

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fentanyl-Piramal

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 78.5 micrograms fentanyl citrate equivalent to 50 micrograms per ml fentanyl base.

Excipient(s) with known effect:

Sodium 3.5 mg/ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

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-Piramal is indicated:

- For analgesic action of short duration during anesthetic periods (premedication, induction and maintenance) and in the immediate postoperative period, as need arises.
- As a narcotic analgesic supplement in general or regional anesthesia.
- For administration with a neuroleptic [*such as droperidol*] as an anesthetic premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia.
- For use as an anaesthetic agent with oxygen in selected, high-risk patients (open heart surgery or certain neurological or orthopedic procedures).

- By the epidural route for the postoperative management of pains following general surgical procedures and cesarean sections and as adjunct to general anesthesia.

4.2 Posology and method of administration

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

To avoid bradycardia, it is recommended to administer a small intravenous dose of an anti-cholinergic just before anesthetic induction.

- Use as an analgesic supplement to general anesthesia

Low dose: 2 µg/kg

Fentanyl in small doses is most useful for minor surgery.

Moderate dose: 2-20 µg/kg

Where surgery becomes more complicated, a larger dose will be required.

The duration of activity is dependent on dosage.

High dose: 20-50 µg/kg

During major surgical procedures, in which surgery is longer, and during which the stress response would be detrimental to the well-being of the patient, doses of 20-50 µg/kg of Fentanyl with nitrous oxide/oxygen have been shown to have an attenuating effect. When doses in this range have been used during surgery, post-operative ventilation and observation are essential in view of the possibility of extended post-operative respiratory depression.

Supplemental doses of 25-250 µg (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 anesthetic agent

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

For immediate use after dilution.

Special populations

- Elderly and debilitated patients

As with other opioids, the initial dose should be reduced in elderly (>65 years of age) and in debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

- Pediatrics

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

Obese Patients

In obese patients there is a risk of overdosing if the dose is calculated based on body weight. Obese patients should be dosed based on estimated lean body mass rather than on body weight only.

Renal Impairment

In patients with renal impairment reduced dosing of should be considered and these patients should be observed carefully for signs of fentanyl toxicity (see Pharmacokinetic properties).

4.3 Contraindications

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

Respiratory depression, obstructive airways disease.

Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of their discontinuation.

4.4 Special warnings and precautions for use

Warnings:

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with fentanyl.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Following intravenous administration of fentanyl, a transient fall in blood pressure may occur, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Respiratory Depression

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early postoperative period. Care should be taken after large doses or infusions of fentanyl to ensure that adequate spontaneous breathing has been established and maintained before discharging the patient from the recovery area.

Significant respiratory depression will occur following the administration of fentanyl in doses in excess of 200 mcg. This, and the other pharmacological effects of fentanyl, can be reversed by specific opioid antagonists, but additional doses may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.

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

Administration in labour may cause respiratory depression in the new-born infant.

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 antagonised by atropine.

Muscle rigidity

Muscular rigidity (morphine-like effect) may occur.

Rigidity, which may also involve the thoracic muscles, can be avoided by the following measures:

- slow IV injection (usually sufficient for lower doses);
- premedication with benzodiazepines;
- use of muscle relaxants.

Non-epileptic (myo)clonic movements can occur.

Precautions:

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

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 transient reduction of the cerebral perfusion pressure.

It is recommended to reduce dosage in the elderly and debilitated patients.

In uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism and hepatic or renal impairment the dosage should be titrated with care and prolonged post-operative monitoring is required.

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

Myasthenia gravis

In patients with myasthenia gravis, careful consideration should be applied in the use of certain anticholinergic agents and neuromuscular-blocking pharmaceutical agents prior to, and during, the administration of a general anaesthetic regimen which includes administering intravenous fentanyl.

Interaction with neuroleptics

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.

Bile duct

As with other opioids, due to the anticholinergic effects, administration of fentanyl may lead to increases of bile duct pressure and, in isolated cases, spasms of the Sphincter of Oddi might be observed.

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, diarrhoea).

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

Risk from concomitant use of Central Nervous System (CNS) depressants, especially benzodiazepines or related drugs

Concomitant use of fentanyl and CNS depressants especially benzodiazepines or related drugs in spontaneously breathing patients, may increase the risk of profound sedation, respiratory depression, coma and death. If a decision is made to administer fentanyl concomitantly with a CNS depressant, especially a benzodiazepine or a related drug, the lowest effective dose of both drugs should be administered, for the shortest period of concomitant use. Patients should be carefully monitored for signs and symptoms of respiratory depression and profound sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see Interactions).

