



# **Public Assessment Report**

**FENTANYL 50 MICROGRAM/ML INJECTION BP**

**(FENTANYL CITRATE)**

**PL 20910/0001**

**FENTANYL 50 MICROGRAM/ML INJECTION BP**

**(fentanyl citrate)**

**PL 20910/0001**

**UKPAR**

**TABLE OF CONTENTS**

Lay Summary	Page 3
Scientific discussion	Page 4
Steps taken for assessment	Page 15
Steps taken after authorisation – summary	Page 16
Summary of Product Characteristics	Page 17
Product Information Leaflet	Page 23
Labelling	Page 25

**FENTANYL 50 MICROGRAM/ML INJECTION BP  
(FENTANYL CITRATE)  
PL 20910/0001**

**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Taro Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Fentanyl 50 microgram/ml Injection BP (PL 20910/0001). Fentanyl is a short acting opioid analgesic (reliever of pain) used, in low doses, as pain relief during short surgical procedures; in high doses as pain relief / agent to slow down breathing rate in patients requiring help with breathing; in combination with a neuroleptic (tranquilizer) in the technique of neuroleptanalgesia (sedated pain relief); and in the treatment of severe pain, such as the pain associated with heart attacks. This is a prescription only medicine [POM].

Fentanyl is a synthetic opioid 50 to 100 times more potent than an equal dose of morphine. It is fast acting but its duration of action is short. In man, a single IV dose of 0.5 mg to 1 mg per 70 kg bodyweight immediately produces a pronounced state of surgical analgesia, respiratory depression, bradycardia (slowing of heart rate), and other typical morphine-like effects. The duration of action of the peak effects is about 30 minutes.

The clinical data presented to the MHRA, before licensing, demonstrated that Fentanyl 50 microgram/ml Injection BP is bioequivalent to the reference product, Sublimaze (PL 00242/5001R) licensed in February 1980 to Janssen-Cilag.

Based on the information provided, Fentanyl 50 microgram/ml Injection BP from Taro Pharmaceuticals Limited is interchangeable with Sublimaze.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Fentanyl 50 microgram/ml Injection BP outweigh the risks, hence a Marketing Authorisation has been granted.

**FENTANYL 50 MICROGRAM/ML INJECTION BP**

**(FENTANYL CITRATE)**

**PL 20910/0001**

**SCIENTIFIC DISCUSSION**

**TABLE OF CONTENTS**

Introduction	Page 5
Pharmaceutical assessment	Page 6
Preclinical assessment	Page 11
Clinical assessment	Page 12
Overall conclusions and risk benefit assessment	Page 14

## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal product Fentanyl 50 microgram/ml Injection BP (PL 20910/0001) to Taro Pharmaceuticals Limited on 21<sup>st</sup> July 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EC as amended, claiming essential similarity to Sublimaze PL 00242/5001R licensed in February 1980 to Janssen-Cilag.

The product contains the active ingredient Fentanyl citrate. Fentanyl is a short acting opioid analgesic indicated in low doses for treatment 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. In the treatment of severe pain, such as the pain of myocardial infarction.

Fentanyl is a synthetic opioid 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 mg to 1 mg per 70 kg bodyweight 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.

# **PHARMACEUTICAL ASSESSMENT**

**LICENCE NO:** PL 20910/0001

**PROPRIETARY NAME:** Fentanyl 50 microgram/ml Injection BP

**ACTIVE(S):** Fentanyl citrate

**COMPANY NAME:** Taro Pharmaceuticals (Ireland) Limited

**E.C. ARTICLE:** Article 10.1 [formerly Article 10.1(a)(iii) of Directive 2001/83/EC]

**LEGAL STATUS:** POM

## **1. INTRODUCTION**

### **1.1 Legal Basis**

This is an application for a sterile aqueous solution for intravenous and intramuscular injection containing fentanyl 50mcg/ml (as the citrate) as the active ingredient. The application is submitted under Article 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EC as amended, claiming essential similarity to Sublimaze PL 00242/5001R licensed in February 1980 to Janssen-Cilag. The reference product in the UK is Sublimaze PL 00242/5001R.

### **1.2 Use**

Fentanyl is a short acting opioid analgesic. The proposed indications are

- Treatment of severe pain, such as pain of myocardial infarction
- To provide analgesia during short surgical procedures
- As an analgesic/respiratory depressant in patients who need assisted ventilation
- In combination with a neuroleptic drug as part of the technique of neuroleptanalgesia.

