Product Summary

1. Trade 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. (100 micrograms/2ml and 500micrograms/10ml total volume)
For excipients, see Section 6.1.

3. Pharmaceutical Form
Solution for injection
(Colorless solution)

Clinical Particulars

4.1. Therapeutic Indications
Fentanyl 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.
- In the treatment of severe pain, such as the pain of myocardial infarction.

4.2. Posology and Method of Administration
Method of administration:
Intravenous administration either as a bolus or by infusion.
Intramuscular 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).

Fentanyl, by the intravenous route, can be administered to both adults and children. The dose should be individualised according to age, bodyweight, physical status, underlying pathological condition, use of other drugs and type of surgery and anaesthesia.

The usual dosage regimen is as follows:

<table>
<thead>
<tr>
<th>Adults</th>
<th>Initial</th>
<th>Supplemental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Respiration</td>
<td>50-200 micrograms</td>
<td>50 micrograms</td>
</tr>
<tr>
<td>Assisted Ventilation</td>
<td>300-3500 micrograms</td>
<td>100-200 micrograms</td>
</tr>
</tbody>
</table>
Paediatric population

Children aged 12 to 17 years old—follow adult dosage:

Children aged 2 to 11 years old:

<table>
<thead>
<tr>
<th>Children Age</th>
<th>Initial Supplemental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Respiration 2-11 years</td>
<td>1-3 micrograms/kg</td>
</tr>
<tr>
<td>Assisted Ventilation 2-11 years</td>
<td>1-3 micrograms/kg</td>
</tr>
</tbody>
</table>

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).

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/minute for the first 10 minutes followed by an infusion of approximately 0.1 micrograms /kg/minute. 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 post-operatively, the infusion should be terminated at about 40 minutes before the end of surgery.

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

Fentanyl 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 the initial dose should be taken into account in determining supplemental doses.

4.3 Contraindications

1) Known intolerance to fentanyl or other morphinomimetics.
2) Respiratory depression and obstructive airways disease.
3) Concurrent administration with monoamine oxidase inhibitors (including moclobemide) or within 2 weeks of their discontinuation.

4.4 Special warnings and precautions for use
Fentanyl is controlled under the Misuse of Drugs Act 1971 (Schedule 2). Fentanyl should be used with great caution in patients with acute alcoholism, head injuries and raised intracranial pressure.

Tolerance and dependence may occur.

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 (eg 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.

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.

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

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.

Muscular rigidity (morphine-like effect) may occur.

Rigidity, which may also involve the thoracic muscles, can be avoided by the following measures:
- slow intravenous 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 the dosage in the elderly and debilitated patients (see 4.2 Posology and Method of Administration).

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.

Drug withdrawal symptoms may occur on discontinuation of treatment. Withdrawal symptoms may also occur in neonates of opioid-dependent mothers.

Administration of opioid analgesics during labour may cause respiratory depression in the perinatal child and may cause gastric stasis and increase the risk of inhalation pneumonia in the mother.

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 carbon dioxide, 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

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

Monoamine Oxidase Inhibitors
The concurrent use of MAOIs (including moclobemide) is contra-indicated (see 4.3 Contra-indications) as they may result in an unpredictable, severe and occasionally fatal reaction, consisting of excitation, sweating, rigidity, hypertension, respiratory depression, seizures and hyperpyrexia.

**CNS depressants**

CNS depressants such as alcohol, hypnotics, anxiolytics and sedatives, barbiturates, neuroleptics, halogenic gases and tricyclic antidepressants may enhance or prolong the respiratory depression effects of fentanyl as well as increasing the general depressant effects. When patients have received CNS-depressants, the dose of fentanyl required may, therefore, be less than usual. Similarly, the dose of other CNS-depressant drugs should be reduced following the administration of fentanyl.

**Opioid agonists**

Additive effects on CNS depression, respiratory depression and hypotension can occur with concomitant use of opioid agonist analgesics. However, buprenorphine may antagonise the analgesic effect of previously administered opioids and concomitant use is generally not recommended.

**Muscle relaxants**

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

**Anti-virals**

Oral ritonavir reduced the clearance of intravenous fentanyl by two thirds; however, peak plasma concentrations after a single dose of intravenous 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.

