration

The dosage of Fentanyl Panpharma should be individualized according to age, body weight, physical status, underlying pathological condition, use of other drugs, and type of surgery and anesthesia.

The initial dose should be reduced in the elderly and in debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

To avoid bradycardia, it is recommended to administer a small intravenous dose of an anticholinergic just before induction. An anti-emetic may be used to prevent nausea and vomiting.

Use as an analgesic supplement to general anesthesia

Low dose: 2 mcg/kg.

Fentanyl Panpharma in small doses is most useful for minor, but painful, surgery.

Moderate dose: 2-20 mcg/kg.

Where surgery becomes more complicated, a larger dose will be required. The duration of activity is dependent on dosage.

High dose: 20-50 mcg/kg.

During major surgical procedures, in which surgery is longer, and during which the stress response would be detrimental to the wellbeing of the patient, dosages of 20-50 mcg/kg of fentanyl with nitrous oxide/oxygen have been shown to have an attenuating effect. When dosages in this range have been used during surgery, postoperative ventilation and observation are essential in view of the possibility of extended postoperative respiratory depression. Supplemental doses of 25-250 mcg (0.5-5 ml) should be tailored to the needs of the patient and to the anticipated time until completion of the operation.

Use as an anaesthetic agent

When attenuation of the response to surgical stress is especially important, doses of 50-100 mcg/kg may be administered with oxygen and a muscle relaxant. This technique provides anaesthesia without necessitating the use of additional anaesthetic agents. In certain cases, doses up to 150 mcg/kg may be required to produce this anaesthetic effect.

Fentanyl Panpharma has been used in this fashion for open-heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated.

Epidural administration for postoperative management of pain

100 mcg may be administered epidurally. The 2 ml ampoule should be diluted with 8 ml of 0.9% Sodium Chloride Injection, resulting in a final concentration of 10 mcg/ml. The quality and duration of epidural analgesia with fentanyl appears to be concentration-dependent below serum levels of 10 mcg/ml with no significant improvement obtained by increasing concentrations above this value. Additional boluses may be administered if there is evidence of lightening of analgesia.

Use in the elderly

As with other opioids, the dose should be reduced in elderly or debilitated patients.

Use in children

For induction and maintenance in children aged 2-12 years, a dose of 2-3 mcg/kg is recommended.

4.3. Contraindications

- Known intolerance to any of its components or to other opioids.
- Respiratory depression, obstructive airway disease.
- Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of their discontinuation.

4.4. Special warnings and precautions of use

Tolerance and dependence may occur.

Respiratory depression

As with all potent opioids, respiratory depression is dose-related and can be reversed by a specific opioid antagonist, but additional doses 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 postoperative 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 CO_2, thus affecting respiration postoperatively.

Muscle rigidity

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 (myo) clonic movements can occur.

Cardiac disease

Bradycardia, and possibly cardiac arrest, 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 hypovolemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Special dosing conditions

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

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

It is recommended to reduce the dosage in the elderly and in debilitated patients. Opioids should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism; pulmonary disease; decreased respiratory reserve; alcoholism; or impaired hepatic or renal function. Such patients also require prolonged post-operative monitoring.

Interaction with neuroleptic

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.

Serotonin syndrome

Caution is advised when fentanyl is co-administered with drugs that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as selective serotonin re-uptake inhibitors (SSRIs) and serotonin norepinephrine re-uptake inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]). This may occur within the recommended dose.

Serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

If serotonin syndrome is suspected, rapid discontinuation of fentanyl should be considered.

As with all opioid analgesics, care should be observed when administering fentanyl to patients with myasthenia gravis.

Administration in labor may cause respiratory depression in the newborn infant.

4.5. Interactions with other medicinal products and other forms of interactions

Effect of other drugs on fentanyl

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

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

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

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

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

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

Bradycardia and possibly asystole can occur when fentanyl is combined with non-vagolytic muscle relaxants.

The concomitant use of droperidol can result in a higher incidence of hypotension.

Monoamine oxidase inhibitors (MAOI)

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

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.

Effect of fentanyl on other drugs

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 of 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. Pregnancy, breast-feeding and fertility

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, Non-clinical information). The potential risk for humans is unknown.