The product is administered by IV as a bolus or by infusion or by IM injection.

## **2. MARKETING AUTHORISATION APPLICATION FORM**

### **2.1 Name(s)**

The proposed name of the product is Fentanyl 50 microgram/ml Injection BP and is satisfactory.

### **2.2 Strength, pharmaceutical form, route of administration, container and pack sizes**

The products contain Fentanyl citrate 78.5 micrograms per ml equivalent to 50 micrograms per ml fentanyl. The solution for injection is filled into clear and colourless, type 1 glass ampoules. Pack sizes available are 2 ml and 10 ml. The proposed shelf-life (3 years; to be used immediately if opened) is supported by the stability data submitted.

### **2.3 Legal status**

These products will be subject to a medical prescription.

### **2.4 Marketing authorisation holder/Contact Persons/Company**

The proposed Marketing Authorisation holder is Taro Pharmaceuticals Limited, Lourdes Road, Roscrea, Co. Tipperary, Ireland.

The Qualified Person responsible for pharmacovigilance is stated and their CV is included.

## 2.5 TSE

The applicant has provided a declaration that no materials of animal origin are used in manufacture of the finished product. A declaration is also provided by the active ingredient manufacturer that during synthesis and purification, no direct or indirect use is made of products with risk of TSE

## 3. DRUG SUBSTANCE

An EDQM Certificate of Suitability has been submitted to provide information on the drug substance. The active source has been approved for other UK licensed parenteral products. The Active Ingredient Manufacturer has provided an assurance that the applicant would be informed of any changes in the manufacturing process or final purification that interfere with the quality and or stability of the product.

The specification proposed for the drug substance complies with Ph.Eur requirements and includes additional tests specified on the EDQM Certificate of Suitability and is supported by batch analytical data.

Analytical procedures are described. Satisfactory validation data are provided for the in-house methods.

Results of industrial scale batches of fentanyl citrate provided by the Active Ingredient Manufacturer are within specification. Certificates of Analysis (CoAs) for batches of the drug substance tested on receipt by Taro Pharmaceuticals Ireland Ltd (finished product manufacturer) have been provided and are satisfactory.

Taro Pharmaceuticals Ireland Ltd. will fully test every batch of fentanyl citrate to specification requirements prior to use in the manufacture of the finished product

## 4. FINISHED PRODUCT

### COMPOSITION

The composition is tabulated below.

Name of constituents	Function	Reference to Standards
Active constituent		
Fentanyl citrate	Active	Ph. Eur
Other constituents		
Sodium chloride	Isotonic agent	Ph. Eur
Sodium hydroxide	pH adjuster	Ph. Eur
Water for injections	Solvent	Ph. Eur

## PHARMACEUTICAL DEVELOPMENT

### Drug Substance

Fentanyl is soluble in water, sparingly soluble in alcohol, freely soluble in methyl alcohol.

### **Excipients**

All excipients comply with their respective current Ph. Eur monograph. Specifications and analytical test methods used (Ph. Eur) are given. Satisfactory checks are performed by the dosage form manufacturer before use. Typical certificates of analysis from the suppliers and retest batch data from the dosage form manufacturer are provided.

### **Container Closure System**

The 50 microgram/ml Injection are packed into clear and colourless, type 1 glass ampoules. Pack sizes of 2 and 10 ml are approved for marketing.

### **Microbiological Attributes**

This is a sterile liquid preparation. The microbiological attributes are satisfactorily controlled in the finished product specification to Ph. Eur. 5.1.4 category 1 requirements.

### **Compatibility**

The product may be given by IV, either as a bolus injection or by infusion. For IV infusion the product may be diluted with Glucose 5% Intravenous infusion BP and Sodium chloride (NaCl) 0.9% intravenous Infusion BP solutions. Chemical and physical in-use stability has been demonstrated for up to 48 hours at 2-8°C in the dark and up to 48 hours at ambient room temperature, exposed to light, when mixed with 0.9% sodium chloride intravenous infusion or 5% Glucose Intravenous Infusion. However from a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

## **MANUFACTURE**

### **GMP Statement and Manufacturing Chain**

Taro Pharmaceuticals is the site for batch release, manufacture, assembly and QC. A copy of the current Manufacturing Authorisation (M1019) for the named site is given and is satisfactory. The operations and product categories handled cover the proposed product (terminally sterilised products, glass ampoules and vials having a volume not exceeding 100ml).

### **Description of the Manufacturing Process**

A satisfactory formula and description of manufacture are provided.