**Anti-fungals**

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

**Histamine H2 antagonists**

Cimetidine can reduce the metabolism of opioid analgesics resulting in increased plasma concentration.

**Neuroleptics**

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

**Anti-emetics**

The effects of metoclopramide or domperidone on gastro-intestinal activity is antagonised by opioid analgesics.

**Effects on other drugs**

The plasma levels of ciprofloxacin may be reduced in the presence of opiate premedicants. Plasma levels of mexiletine may also be reduced in the presence of opioid analgesics.

4.6  **Pregnancy and lactation**

Although no teratogenic or acute embryotoxic effects have been observed in animal experiments, insufficient data are available to evaluate any harmful effects in humans. As with other drugs, possible risks should be weighed against 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 administered, an antidote for the child should always be at hand. The mother is also at risk of gastric stasis and inhalation pneumonia if an opioid analgesic is administered during labour. Withdrawal symptoms may occur in neonates of dependent mothers.

Lactation: Fentanyl may enter breast milk and although only low levels may occur, it is recommended that breast feeding is not initiated within 24 hours of treatment.

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, the following table displays ADRs that have been reported with the use of Fentanyl IV from either clinical trials or post marketing 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); and not known (cannot be estimated from the available clinical trial data).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reactions</th>
<th>Frequency Category</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System Disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, Urticaria)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
<td>Euphoric Mood</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Dyskinesia; Sedation; Dizziness</td>
<td></td>
<td>Insomnia, Agitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Convulsions; Loss of Consciousness; Myoclonus</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
<td>Visual Disturbance</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Bradycardia; Tachycardia; Arrhythmia</td>
<td></td>
<td>Cardiac Arrest, Asystole</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>Hypotension; Hypertension; Vein Pain</td>
<td></td>
<td>Phlebitis; Blood Pressure Fluctuation</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>Laryngospasm; Bronchospasm; Apnoea</td>
<td></td>
<td>Hyperventilation; Hiccups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Respiratory Depression</td>
</tr>
</tbody>
</table>
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:**
Treatment is supportive.
If there is hypoventilation or apnoea, a patent airway must be established, oxygen should be given and the requirement for assisted or controlled ventilation should be assessed. Narcotic antagonists may be required if there is evidence of significant respiratory or cardiovascular depression. Naloxone should be given intravenously as soon as possible and repeated every 2-3 minutes if necessary (refer to naloxone product literature for details). Intravenous neuromuscular blocking agents may be given if muscular rigidity is present. Intravenous fluids and other supportive measures should be employed as indicated.

### Pharmacological Properties

#### 5.1. Pharmacodynamic Properties

Pharmacotherapeutic group:
- Analgesics – derivatives. ATC code: N02A B03
- General Anaesthetics. ATC code: N01A H01

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 intravenous dose of 0.5-1 mg/70 kg body weight 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 release of histamine and 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.

Fentanyl is rapidly absorbed following intramuscular injection, however, there are wide inter-individual variations. Fentanyl is rapidly and extensively metabolised in the liver mainly by CYP3A4 enzymes. The metabolites are considered to be inactive. Fentanyl crosses the placenta and is excreted in breast milk.

5.3. Preclinical Safety Data

There is no preclinical data of relevance to the prescriber additional to those already included in other sections of the SPC.

Pharmaceutical Particulars

6.1. List of Excipients

- Sodium chloride
- 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

24 months

6.4. Special Precautions for Storage

Do not store above 25°C.
Keep the container in the outer carton.

6.5. Nature and Contents of Container
2ml and 10ml clear glass (Ph. Eur. Type I) ampoules containing 2ml or 10ml solution for injection.
Pack size: 10 ampoules per carton.

6.6. Instruction for Use/Handling

Fentanyl is controlled under the Misuse of Drugs Act 1971 (Schedule 2).

7 Marketing authorisation holder

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Ruislip
Middlesex
HA4 7TL
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8. Marketing Authorisation Number

PL 17507/0024

9. Date of First Authorisation/Renewal of Authorisation

20 September 2002

10 DATE OF REVISION OF THE TEXT

30/12/2011