Administration (I.M. or I.V.) during childbirth (including Cesarean section) is not recommended because fentanyl crosses the placenta and may suppress spontaneous respiration in the newborn period. If fentanyl is administered, assisted ventilation equipment must be immediately available for the mother and infant if required. An opioid antagonist for the child must always be available.

Breast-feeding

Fentanyl is excreted into human milk. Therefore, breast-feeding or use of expressed breast milk is not recommended for 24 hours following the administration of this drug. The risk/benefit of breast-feeding 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, Non-clinical information).

4.7. Effects on ability to drive and use machines

Patients should only drive or operate a machine if sufficient time has elapsed (at least 24 hours) after the administration of fentanyl.

4.8. Adverse reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of fentanyl citrate based on the comprehensive assessment of the available adverse event information. A causal relationship with fentanyl citrate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

The safety of fentanyl was evaluated in 376 subjects who participated in 20 clinical trials evaluating fentanyl used as an anaesthetic. These subjects took at least 1 dose of fentanyl and provided safety data.

Adverse Reactions, as identified by the investigator, reported for ≥1% of fentanyl-treated subjects in these studies, are shown in Table 1.

Table 1. Adverse reactions reported by ≥ 1% of fentanyl-treated subjects in 20 clinical trials of fentanyl

System/Organ Class Adverse Reaction	**FENTANYL (n=376) %**
Nervous System Disorders	
Sedation	5.3
Dizziness	3.7
Dyskinesia	3.2

Eye Disorders	
Visual disturbance	1.9
Cardiac Disorders	
Bradycardia	6.1
Tachycardia	4.0
Arrhythmia	2.9
Vascular Disorders	
Hypotension	8.8
Hypertension	8.8
Vein pain	2.9
Respiratory, Thoracic and Mediastinal Disorders	
Apnea	3.5
Bronchospasm	1.3
Laryngospasm	1.3
Gastrointestinal Disorders	
Nausea	26.1
Vomiting	18.6
Skin and Subcutaneous Tissue Disorders	
Dermatitis allergic	1.3
Musculoskeletal and Connective Tissue Disorders	
Muscle rigidity (which may also involve the thoracic muscles)	10.4
Injury, Poisoning and Procedural Complications	
Confusion postoperative	1.9
Anesthetic complication neurological	1.1

Additional adverse reactions that occurred in <1% of fentanyl-treated subjects in the 20 clinical trials are listed below in Table 2.

Table 2. Adverse reactions reported by < 1% of fentanyl-treated subjects in 20 clinical trials of fentanyl

System/Organ Class Adverse Reaction
Psychiatric Disorders
Euphoric mood
Nervous System Disorders
Headache
Vascular Disorders
Blood pressure fluctuation
Phlebitis
Respiratory, Thoracic and Mediastinal Disorders
Hiccups
Hyperventilation
General Disorders and Administration Site Conditions
Chills
Hypothermia
Injury, Poisoning and Procedural Complications
Agitation postoperative
Procedural complication
Airway complication of anesthesia

Postmarketing data

Adverse reactions first identified during postmarketing experience with fentanyl are included in Table 3.

The frequencies are provided according to 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, including isolated reports

In Table 3, adverse reactions are presented by frequency category based on spontaneous reporting rates. The frequency category "not known" is used for adverse reactions for which no valid estimate of the incidence rate can be derived from clinical trials.

Table 3: Adverse reactions identified during postmarketing experience with fentanyl by frequency category estimated from spontaneous reporting rates

Immune System Disorders	
Very rare	Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Nervous System Disorders	
Very rare	Convulsions, Loss of consciousness, Myoclonus
Cardiac Disorders	
Very rare	Cardiac arrest (see section 4.4. Special warnings and precautions of use)
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Respiratory depression (see section 4.4. Special warnings and precautions of use)
Skin and Subcutaneous Tissue Disorders	
Very Rare	Pruritus

When a neuroleptic is used with fentanyl, the following adverse reactions may be observed: chills and/or shivering, restlessness, postoperative hallucinatory episodes and extrapyramidal symptoms (see Section 4.4., Special warnings and precautions of use).

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9. Overdose

Signs and symptoms

An overdosage of fentanyl manifests itself as an extension of its pharmacologic actions. Respiratory depression which can vary in severity from bradypnea to apnea may occur.