Critical phases of the manufacturing process have been satisfactorily identified and appropriate in-process controls are in place.

In-process batch data for validation batches are satisfactory. The validation results demonstrate consistent manufacture. The validation protocol provided is considered adequate for the purpose.

## **CONTROL OF EXCIPIENTS**

The excipients comply with Ph. Eur. Requirements. Satisfactory Certificates of Analysis have been provided for each excipient and are accepted. Where relevant, the compendial methodology is used in testing.



## **CONTROL OF DRUG PRODUCT**

### **Specifications**

The finished product specification is satisfactory. The specification proposed complies with BP requirements for Fentanyl Injection and is supported by batch analytical and stability data.

### **Analytical Procedures**

Test methods have been described and adequately validated as appropriate.

### **Batch data**

Satisfactory data are provided for batches manufactured at the proposed site and are considered representative of the product to be marketed.

### **Characterisation of Impurities**

This is satisfactory.

## **REFERENCE STANDARDS OR MATERIALS**

Reference standards are identified and are satisfactory.

## **CONTAINER CLOSURE SYSTEM**

Satisfactory details of supplier specification, product construction, standards and compliance statements are provided. In-house specification giving details of tests performed on receipt are provided and are satisfactory.

## **STABILITY**

Stability studies have been reported at normal, intermediate and accelerated conditions. The stability samples are representative of the product to be marketed in the proposed pack.

The data provided supports the product shelf-life of 36 months (unopened) and the storage conditions (please refer to Summary of Products Characteristics (SPC), section 6.3 for details.

The programme is ongoing. The stability programme is satisfactory as the applicant has agreed to place the first commercial batches on stability.

## **BIOEQUIVALENCE / BIOAVAILABILITY**

No new data submitted and none required. No bioequivalence study is required because the product is an aqueous solution for intravenous or intramuscular injection. 100% bioavailability is assumed and there is no requirement for comparative bioavailability studies.

## **5. QUALITY OVERALL SUMMARY**

This is satisfactory.

## **6. PRODUCT PARTICULARS**

### **Product Brand Name**

This is considered satisfactory.

### **Summary of Product Characteristics**

Satisfactory SPC provided.

### **Patient Information Leaflet**

Satisfactory coloured mock-ups are provided. The applicant has until 1<sup>st</sup> July 2008 to amend the order in which the information appears in the leaflet and provide user testing data (both parts of Article 59, Directive 2004/27/EC must be complied with at the same time).

### **Labelling**

Satisfactory.

### **MARKETING AUTHORISATION APPLICATION (MAA) form**

Satisfactory

### **ADDITIONAL DATA REQUIREMENTS**

Satisfactory.

## **7. CONCLUSION**

A product licence may be granted for this product.

## **PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with these applications and none are required for an application of this type.

## **CLINICAL ASSESSMENT**

### **1. INTRODUCTION AND BACKGROUND**

This is a National Abridged application claiming essential similarity with the UK brand leader Sublimaze, PL 0242/5001R, which has been licensed in the UK for more than 10 years. A number of generic equivalents are already licensed in the UK.

Fentanyl is well characterised in the literature. It is a synthetic opiate with a clinical potency of 50 to 100 times that of morphine.

### **2. INDICATIONS**

The applicant has submitted the following:

- 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.
- In the treatment of severe pain, such as the pain of myocardial infarction.

The above is essentially identical to the SPC text for the licensed indications of the reference product.

### **3. DOSE & DOSE SCHEDULE**

The proposed text for section 4.2 of the SPC is essentially identical to that for the reference product and is satisfactory.

### **4. TOXICOLOGY**

No new data are submitted and the pre-clinical expert report identifies no new concerns.

### **5. CLINICAL PHARMACOLOGY**

No new data submitted and none required. No bioequivalence study is required because the product is an aqueous solution for intravenous or intramuscular injection.

### **6. EFFICACY**

Efficacy of Fentanyl is known through its clinical use over many years and extensive publications. No new data has been submitted and none is required.

## **7. SAFETY**

The clinical safety of the product is well established. No new data has been submitted and none is required.

## **8. EXPERT REPORT**

A Clinical Overview has been provided in CTD Module 2.5.

A Clinical Summary has not been provided in CTD Module 2.7.

Information about the Clinical Expert is provided in CTD Module 1.4.3.

## **9. SUMMARY OF PRODUCT CHARACTERISTICS**

The SPC is considered satisfactory and consistent with the SPC for the reference product.