Paediatric population

Techniques that involve analgesia in a spontaneously 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.

Fentanyl-Piramal contains 3.5 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs on fentanyl

Central Nervous System (CNS) depressants

The use of opioid premedication, barbiturates, benzodiazepines or related drugs, neuroleptics, general anaesthetics and other non-selective CNS depressants (e.g. alcohol) may enhance or prolong the respiratory depression of fentanyl.

When patients have received other CNS-depressants, the dose of fentanyl required may be less than usual. Concomitant use with Fentanyl-Piramal in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death (see warnings and precautions).

Cytochrome P450 3A4 (CYP3A4) inhibitors

Fentanyl, a high clearance drug, is rapidly and extensively metabolised mainly by CYP3A4. When Fentanyl-Piramal is used, the concomitant use of a CYP3A4 inhibitor may result in a decrease in fentanyl clearance. With single-dose Fentanyl-Piramal administration, the period of risk for respiratory depression may be prolonged, which may require special patient care and longer observation. With multiple-dose Fentanyl-Piramal administration, the risk for acute and/or delayed respiratory depression may be increased, and a dose reduction of Fentanyl-Piramal may be required to avoid accumulation of fentanyl. Oral ritonavir (a potent CYP3A4 inhibitor) reduced the clearance of a single intravenous Fentanyl-Piramal dose by two thirds, although peak plasma concentrations of fentanyl were not affected. However, itraconazole (another potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of a single intravenous Fentanyl-Piramal dose. Co-administration of other potent or less potent CYP3A4 inhibitors, such as voriconazole or fluconazole, and Fentanyl-Piramal may also result in an increased and/or prolonged exposure to fentanyl.

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

Serotonergic Drugs

Coadministration 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 (see section 4.3 Contraindications).

Effect of fentanyl on other drugs

Following the administration of Fentanyl-Piramal, the dose of other CNS depressant drugs should be reduced. This is particularly important after surgery, because profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the postoperative period. Administration of a CNS depressant, such as a benzodiazepine or related drugs, during this period may disproportionately increase the risk for respiratory depression (see warnings and precautions).

Plasma concentrations of etomidate increased considerably (by a factor 2-3) when combined with fentanyl. 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 Fertility, pregnancy and lactation

Pregnancy

Fentanyl can cross the placenta in early pregnancy. Studies in animals have shown some reproductive toxicity (see Section 5.3, Preclinical safety data).

Administration during childbirth (including Caesarean section) is not recommended because fentanyl crosses the placenta and may suppress spontaneous respiration in the new-born 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.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Administration to nursing women is not recommended as fentanyl may be secreted in breast milk and may cause respiratory depression in the infant. 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 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Where early discharge is envisaged, patients should be advised not to drive or operate machinery for at least 24 hours following administration.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you

4.8 Undesirable effects

The safety of fentanyl IV was evaluated in 376 subjects who participated in 20 clinical trials evaluating fentanyl IV as an anaesthetic. These subjects took at least 1 dose of fentanyl IV and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported ($\geq 5\%$ incidence) Adverse Reactions were (with % incidence): nausea (26.1); vomiting (18.6); muscle rigidity (10.4); hypotension (8.8); hypertension (8.8); bradycardia (6.1); and sedation (5.3).

Including the above-mentioned adverse reactions, Table 1 displays adverse reactions that have been reported with the use of fentanyl IV from either clinical trials or post-marketing experience.

The displayed frequency categories use the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); and not known (cannot be estimated from the available clinical trial data).

Table 1: Adverse Reactions

System Organ Class	Adverse Reactions			
	Frequency Category			
	Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Not Known
Immune System Disorders				Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric Disorders		Agitation	Euphoric mood	Delirium Drug dependence (see section 4.4)
Nervous System Disorders	Muscle rigidity (which may also involve the thoracic muscles)	Dyskinesia; Sedation; Dizziness	Headache	Convulsions; Loss of consciousness; Myoclonus
Eye Disorders		Visual disturbance		
Cardiac Disorders		Bradycardia; Tachycardia; Arrhythmia		Cardiac arrest
Vascular Disorders		Hypotension; Hypertension; Venous pain	Phlebitis; Blood pressure fluctuation	
Respiratory, Thoracic and Mediastinal Disorders		Laryngospasm; Bronchospasm; Apnoea	Hyperventilation; Hiccups	Respiratory depression
Gastrointestinal Disorders	Nausea; Vomiting			
Skin and Subcutaneous Tissue Disorders		Allergic dermatitis		Pruritus
General Disorders and Administration Site Conditions			Chills; Hypothermia Drug withdrawal syndrome	Drug withdrawal syndrome (see section 4.4)
Injury, Poisoning and Procedural Complications		Postoperative confusion	Airway complication of anaesthesia	

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).

