# PRODUCT INFORMATION

# MARTINDALE PHARMA FENTANYL SOLUTION FOR INJECTION 50 MICROGRAMS/ML

## 1 NAME OF THE MEDICINAL PRODUCT

Fentanyl 50 micrograms/ml Solution for Injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fentanyl citrate 78.5 micrograms 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

Clear, colourless, sterile solution for Injection

## 4 PHARMACOLOGICAL PROPERTIES

### 4.1 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 anaesthesia, respiratory depression, bradycardia and other typical morphine-like effects. The duration of action of the peak effects 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.

### 4.2 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).

### 4.3 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.

## 5 CLINICAL PARTICULARS

### 5.1 Therapeutic indications

Fentanyl citrate is an opioid analgesic used:
In low doses to provide analgesia during short surgical procedures.
In high doses as an analgesic/respiratory depressant in patients requiring assisted ventilation.
In combination with a neuroleptic in the technique of neuroleptanalgesia.

### 5.2 Posology and method of administration

Routes of administration

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

Intravenous administration, either as a bolus or by infusion.
Intramuscular administration.

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

Posology
Fentanyl Injection 50 micrograms/ml, by the intravenous route, can be administered to both adults and children. The dose of Fentanyl Injection 50 micrograms/ml should be individualised according to age, body weight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.

Adults
The usual dosage regime is as follows:

| | Initial | Supplemental |
|---|---|---|
| Spontaneous respiration | 50-200 micrograms | 50 micrograms |
| Assisted ventilation | 300-3500 micrograms | 100-200 micrograms |

Doses in excess of 200 micrograms are for use in anaesthesia only.
As a premedicant, 1-2 ml Fentanyl Injection 50 micrograms/ml may be administered intramuscularly 45 minutes before induction of anaesthesia.

After intravenous administration in unpremedicated adult patients, 2 ml of Fentanyl Injection 50 micrograms/ml may be expected to provide sufficient analgesia for 10 - 20 minutes in surgical procedures involving low pain intensity. 10 ml Fentanyl Injection 50 micrograms/ml injected as a bolus gives analgesia lasting about one hour. The analgesia produced is sufficient for surgery involving moderately painful procedures. Giving a dose of 50mcg/kg Fentanyl Injection 50 micrograms/ml will provide intense analgesia for some four to six hours for intensely stimulating surgery.

Fentanyl Injection 50 micrograms/ml may also be given as an infusion. In ventilated patients, a loading dose of Fentanyl Injection 50 micrograms/ml may be given as a fast infusion of approximately 1 mcg/kg/min for the first 10 minutes followed by an infusion of approximately 0.1 mcg/kg/min. Alternatively the loading dose of Fentanyl Injection 50 micrograms/ml may be given as a bolus. Infusion rates should be titrated to individual patient response; lower infusion rates may be adequate. Unless it is planned to ventilate post-operatively, the infusion should be terminated at about 40 minutes before the end of surgery.

Lower infusion rates, e.g. 0.05-0.08 mcg/kg/minute are necessary if spontaneous ventilation is to be maintained. Higher infusion rates (up to 3 mcg/kg/minute) have been used in cardiac surgery.

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

*Use in elderly and debilitated patients*:
It is wise to reduce the dosage in the elderly and debilitated patients. The effect of initial dose should be taken into account in determining supplemental doses.

*Paediatric population*
The doctor calculates the best dosage based on the child's weight, severity of pain and length of pain relief required. The initial dose being 3 – 5mcg per kilogram body weight followed as required by 1mcg per kilogram body weight. If breathing is artificially assisted, the initial dose can be increased up to a maximum of 15mcg per kilogram body weight, followed as required by 1-3mcg per kilogram body weight.

*Use in children:*
Analgesia during operation, enhancement of anaesthesia with spontaneous respiration.

Techniques that involve analgesia in a spontaneous breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/analgesia technique with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support (see section 4.4).

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.

*Obese patients:*
In obese patients there is a risk of overdosing if the dose is calculated based on body weight. Obese patients should have dosage calculated according to their estimated ideal body mass.
*Renal Impairment*
In patients with renal impairment reduced dosing of fentanyl should be considered and these patients should be observed carefully for signs of fentanyl toxicity (see section 5.2 Pharmacokinetic properties).

## 5.3 Contraindications

Hypersensitivity to the Fentanyl citrate or to any of the excipients listed in section 6.1 Respiratory depression, obstructive airways disease. Concurrent administration with monoamine oxidase inhibitors, or within 2 weeks of their discontinuation. Known intolerance to fentanyl citrate or other morphinomimetics.