## **10. PATIENT INFORMATION LEAFLET**

The PIL is considered satisfactory and consistent with the PIL for the reference product.

## **11. LABELLING**

The labelling is considered satisfactory.

## **12. DISCUSSION**

The clinical use of Fentanyl is well established in the indications proposed. No new clinical efficacy and safety data has been submitted and none is required.

## **13. CONCLUSIONS**

Overall, there is no clinical objection to the grant of marketing authorisation for this application. No new or unexpected safety concerns arise from these applications.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The data for these applications are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

Fentanyl is a well known drug and has been used as an opioid analgesic for many years. No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with Fentanyl is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

**FENTANYL 50 MICROGRAM/ML INJECTION BP  
(FENTANYL CITRATE)  
PL 20910/0001**

**STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation application on 29 <sup>th</sup> March 2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 5 <sup>th</sup> May 2004.
3	Following assessment of the application the MHRA requested further information relating to the dossier on 02/11/2004, 24//08/2005, 22/06/2006, and again on 23/06/2006.
4	The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 31/01/2005, 09/09/2005, 26/06/2006, 27/06/2006 and 29/06/2006.
5	The application was determined and the Marketing authorisation granted on 21 <sup>st</sup> July 2006.

**FENTANYL 50 MICROGRAM/ML INJECTION BP**

**(FENTANYL CITRATE)**

**PL 20910/0001**

**STEPS TAKEN AFTER ASSESSMENT**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>



**FENTANYL 50 MICROGRAM/ML INJECTION BP  
(FENTANYL CITRATE)  
PL 20910/0001**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**1. NAME OF THE MEDICINAL PRODUCT**

Fentanyl 50 micrograms/ml Injection BP

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Fentanyl citrate 78.5 micrograms equivalent to 50 micrograms per ml fentanyl.

2ml solution contains 157 micrograms of fentanyl citrate equivalent to 100 micrograms of fentanyl.

10ml solution contains 785 micrograms of fentanyl citrate equivalent to 500 micrograms of fentanyl.

For excipients, see 6.1.

**3. PHARMACEUTICAL FORM**

Solution for injection

Clear, colourless solution.

**4. CLINICAL PARTICULARS**

**4.1. Therapeutic indications**

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.

In the treatment of severe pain, such as the pain of myocardial infarction.

**4.2. Posology and method of administration**

Route of administration:

-Intravenous administration either as a bolus or by infusion.

-Intramuscular administration.

-Fentanyl, by the intravenous route, can be administered to both adults and children. The dose 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 usual dosage regimen is as follows:

	Adults		Children	
	Initial	Supplemental	Initial	Supplemental
Spontaneous Respiration	50-200 mcg	50 mcg	3-5 mcg/kg body weight	1 mcg/kg body weight
Assisted Ventilation	300-3500 mcg	100-200 mcg	15 mcg/kg body weight	1-3 mcg/kg body weight

Doses in excess of 200 micrograms are for use in anaesthesia only. As a premedicant, 1-2 ml fentanyl may be given intramuscularly 45 minutes before induction of anaesthesia.

After intravenous administration in unpremedicated adult patients, 2 ml fentanyl may be expected to provide sufficient analgesia for 10-20 minutes in surgical procedures involving low pain intensity. 10 ml fentanyl 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 50 micrograms/kg fentanyl will provide intense analgesia for some four to six hours, for intensely stimulating surgery.

Fentanyl may also be given as an infusion. In ventilated patients, a loading dose of fentanyl may be given as a fast infusion of approximately 1 microgram/kg/min for the first 10 minutes followed by an infusion of approximately 0.1 micrograms/kg/min. Alternatively the loading dose of fentanyl 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 postoperatively, the infusion should be terminated at about 40 minutes before the end of surgery.

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

For intravenous infusion fentanyl may be diluted with 0.9% Sodium Chloride Intravenous Infusion or 5% Glucose Intravenous Infusion before use. Refer also to sections 6.3 and 6.6.

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

#### 4.3. Contraindications

Respiratory depression, obstructive airways disease. Concurrent administration with monoamine oxidase inhibitors, are within two weeks of their discontinuation. Known hypersensitivity to fentanyl or excipients or to other morphinomimetics

#### 4.4. 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.

Significant respiratory depression will occur following the administration of fentanyl in doses in excess of 200 micrograms. 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.

Bradycardia and possibly asystole can occur in non-atropinised patients and can be antagonised by atropine.

