1. NAME OF THE MEDICINAL PRODUCT

Fentanyl Médis 50 micrograms/ml Solution for Injection/Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains Fentanyl citrate the equivalent of 50 micrograms of Fentanyl in 1ml.

Each 2ml ampoule contains 100 micrograms of Fentanyl as Fentanyl citrate.

Each 10ml ampoule contains 500 micrograms of Fentanyl as Fentanyl citrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection.

A limpid colorless liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fentanyl citrate is a narcotic analgesic. In low doses it is used to provide analgesia during short surgical procedures and as a premedicant. In higher doses it is employed as an analgesic/respiratory depressant in patients who need assisted ventilation. In combination with a neuroleptic drug, fentanyl is employed as part of the technique of neuroleptanalgesia. Fentanyl is also used in the treatment of severe pain, such as that of myocardial infarction.

4.2 Posology and method of administration

Posology:

Adult:

The usual dosage regimen is as follows:

	Initial micrograms	Supplemental micrograms
Spontaneous Respiration	50 – 200	50
Assisted ventilation	300 - 3500	100 - 200

Doses greater than 200 micrograms are solely for use in anaesthesia.

As a premedicant, 1 - 2ml may be administered intramuscularly before induction of anaesthesia.

Following intravenous administration in the non-premedicated adult patient, 2ml fentanyl may be anticipated to provide adequate analgesia for 10 – 20 minutes in surgical procedures involving low pain intensity. A bolus of 10ml of fentanyl can be expected to provide analgesia for about one hour. The analgesia produced is generally adequate for surgery involving moderate pain intensity. Administration of 50 microgram/kg will provide intense analgesia for some four to six hours for surgery associated with intense stimulation.

Fentanyl 50 micrograms/ml Solution for Injection/Infusion may also be administered as an intravenous infusion.

Ventilated patients may be given a loading dose as a fast infusion of approximately 1 microgram/kg/minute for the first 10 minutes, followed by an infusion of approximately 0.1 microgram/kg/minute. Alternatively, the loading dose may be administered as a bolus. The rate of infusion should be titrated to the individual patient response and lower infusion rates may be adequate. The infusion should be discontinued approximately 40 minutes before the end of surgery, unless post-operative ventilation is intended.

Lower infusion rates, e.g. 0.05 - 0.08 microgram/kg/minute, are required if spontaneous ventilation is to be maintained. Higher infusion rates of up to 3 micrograms/kg/minute have been employed in cardiac surgery.

It is important when estimating the required dose to assess the likely degree of surgical stimulation, the effect of premedicant drugs, and the duration of the procedure.

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 years	1-3 micrograms/kg	1-1.25 micrograms/kg
Assisted Ventilation	2-11 years	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.

<u>Method of administration:</u>

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

Intravenous and epidural routes. Fentanyl 50 micrograms/ml Solution for Injection/Infusion can be administered to both adults and children via the intravenous route as a bolus or as an infusion.

The dosage of fentanyl should be individualised according to age, body weight, physical status, underlying pathological condition, use of other drugs, and type of surgery and anaesthesia.

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.

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.
- Respiratory depression.
- Obstructive airways disease.
- In patients after operative interventions in the biliary tract.

4.4 Special warnings and precautions for use

Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway.
As with all potent opioids.
Respiratory depression is dose related and can be reversed by a specific narcotic 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 narcotic antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's response to CO2, thus affecting respiration post-operatively.
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 movement can occur.
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.
It is imperative to ensure that adequate spontaneous breathing has been established and maintained before discharge from the recovery area whenever large doses or infusions of Fentanyl 50 micrograms/ml Solution for Injection/Infusion have been administered.
Repeated use of fentanyl may result in the development of tolerance and dependence.
Opioids may induce hypotension, especially in hypovolemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.
The use of rapid bolus injection of opioids should be avoided in patients with compromised intracerebral compliance; in such patient 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 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 renal or hepatic function. Such patients also require prolonged postoperative monitoring.
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 higher incidence of hypotension. Neuroleptics can induce extrapyramidal symptoms that can be controlled with anti-Parkinson agents.
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.
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 anesthetics regimen which includes administering intravenous fentanyl.
Administration of fentanyl during labour may result in neonatal respiratory depression.
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, diarrhoea).
If serotonin syndrome is suspected, rapid discontinuation of fentanyl should be considered.
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.

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, and other non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depression of narcotics. 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 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 I.V. fentanyl.