## 5.4 Special warnings and precautions for use

*Warnings:*
Tolerance and dependence may occur. 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 narcotic antagonists (e.g. naloxone). Additional doses of the latter 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 patients response to $CO_2$, thus affecting respiration postoperatively.

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

*Cardiac disease*
Bradycardia and possibly asystole can occur if the patient has received an insufficient amount of anticholinergic, or when fentanyl is combined with non-vagolytic muscle relaxant. 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 I.V. injection (usually sufficient for lower doses)
- premedication with benzodiazepines
- use of muscle relaxants.

Non-epileptic (myo)clonic movement can occur

*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 wise to reduce dosage in the elderly and debilitated patients.

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

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

*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., hyperoreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).
If serotonin syndrome is suspected, rapid discontinuation of fentanyl should be considered.

*Paediatric population*
Techniques that involve analgesia in a spontaneous breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/analgesia technique with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support.

Fentanyl Injection contains 3.5 mg sodium per ml of solution, equivalent to 0.18% of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

**5.5 Interaction with other medicinal products and other forms of interaction**
*Effect of other drugs on fentanyl*
The use of opioid premedication, barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non-selective CNS depressants (e.g. alcohol) may enhance or prolong the respiratory depression of fentanyl.

When the patients have received CNS-depressants, the dose of fentanyl required will be less than usual.

Concomitant use with Fentanyl in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death.

Fentanyl, a high clearance drug, is rapidly and extensively metabolised mainly by CYP3A4.

Itraconazole (a potent CYP3A4 inhibitor) at 200mg/day given orally for 4 days had no significant effect on the pharmacokinetics of IV fentanyl.

Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of IV fentanyl by two thirds; however, peak plasma concentrations after a single dose of IV fentanyl were not affected.

When fentanyl is used in a single dose, the concomitant use of potent CYP3A4 inhibitors such as ritonavir requires special patient care and observation.

Co-administration of fluconazole or voriconazole (moderate CYP3A4 inhibitors) and fentanyl may result in an increased exposure to fentanyl.

With continuous treatment of fentanyl and concomitant administration of CYP3A4 inhibitors, a dose reduction of fentanyl may be required to avoid

accumulation, which may increase the risk of prolonged or delayed respiratory depression.

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

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

*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. 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, during this period may disproportionally increase the risk for respiratory depression.
Plasma concentration of etomidate increased considerably (by a factor of 2 to 3) when combined with fentanyl

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.

## 5.6 Fertility, pregnancy and lactation

**Pregnancy**
There are no adequate data from the use of fentanyl in pregnant women. Fentanyl can cross the placenta in early pregnancy. Studies in animals have shown some reproductive toxicity (see Section 5.3, Preclinical safety data). The potential risk for humans is unknown.

Administration during childbirth (including Caesarean section) is not recommended because fentanyl crosses the placenta and the foetal respiratory centre is particularly sensitive to opioids. 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.

**Breast-feeding**
Fentanyl is excreted into human milk. It is therefore recommended that breast feeding is not initiated within 24 hours of treatment. 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).

## 5.7 Effects on ability to drive and use machines

Where early discharge is envisaged, patients should be advised not to drive or to operate machinery for 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
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

## 5.8 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 (≥ 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, Table 1 displays ADRs that have been reported with the use of fentanyl IV from either clinical trials or postmarketing experience.

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 <1,1000); very rare (<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 |
| Immune System Disorders | | | | Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria) |

| | | | | |
|---|---|---|---|---|
| Psychiatric disorders | | Agitation | Euphoric mood | |
| 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; Arrythmia | | 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 | | Pruritis |
| General Disorders and Administration Site Conditions | | | Chills; Hypothermi a | |
| 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. Healthcare professionals are asked to report any suspected adverse reactions.

### 5.9 Overdose

*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 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 narcotic antagonist (e.g. naloxone). 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.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium Chloride, Sodium Hydroxide, 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.

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Protect from light.
Keep container in the outer carton.
Do not store above 30°C.
Keep out of the sight and reach of children

### 6.5 Nature and contents of container

2 ml or 10 ml clear glass ampoules, glass type I borosilicate glass, packed in cardboard cartons and contain 10 x 2 ml/10 ml ampoules.

Not all pack sizes maybe marketed.

**6.6 Special precautions for disposal**

If only part used, discard the remaining solution.

## 7 MANUFACTURER AND PRODUCT OWNER

Macarthys Laboratories Ltd T/A Martindale Pharma
Bampton Road, Harold Hill, Romford, Essex RM3 8UG, United Kingdom

## 8 REGISTRATION NUMBER

SIN123456P

## 9 DATE OF REVISION OF THE TEXT

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