Muscular rigidity (morphine-like effect) may occur. Rigidity, which may also involve thoracic muscles, can be avoided by the following measures:

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

*Precautions:*

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

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

In hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism, and liver or renal impairment, the dosage should be titrated with care and prolonged monitoring may be required. Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses.

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

Resuscitation equipment and opioid antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's response to CO<sub>2</sub>, thus affecting respiration postoperatively.

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 main arterial pressure has occasionally been accompanied by a transient reduction of cerebral perfusion pressure.

#### **4.5. Interactions with other medicinal products and other forms of interaction**

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 patients have received CNS-depressants, the dose of fentanyl required will be less than usual. Likewise, following the administration of fentanyl the dose of other CNS-depressant drugs should be reduced.

Fentanyl, a high clearance drug is rapidly and extensively metabolised mainly by CYP3A4. Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for four 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. With continuous treatment, 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 nonvagolytic muscle relaxants. The concomitant use of droperidol can result in a higher incidence of hypotension.

#### **4.6. Pregnancy and lactation**

Although no teratogenic or acute embryotoxic effects of fentanyl have been observed in animal experiments, insufficient data is available to evaluate any harmful effects in humans. As with other drugs, possible risks should be weighed against the potential benefits to the patient.

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, an antidote for the child should always be at hand.

Fentanyl may enter the maternal milk. It is therefore recommended that breastfeeding is not initiated within 24 hours of treatment.

**4.7. Effects on ability to drive and use machines**

When early discharge is envisaged, the patient should be advised not to drive or operate machinery for 24 hours following administration.

**4.8. Undesirable effects**

The side effects are those associated with intravenous opioids, e.g., respiratory depression, apnoea, muscular rigidity (which may also involve the thoracic muscles), myoclonic movements, bradycardia, transient hypotension, nausea, vomiting, dizziness, insomnia, and sexual dysfunction (e.g. decreased libido).

Other less frequently reported adverse reactions are:

-laryngospasm;

-allergic reactions (e.g., anaphylaxis, bronchospasm, pruritus, urticaria) and asystole (although it is uncertain whether there is a causative relationship as several drugs were co-administered).

Secondary rebound respiratory depression has rarely been reported.

When a neuroleptic such as droperidol is used with fentanyl, the following adverse reactions may be observed: chills and/or shivering, restlessness, postoperative hallucinatory episodes, and extrapyramidal symptoms.

**4.9. Overdose**

*Symptoms:*

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<sub>2</sub> administration, assisted or controlled respiration.

Respiratory depression:

Specific narcotic antagonist (e.g. naloxone). This does not preclude the use of immediate countermeasures.

Muscular rigidity:

Intravenous neuromuscular blocking agent.

In all cases the patient should be carefully observed; body warmth and adequate fluid intake should be maintained. If hypotension is severe, 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: Opioid anesthetics

ATC code: N01 AH

Fentanyl is a synthetic opioid 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 mg to 1 mg per 70 kg bodyweight 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) =  $13 \pm 2$ .

Volume of distribution (litres/kg) =  $4.0 \pm 0.4$ .

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

**5.3. Preclinical safety data**

No further relevant information.

**6. PHARMACEUTICAL PARTICULARS**

**6.1. List of excipients**

Sodium chloride, sodium hydroxide and Water for Injections.

**6.2. Incompatibilities**

The product is chemically incompatible with induction agents, thiopentone and methohexitone because of the wide differences in pH. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

**6.3. Shelf life**

Shelf-life as packaged for sale:

3 years.

Shelf-life after first opening:

Use Immediately.

Shelf-life after dilution: Chemical and physical in-use stability has been demonstrated for up to 48 hours at 2-8°C in the dark and up to 48 hours at ambient room temperature, exposed to light, when mixed with 0.9% sodium chloride intravenous infusion or 5% Glucose Intravenous Infusion.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

**6.4. Special precautions for storage**

Do not store above 25°C.

Keep ampoules in the outer carton in order to protect from light.

For storage of the diluted product refer to section 6.3.

**6.5. Nature and contents of container**

Clear and colourless, type 1 glass ampoules, 2 ml, 10 ml.

Pack sizes: 10 x 2 ml ampoules, 10 x 10 ml ampoules.

**6.6. Instruction for use and handling (, and disposal)**

The injection is for single dose use only and should be used immediately after opening. Any unused portion should be discarded. The injection should not be used if visible particles are present.

