

J-C Health Care Ltd.

אוגוסט 2015

רופא/ה נכבד/ה  
רוקח/ת נכבד/ת

ברצוננו להביא לידיעתכם את העדכונים בעלונים לרופא של התכשיר :  
Fentanyl

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו  
הטקסט המחוקק בכחול נגרע ממנו.

העלון מפורסם במלואו במאגר התרופות שבאתר משרד הבריאות.

כמו כן, ניתן לקבל את העלון המודפס בפניה אלינו לטלפון 09-9591111 .

להלן העדכונים.

בברכה,

ליליאנה בלטר  
רוקחת ממונה

## PRODUCT NAME

**FENTANYL JANSSEN**  
(fentanyl citrate)

## DOSAGE FORMS AND STRENGTHS

Fentanyl is a sterile, preservative-free, isotonic aqueous solution for intravenous use.

Each ml contains 50 µg Fentanyl (*as fentanyl citrate*).

For excipients, see List of Excipients.

## CLINICAL INFORMATION

### Indications

Fentanyl 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 surgical procedures and cesarean sections, and as adjunct to general anesthesia.

## Dosage and administration

### Dosage

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. ~~[Droperidol may be given to prevent nausea and vomiting.]~~

***- Use as an analgesic supplement to general anesthesia***

Low dose: 2 µg/kg

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

**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).

## Contraindications

Known intolerance to any of its components or to other opioids.

Respiratory depression, obstructive airways disease. Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of their discontinuation.

## warnings and precautions

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 ~~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 postoperative period. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anesthesia may alter the patient's responses to CO<sub>2</sub>, 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, *[such as droperidol]*, 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 coadministered 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 labour may cause respiratory depression in the new born infant.

## **Interactions**

### *Effect of other drugs on Fentanyl*

Drugs such as barbiturates, benzodiazepines, neuroleptics, halogenic gases and other, non-selective 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 MAOIs 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 MAOIs.

#### *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.

#### *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 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.

## **Pregnancy, Breast-feeding and fertility**

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

Administration (intramuscular (IM) or IV) during childbirth (including cesarean section) is not recommended because Fentanyl crosses the placenta and **may suppress spontaneous respiration in the newborn period** ~~because the fetal respiratory center is particularly sensitive to opiates~~. If Fentanyl is ~~nevertheless~~ administered, **assisted ventilation equipment must be immediately available for the mother and infant if required.** ~~an antidote for the child should always be at hand.~~ **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 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 Non-clinical Information).**

## **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.

## **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 anesthetic. These subjects took at least one dose of fentanyl and provided safety data. Adverse Reactions as identified by the investigator, reported for  $\geq 1\%$  of fentanyl -treated subjects in these studies are shown in Table 1.

**Table 1. Adverse Reactions Reported by  $\geq 1\%$  of FENTANYL -treated Subjects in 20 Clinical Trials of FENTANYL**

System/Organ Class Adverse Reaction	FENTANYL (n=376) %
<b>Nervous System Disorders</b>	
Sedation	5.3
Dizziness	3.7
Dyskinesia	3.2
<b>Eye Disorders</b>	
Visual disturbance	1.9
<b>Cardiac Disorders</b>	
Bradycardia	6.1
Tachycardia	4.0
Arrhythmia	2.9
<b>Vascular Disorders</b>	
Hypotension	8.8
Hypertension	8.8
Vein pain	2.9
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	
Apnea	3.5
Bronchospasm	1.3
Laryngospasm	1.3
<b>Gastrointestinal Disorders</b>	
Nausea	26.1
Vomiting	18.6
<b>Skin and Subcutaneous Tissue Disorders</b>	
Dermatitis allergic	1.3
<b>Musculoskeletal and Connective Tissue Disorders</b>	
Muscle rigidity (which may also involve the thoracic muscles)	10.4
<b>Injury, Poisoning and Procedural Complications</b>	
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**

<b>System/Organ Class</b>
<b>Adverse Reaction</b>
<b>Psychiatric Disorders</b>
Euphoric mood
<b>Nervous System Disorders</b>
Headache
<b>Vascular Disorders</b>
Blood pressure fluctuation
Phlebitis
<b>Respiratory, Thoracic and Mediastinal Disorders</b>
Hiccups
Hyperventilation
<b>General Disorders and Administration Site Conditions</b>
Chills
Hypothermia
<b>Injury, Poisoning and Procedural Complications</b>
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 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, 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**

<b>Immune System Disorders</b>	
<i>Very rare</i>	Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
<b>Nervous System Disorders</b>	
<i>Very rare</i>	Convulsions, Loss of consciousness, Myoclonus
<b>Cardiac Disorders</b>	
<i>Very rare</i>	Cardiac arrest (see section Warnings and Precautions)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	
<i>Very rare</i>	Respiratory depression (see section Warnings and Precautions)
<b>Skin and Subcutaneous Tissue Disorders</b>	
<i>Very Rare</i>	Pruritus

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 Warnings and Precautions).

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=AdverseEffectMedic@moh.health.gov.il>) or by email ([adr@MOH.HEALTH.GOV.IL](mailto:adr@MOH.HEALTH.GOV.IL)).

## Overdose

### Symptoms and signs

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.**

~~Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnea to apnea.~~

### 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, **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 hypovolemia should be considered, and if present, should be controlled with appropriate parenteral fluid administration.

## **PHARMACOLOGICAL PROPERTIES**

### **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  $\mu$ -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  $\mu$ g (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  $\mu$ g. 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.

### **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 metabolized, 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% which is 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 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 Dosage and 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).

## **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 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 tumors 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.

### **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.

## **PHARMACEUTICAL PARTICULARS**

### **List of excipients**

Sodium chloride

Water for injections.

### **Incompatibilities**

The injectable solution must not be mixed with other products.

If desired, Fentanyl may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with plastic infusion sets. These should be used within 24 hours of preparation.

### **Special precautions for storage**

Protect from light.

Store between 15 and 30° C.

Keep ampoule in outer carton.

Keep out of reach of children

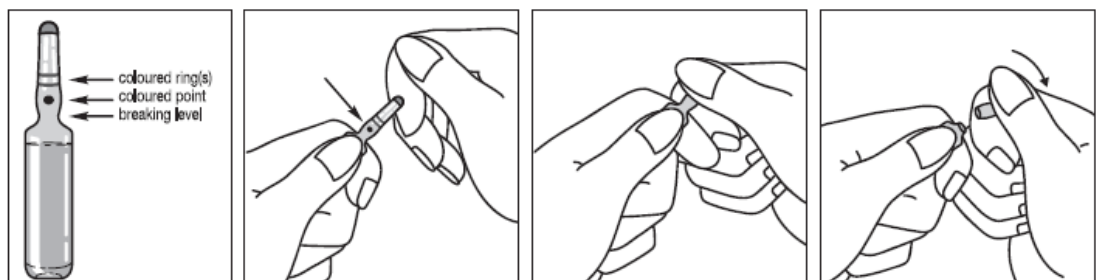
## Nature and contents of container

Fentanyl is supplied in 2 ml and 10 ml ampoules.

## Instructions for use/handling

**Wear gloves while opening ampule.**

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.



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

**MANUFACTURER:** GlaxoSmithKline Manufacturing S.P.A, Torrice,  
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