Treatment

In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific opioid antagonist 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 hypovolemia should be considered, and if present, should be controlled with appropriate parenteral fluid administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anesthetics general, opioid anesthetics.

ATC Code: N01AH01.

Mechanism of action

Fentanyl is a potent opioid analgesic.

Pharmacodynamic effects

Fentanyl is an opioid analgesic, interacting predominantly with the μ-opioid receptor. Fentanyl can be used as an analgesic supplement to general anesthesia or as the sole anesthetic. Fentanyl preserves cardiac stability and obtunds stress-related hormonal changes at higher doses. A dose of 100 mcg (2.0 ml) is approximately equivalent in analgesic activity to 10 mg of morphine. The onset of action is rapid. However, the maximum analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is approximately 30 minutes after a single I.V. dose of up to 100 mcg.

Depth of analgesia is dose-related and can be adjusted to the pain level of the surgical procedure.

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 have indicated that clinically significant histamine release is rare with fentanyl.

All actions of fentanyl are reversed by a specific opioid antagonist.

5.2. Pharmacokinetic properties

Distribution

After intravenous injection, fentanyl plasma concentrations fall rapidly, with sequential distribution half-lives of about 1 minute and 18 minutes and a terminal elimination half-life of 475 minutes. Fentanyl has a V_c (volume of distribution of the central compartment) of 13 L, and a total V_{dss} (distribution volume at steady-state) of 339 L. The plasma protein binding of fentanyl is about 84%.

Metabolism

Fentanyl is rapidly metabolised, mainly in the liver, by CYP3A4. The major metabolite is norfentanyl. Fentanyl clearance is 574 ml/min.

Elimination

Approximately 75% of the administered dose is excreted in the urine within 24 hours and only 10% of the dose eliminated in urine is present as unchanged drug.

Special populations

Pediatrics

The plasma protein binding of fentanyl in newborns is approximately 62% and lower than in adults. The clearance and the volume of distribution are higher in infants and children. This may result in an increased dose requirement for fentanyl.

Renal impairment

Data obtained from a study administering I.V. fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see Section 4.2., Posology and method of administration).

Adult patients with burns

An increase in clearance up to 44% together with a larger volume of distribution results in lower fentanyl plasma concentrations. This may require an increased dose of fentanyl.

Obese patients

An increase in clearance of fentanyl is observed with increased body weight. In patients with a BMI>30, clearance of fentanyl increases by approximately 10% per 10 kg increase of the fat free mass (lean body mass).

5.3. Non-clinical information

Fentanyl has a broad safety margin. In rats, the ratio LD50/ED50 for the lowest level of analgesia is 281.8, as compared with 69.5 and 4.8 for morphine and pethidine, respectively.

Carcinogenicity and mutagenicity

In vitro fentanyl showed, like other opioid analgesics, mutagenic effects in the 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 tumors at subcutaneous doses up to 33 mcg/kg/day in males or 100 mcg/kg/day in females, which were the maximum tolerated doses for males and females.

Reproductive toxicology

Fertility

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 PROPERTIES

6.1 List of excipients

Sodium chloride, sodium hydroxide, water for injections.

6.2. Incompatibilities

The injectable solution must not be mixed with other products.

6.3. Shelf life

3 years

After opening: The product must be used immediately.

6.4. Dilution of the product

The drug product Fentanyl Panpharma may be diluted with Saline or Glucose 5%. Such dilutions are compatible with plastic infusion sets.

The solution is stable for use up to 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are only the responsibility of the user and would normally not be longer than 24 hours at a temperature of 15-25°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5. Special precautions for storage

Store at a temperature below 25°C and protect from light.

Keep ampoule in outer carton.

Keep out of reach of children.

6.6. Presentations:

Box of 10 ampoules (glass type 1) of 2 ml.

Box of 10 ampoules (glass type 1) of 10 ml.

7. MANUFACTURER

Panpharma France,

Z.I. du Clairay-35133, Luitré,

France

8. LICENSE HOLDER AND IMPORTER

Pharmalogic Ltd.,

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Reg. No.: 152-49-33974-00

The content of this leaflet was approved by the Ministry of Health in August 2014 and updated according to the guidelines of Ministry of Health in June 2019.