The product can be used either undiluted or diluted. Fentanyl for infusion may be prepared by dilution with 5% Glucose Intravenous Infusion or 0.9% Sodium Chloride Intravenous Solution.

**7. MARKETING AUTHORISATION HOLDER**

Taro Pharmaceuticals Ireland Ltd.,  
Lourdes Road,

Roscrea,  
Co. Tipperary,  
Ireland.

- 8.     MARKETING AUTHORISATION NUMBER**  
PL 20910/0001
- 9     DATE OF FIRST AUTHORISATION/RENEWAL OF THE   AUTHORISATION**  
21/07/2006
- 10    DATE OF REVISION OF THE TEXT**  
21/07/2006

**FENTANYL 50 MICROGRAM/ML INJECTION BP  
(FENTANYL CITRATE)  
PL 20910/0001  
PATIENT INFORMATION LEAFLET**

175mm

5mm

Patient Information Leaflet  
**Fentanyl 50 micrograms/ml Injection BP**

This leaflet contains important information about your medicine. If there is anything that you do not understand or if you need further information or advice, you should ask your doctor. This leaflet applies only to fentanyl. Please do not throw it away - you may need to refer to it later.

**WHAT IS FENTANYL 50 MICROGRAMS/ML INJECTION BP**  
The name of your medicine is fentanyl, and its active ingredient is fentanyl citrate. It is an injection which comes in 2 ml and 10 ml ampoules. Each ml of sterile solution for injection contains 50 micrograms of fentanyl as fentanyl citrate. The solution also contains sodium chloride, sodium hydroxide and water for injections.  
Fentanyl is one of a group of medicines known as opioid analgesics which relieve or prevent pain.  
The product is packed in cartons containing 10 ampoules of 2 ml or 10ml.  
*Manufacturer and Product Licence Holder:* Taro Pharmaceuticals Ireland Ltd., Lourdes Road, Roscrea, Co Tipperary, Ireland.

**WHAT IS THIS MEDICINE USED FOR**  
In low doses, fentanyl is used to control pain during short operations in hospital. As well as providing pain control, high doses of fentanyl are used to lower your natural breathing rate when you are on a ventilator. During major operations, it is used together with a sedative known as a neuroleptic to put you to sleep.

**BEFORE YOU RECEIVE YOUR MEDICINE**  
Always inform your doctor if you are pregnant, think you might be pregnant or are trying to become pregnant.

**When should this medicine not be used**  
You should not be given fentanyl:

- if you suffer from any illness which causes breathing difficulties, e.g., asthma, chronic bronchitis. You should make sure that you discuss this with your doctor before your operation.
- if you are taking or have recently been taking any of the antidepressant medicines known as monoamine oxidase inhibitors (MAOIs). Always tell the doctor about any medicines which you have recently taken or are taking now.

- if you think that you may have had an allergic or any other type of reaction to fentanyl or a similar medicine in the past. An allergic reaction may be recognized as a rash, itching, swollen face or lips, or shortness of breath.

**Warnings**  
Medicines like fentanyl may cause a drop in blood pressure and breathing rate. These effects are usually short-lived. It may also cause the heart to beat more slowly. Your blood pressure, heart rate, and breathing rate are monitored whilst you are being given fentanyl so that any unwanted effects of this nature can be reversed with other medicines.  
Particular care has to be taken following treatment with other medicines, which have similar effects, as their combined effect may be too strong.  
The doctor who would be giving fentanyl will be aware of the possibility of all these unwanted effects and will take steps to avoid them.

**Special precautions**  
The dose of fentanyl is normally reduced in elderly patients and patients who are weak due to ill health. Patients with thyroid, liver, lung, or kidney problems and those with alcoholism will also have their dose tailored to their particular needs and their response closely monitored.  
Particular care has to be taken in patients who suffer from a disease known as myasthenia gravis which causes abnormal tiredness and muscle weakness. You should talk to your doctor before the operation if you think this could apply to you.  
As with all strong painkillers of this type, good pain relief is accompanied by lowering of the breathing rate. This may last into the recovery period or occur again during this time. This effect may be increased if you have recently used similar medicines for pain relief. Your breathing will be carefully monitored until it returns to normal. Your doctor will have special equipment and drugs available for reversing any unplanned lowering of your breathing rate. Continued medical use or previous abuse of this type of medicine can reduce its effectiveness, and the dose may need to be higher.  
It is not usual to use fentanyl during labour as it may affect your baby's breathing. However, if your doctor decides that it is necessary, treatment is available to reverse any adverse effect that occurs.  
Quick injections of this type of medicine should not be used in patients who have problems with mental or other brain function. In these patients, the resulting decrease in blood pressure has sometimes resulted in reduction of blood pressure in the brain.