Co-administration of fluconazole or voriconazole and fentanyl may result in an increased exposure to fentanyl.
Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of I.V. fentanyl by two thirds; however, peak plasma concentrations after a single dose of I.V. 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.
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.
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 anaesthetic procedures in patients on MAO- inhibitors.
When fentanyl is used in combination with non-vagolytic muscle relaxants, bardycardia and possibly asystole may occur.
Concomitant use of fentanyl and droperidol can result in higher incidence of hypotension.
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.
Effect of fentanyl on other drugs
Following the administration of fentanyl, the dose of other CNS depressant drugs should be reduced.
Plasma concentration of etomidate increased considerably (by a factor 2 to 3) when combined with fentanyl. The total plasma clearance and volume of distribution of etomidate are 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 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.
Pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
I.M. or I.V. administration during childbirth, (including caesarean section) is not recommended because Fentanyl crosses the placenta and because the foetal respiratory centre is particularly sensitive to opiates. If fentanyl is nevertheless administered, an antidote for the child should always be at hand.

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

4.7 Effects on ability to drive and use machines

Fentanyl has a moderate influence on the ability to drive and use machines. Patients should only drive or operate a machine if sufficient time has elapsed after the administration of fentanyl. 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

• It is an offence to drive while under the influence of this medicine

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 anesthetic. 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 (≥5% incidence) Adverse Drug Reactions (ADRs) 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 ADRs, 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).
Table 1: Adverse Drug Reactions

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	
Nervous System Disorders		Dyskinesia; Sedation;	Headache	Convulsions; Loss of

		Dizziness		consciousness; Myoclonus; 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 Disorder	Muscle Rigidity (which may also involve the thoracic muscles)			
General Disorders and Administration Site Conditions			Chills; Hypothermia	
Injury, Poisoning and Procedural Complications		Confusion postoperative	Airway complication of anaesthesia Agitation postoperative	

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. Healthcare professionals are asked to report any suspected adverse reactions via National pharmaco vigilance system.

4.9 Overdose

Symptoms

An overdosage 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.

Management

In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific narcotic 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

Mechanism of Action

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 micrograms (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 micrograms. 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 LD_{50}/ED_{50} 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

Absorption

Fentanyl is a lipid-soluble drug and its pharmacokinetics can be described in terms of a three-compartment model. Following intravenous injection, there is a short distribution phase during

which high concentrations of fentanyl are achieved quickly in well-perfused tissues such as the lungs, kidneys and brain.

Distribution

The drug is redistributed to other tissues; it accumulates more slowly in skeletal muscle and yet more slowly in fat, from which it is gradually released into the blood. Up to 80% of fentanyl is bound to plasma proteins.

Elimination

Fentanyl is primarily metabolised in the liver, probably by N-dealkylation, and it is excreted mainly in the urine with less than 10% representing the unchanged drug. The terminal half-life of fentanyl is 3.7 hours.

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. There are no long-term animal studies to investigate the tumor-forming potential of fentanyl. 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 Injection

6.2 Incompatibilities

Fentanyl citrate is incompatible with alkaline solutions (due to reduced solubility) and some drugs. Published data show that Fentanyl 50 micrograms/ml Solution for Injection/Infusion is incompatible with alkaline injections including methohexital and thiopental.
Loss of fentanyl citrate due to absorption to PVC containers has been reported when the solution pH was adjusted to the alkaline range (but see section 6.6).
Compatibility must be checked before administration.

6.3 Shelf life

Fentanyl MédiS 0.5 mg/10 ml: 24 months

Fentanyl MédiS 0.1 mg/2 ml: 36 months

6.4 Special precautions for storage

Do not store above 30°C.
Protect from light

6.5 Nature and contents of container

Fentanyl MédiS 0.5 mg/10 ml available in glass ampoules of 10 ml

Fentanyl MédiS 0.1 mg/2 ml available in glass ampoules of 2 ml

6.6 Special precautions for disposal and other handling

The injection is for single patient use and should be used immediately after opening. The injection should not be used if particles are present. Any unused portion should be discarded. Fentanyl for infusion may be prepared by dilution with infusion fluids containing 5% glucose or 0.9% sodium chloride.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires « MédiS »; Route de Tunis km 7 – BP 206 – 8000 Nabeul, Tunisie.
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E-mail: marketing.ventes@medis.com.tn

8. MARKETING AUTHORISATION NUMBER(S)

Fentanyl Médis 0.1 mg/2 ml: 9233311H

Fentanyl Médis 0.5 mg/10 ml: 9233312H

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Fentanyl MédiS 0.5 mg/10 ml: 03/11/2009 **/** 03/11/2014 **/** 03/11/2019

Fentanyl MédiS 0.1 mg/2 ml: 29/06/2004 **/** 29/06/2009 **/** 29/06/2014 **/** 29/06/2019

10. DATE OF REVISION OF THE TEXT

November 2019