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:

<https://sideeffects.health.gov.il>

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms and signs:

The manifestations of fentanyl overdosage are generally an extension of its pharmacological action. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnoea to apnoea.

Treatment:

Hypoventilation or apnoea:	O ₂ administration, assisted or controlled respiration.
Respiratory depression:	Specific opioid antagonist. This does not preclude the use of immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.
Muscular rigidity:	Intravenous neuromuscular blocking agent 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: Anaesthetic general, opioid anaesthetic, ATC code: N01AH01

Fentanyl is a synthetic opiate with a clinical potency of 50 to 100 times that of morphine. Its onset of action is rapid and its duration of action is short. In man, a single IV dose of 0.5-1 mg/70 kg body weight immediately produces a pronounced state of surgical analgesia, respiratory depression, bradycardia and other typical morphine-like effects. The duration of action of the peak effects is about 30 minutes. All potent morphine-like drugs produce relief from pain, ventilatory depression, emesis, constipation, physical dependence, certain vagal effects and varying degrees of sedation. Fentanyl, however, differs from morphine not only by its short duration of action but also by its lack of emetic effect and minimal hypotensive activity in animals.

5.2 Pharmacokinetic properties

Some pharmacokinetic parameters for fentanyl are as follows:

Urinary excretion = 8%

Bound in plasma = 80%

Clearance (ml/min/kg) = 13 ± 2

Volume of distribution (litres/kg) = 4.0 ± 0.4

Estimates of terminal half-life range from 141 to 853 minutes.

Renal impairment

Data obtained from a study administering IV 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).

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 Preclinical safety data

In vitro fentanyl showed, like other opioid analgesics, 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 rat bioassay, fentanyl was not carcinogenic.

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

Water for injections

6.2 Incompatibilities

The product is chemically incompatible with the induction agents thiopentone and methohexitone because of the wide differences in pH.

For immediate use after dilution.

6.3 Shelf life

The expiry date of the product is indicated on the package materials.

6.4 Special precautions for storage

Protect from light.

Store between 15°C and 30°C.

Protect from light. Keep ampule in the outer carton.

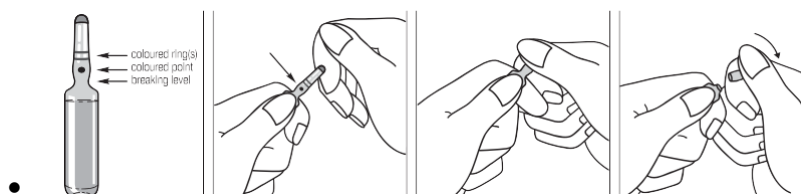
6.5 Nature and contents of container

Glass ampoules (PhEur, Type I).

Pack size: packs of 10 of 2 ml ampoules; packs of 5 of 10 ml ampoules.

Instructions for use/handling

1. Maintain the ampoule between the thumb and index finger, leaving the tip of the ampoule free.
2. With the other hand, hold the tip of ampoule by putting the index finger against the neck of the ampoule and the thumb on the colored point in parallel to the identification colored ring(s).
3. Keeping the thumb on the point, sharply break the tip of the ampoule while holding firmly the other part of the ampoule in the hand.



6.6 Special precautions for disposal and other handling

Wear gloves while opening ampoule.

Accidental dermal exposure should be treated by rinsing the affected area with water. Avoid usage of soap, alcohol, and other cleaning materials that may cause chemical or physical abrasions to the skin.

Store as a CD.

7. MANUFACTURER

GlaxoSmithKline Manufacturing S.P.A, STRADA Provinciale Asolana N.90, 43056 San Polo DI Torrile, Parma, Italy

8. REGISTRATION HOLDER

Pharma Medis Ltd, Fireberg 4 Holon

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