**Pregnancy**  
If you are pregnant or you think you maybe, you should inform your doctor who will decide whether or not you should be given fentanyl.

175mm

35mm

**Breast-feeding**  
Fentanyl may get into the breast milk. It is therefore recommended that you should not breast-feed for 24 hours after treatment with fentanyl.

**Other medicines**  
Always tell your doctor if you are taking any other medicines because taking some medicines together can be harmful. Remember that the doctor at the hospital may not have been informed if you have recently begun a course of treatment for another illness. Tell your doctor if you are taking the protease inhibitor ritonavir, as you may need less fentanyl.

**Driving or operating machinery**  
You should not drive or operate machinery for 24 hours after receiving fentanyl, as you may be less alert than usual.

**HOW SHOULD THIS MEDICINE BE GIVEN**  
Fentanyl 50 micrograms/ml Injection will be injected into a vein or muscle before you go into the operating theatre. It will help to put you to sleep and will prevent you from feeling pain during your operation.

**How much medicine will you be given**  
Your doctor will decide how much fentanyl you need. This will depend on the type and length of your operation that you are having and whether you will be breathing by yourself or whether your breathing will be done for you by a ventilator.  
If you are to breathe by yourself, your initial dose will be 1-4 ml injected into a vein, followed by further injections of 1 ml if necessary.  
If you are on a ventilator, your initial dose will be 6-70 ml injected into a vein, followed by further injections of 2-4 ml if necessary.  
If you are to receive fentanyl before being put to sleep for your operation, you will be given 1-2 ml injected into a muscle 45 minutes before the operation.  
Fentanyl may also be given as an infusion. This method may be used from the beginning or following an initial injection. A typical infusion would consist of an initial infusion dose of 1 micrograms/kg/min for 10 minutes followed by 0.1 micrograms/kg/min, continued until approximately 40 minutes before the end of your operation. The rate of infusion will depend on your response, whether or not your breathing will be done for you by a ventilator and on the type of operation. The rate of infusion can therefore range from 0.05 micrograms/kg/min (breathing by yourself) to 3 micrograms/kg/min (cardiac surgery).  
In elderly patients and patients who are weak due to ill health, the above amounts of fentanyl will be reduced.  
In children, the amount given will always depend on how much the child weighs.

**POSSIBLE SIDE EFFECTS**

Occasionally, fentanyl may cause side effects, such as feeling sick, vomiting, dizziness, sleeplessness, and lack of sexual desire. Other effects, which have been reported, include a slight temporary lowering of blood pressure or irregular heartbeat.

Fentanyl will also cause breathing rates to fall and may cause a lowering of your heart rate. These effects are normal when receiving this type of medicine. It has also been reported that the patient may stop breathing temporarily. The doctor has drugs to reverse this effect.

Fentanyl can make the muscles stiff. Your doctor will take measures to avoid this happening.

Another effect, known as tolerance, is due to the continued use of this type of medicine and such use can reduce its effectiveness. This can also lead to dependence.

Other effects, which have been reported include, spasm of the throat muscles and allergic reactions such as sudden fall in blood pressure, difficulty in breathing, or skin rash.

If fentanyl is used together with other medicines called neuroleptics, which are given before an operation to cause drowsiness, other effects can be experienced such as shivering and restlessness, hallucinations, trembling, pronounced muscle stiffness or spasm, slowness of movement, and excessive saliva.

If you think your medicine has affected you in any other way, you should tell the doctor. See also Warnings/Special Precautions section above.

**STORING THIS MEDICINE**

Keep out of reach and sight of children.

Do not store above 25°C.

Keep the container in the outer carton in order to protect from light.

If only part of the contents of the ampoule is used, the remaining solution should be discarded.

Do not use after the expiry date stated on the label and carton.

**FURTHER INFORMATION**

For any further information about this medicinal product, please contact Taro Pharmaceuticals Ireland Ltd., Lourdes Road, Roscrea, County Tipperary, Ireland.

Tel: + 353 505 24300

Marketing Authorisation Number: PL 20910/0001

This leaflet was last approved on: 22 June 2006.



