Product Summary

1. Trade Name of the Medicinal Product
   Fentanyl Injection 50 micrograms/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3 PHARMACEUTICAL FORM

Injection

4.1 Therapeutic indications

Fentanyl citrate is an opioid analgesic used:
• In low doses to provide analgesia during short surgical procedures.
• In high doses it is used 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

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.

Fentanyl Injection, by the intravenous route, can be administered to both adults and children. The dose of Fentanyl Injection 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 regime is as follows:
Doses in excess of 200 micrograms are for use in anaesthesia only.

As a premedicant, 1-2ml Fentanyl Injection may be given intramuscularly 45 minutes before induction of anaesthesia.

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

Fentanyl Injection may also be given by infusion. In ventilated patients, a loading dose of Fentanyl Injection 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 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 (eg 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 difference in pH.

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

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:

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Initial</th>
<th>Supplemental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>2-11 yrs</td>
<td>1-3 mcg/kg</td>
<td>1-1.25 mcg/kg</td>
</tr>
<tr>
<td>Respiration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assisted Ventilation</td>
<td>2-11 years</td>
<td>1-3 mcg/kg</td>
<td>1-1.25 mcg/kg</td>
</tr>
</tbody>
</table>
**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).

### 4.3 Contra-indications

Respiratory depression, obstructive airways disease. Concurrent administration with monoamine oxidase inhibitors, or within two weeks of their discontinuation. Known intolerance to fentanyl citrate or 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 mcg. This, and the other pharmacological effects of fentanyl, can be reversed by specific narcotic analgesics (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 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.

**Precautions:**
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 opioid analgesics, care should be observed when administering Fentanyl to patients with myasthenia gravis. It is wise to reduce dosage in the elderly and 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 new born 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 CO₂, 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 mean arterial pressure has occasionally been accompanied by a transient reduction of the cerebral perfusion pressure.

**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.

### 4.5 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.

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 inhibitor 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.

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.

4.6 Pregnancy and lactation

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

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of fentanyl IV was evaluated in 376 subjects who participated in 20 clinical trials evaluating fentanyl IV as an anaesthetic. These subjects took at least 1 dose of fentanyl IV and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported (≥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 (<1/10,000); and not known (cannot be estimated from the available clinical trial data).

Table 1: Adverse Drug Reactions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reactions</th>
<th>Frequency</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Very common (≥1/10)</td>
<td>Common (≥1/100 to &lt;1/10)</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td></td>
<td>Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Agitation</td>
<td>Euphoric mood</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Muscle rigidity (which may also involve the thoracic muscles)</td>
<td>Dyskinesia; Sedation; Dizziness</td>
<td>Headache</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Visual disturbance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Bradycardia; Tachycardia; Arrythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Hypotension; Hypertension; Venous pain</td>
<td>Phlebitis; Blood pressure fluctuation</td>
<td></td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Laryngospasm; Bronchospasm; Apnoea</td>
<td>Hyperventilation; Hiccups</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea; Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Allergic dermatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Chills; Hypothermia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>Postoperative</td>
<td>Airway</td>
<td></td>
</tr>
</tbody>
</table>
Poisoning and Procedural Complications

<table>
<thead>
<tr>
<th>confusion</th>
<th>complication of anaesthesia</th>
</tr>
</thead>
</table>

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).

### 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 by the degree of respiratory depression, which varies from bradypnoea to apnoea.

**Treatment:**

<table>
<thead>
<tr>
<th>Hypoventilation or apnoea:</th>
<th>O₂ administration, assisted or controlled respiration.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory depression:</td>
<td>Specific narcotic antagonist (e.g. naloxone). This does not preclude the use of immediate countermeasures.</td>
</tr>
<tr>
<td>Muscular rigidity:</td>
<td>Intravenous neuromuscular blocking agent.</td>
</tr>
</tbody>
</table>

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.

### 5.1. Pharmacodynamic properties

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.

### 5.2. Pharmacokinetic properties

Some pharmacokinetic parameters for fentanyl are as follows:

- Urinary excretion = 8%
- Bound in plasma = 80%
- Clearance (ml/min/kg) = 13±2
Volume of distribution (litres/kg) = 4.0±0.4
Estimates of terminal half-life range from 141 to 853 minutes.

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.

**Pharmaceutical Particulars**

6.1. List of Excipients

Sodium Chloride
Dilute Hydrochloric Acid
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

2 Years

6.4. Special precautions for storage

Protect from light.
Do not store above 25°C
Keep in outer carton.
Keep out of the reach and sight of children

6.5. Nature and Contents of Container

50ml clear Type I glass vial with Type I rubber stopper and aluminium crimp seal.

6.6. Instruction for Use/Handling

Single use only.
Discard any remaining solution in the appropriate manner.

**Administrative Data**

7. **Marketing Authorisation Holder**

   Aurum Pharmaceuticals Ltd  
   Bampton Road  
   Harold Hill  
   Romford  
   Essex  
   RM3 8UG  
   United Kingdom

8. **Marketing Authorisation Number**

   PL 12064/0078

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

   24/03/2009

10. **DATE OF REVISION OF THE TEXT**

    29/10/2010