Taro Pharmaceuticals Ireland Ltd.  
Lourdes Rd, Roscrea,  
County Tipperary, Ireland.  
Tel: + 353 505 24300



**FENTANYL 50 MICROGRAM/ML INJECTION BP  
(FENTANYL CITRATE)  
PL 20910/0001**

**2 ML AMPOULE LABEL**



2ml 29 x 32 Cutter D17960 Antigen  
P662161-01 5/5/99 14694

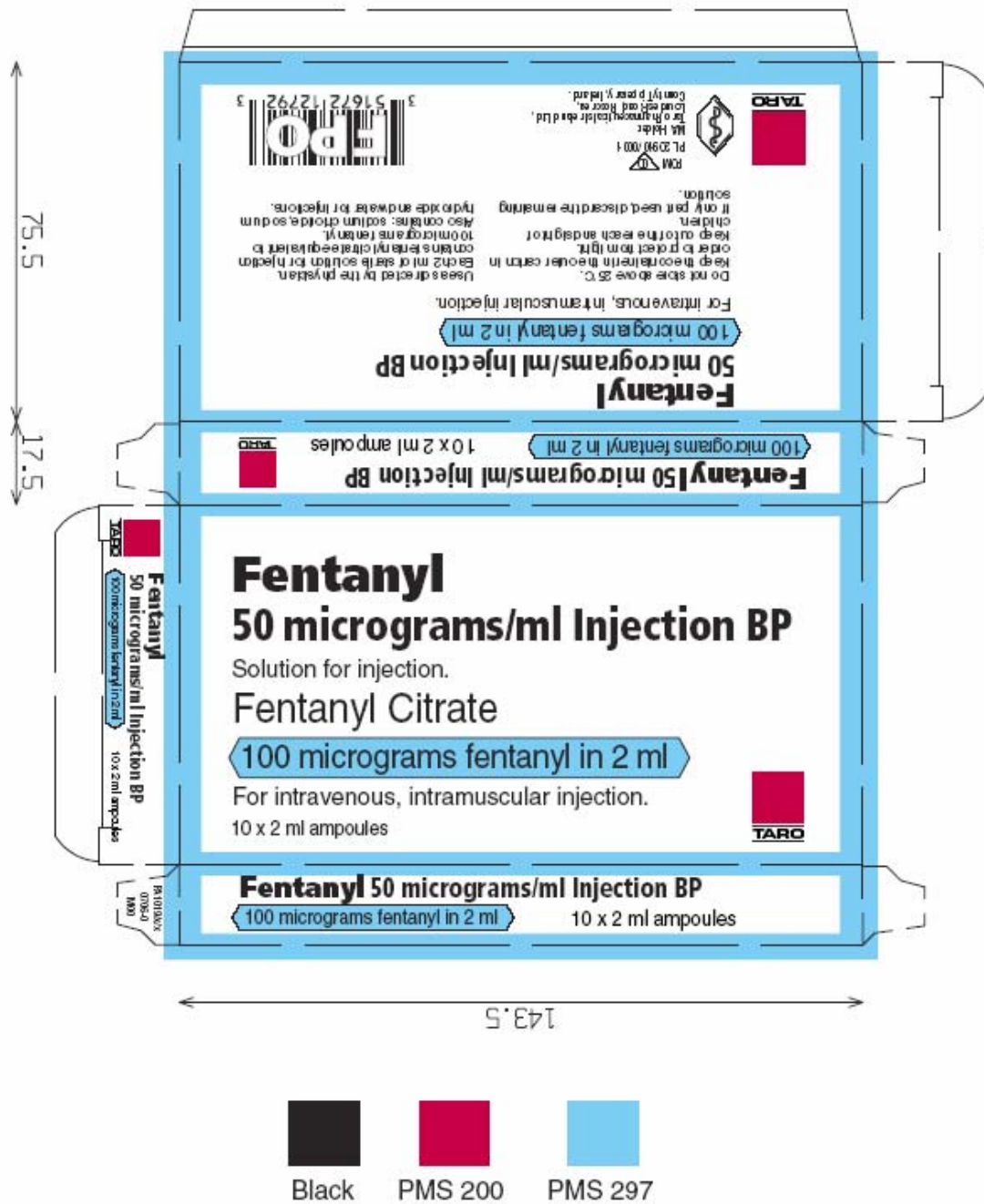


Black



PMS  
297

**2 ML CARTON LABEL**



**10 ML AMPOULE LABEL**



PMS  
302



PMS  
297

# 10 ML CARTON LABEL



APPROVAL				
DATE	62506	FOR	BY	APPROVAL
CLIENT				

