Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fentanyl-Hameln 50 microgram/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains
Fentanyl citrate 0.0785 mg
Equivalent to Fentanyl 0.050 mg

I ampoule with 2 ml solution for injection contains
Fentanyl citrate 0.157 mg
Equivalent to Fentanyl 0.10 mg

I ampoule with 10ml solution for injection contains
Fentanyl citrate 0.785 mg
Equivalent to Fentanyl 0.50 mg

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

The product is a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Fentanyl is a short acting opioid used
- for neurolept analgesia and neurolept anaesthesia
- as an analgesic component in general anaesthesia with intubation and ventilation of the patient
- for analgesic treatment in the intensive care unit in patients under the condition of assisted ventilation

4.2 Posology and method of adminstration

The dose of fentanyl is adjusted individually according to age, body weight, physical status, pathological condition and co-medication as well as type of surgical procedure and type of anaesthesia.
For guidance, the following dosage schedules are proposed. For other, special dosage recommendations please refer to the literature.

Neurolept analgesia and neurolept anaesthesia

For neurolept analgesia adults normally will require an initial dose of 50 to 100 microgram (0.7-1.4 microgram/kg) fentanyl slowly injected intravenously in a combination with a neuroleptic (preferably Droperidol). If necessary a second dosage of 50 to 100 microgram (0.7-1.4 microgram/kg) fentanyl can be given 30 to 45 minutes after the initial dose.

For neurolept anaesthesia under the condition of assisted ventilation adults in general will require an initial dose of

200 to 600 microgram (2.8-8.4 microgram/kg) fentanyl slowly injected intravenously in combination with a neuroleptic (preferably Droperidol). The dosage depends on the duration and the severity of the surgical procedure and on the medication used for general anaesthesia. For maintenance of anaesthesia additional doses of 50 to 100 microgram (0.7-1.4 microgram/kg) fentanyl can be given every 30 to 45 minutes. The time intervals and doses of these additional administrations have to be adjusted according to the course of the surgical procedure.

Analgesic component in general anaesthesia

Adults:
For induction: If fentanyl is used as an analgesic component in general anaesthesia with intubation and ventilation of the patient, in adults initial fentanyl doses of 70 – 600 microgram (1-8.4 microgram/kg) can be applied as adjunct to general anaesthesia.

For maintenance of analgesia during general anaesthesia additional doses of 25-100 microgram (0.35-1.4 microgram/kg) fentanyl are to be injected subsequently. The time intervals and the dosage are to be adjusted according to the course of the surgical procedure.

Children:
In children of 2 to 12 years of age, a single analgesic dose of 1-3 microgram fentanyl/kg body weight is used, for example in combination with inhalational anaesthesia. If only nitrous oxide is used in combination with fentanyl, the initial dose is in the range of 5 – 10 microgram fentanyl/kg body weight.

For maintenance of analgesia during general anaesthesia, additional doses of 1.25 microgram/kg fentanyl may be given, depending on the course of the operation.

Pain management in the intensive care unit

For use in pain management of ventilated patients in the intensive care unit the dosage of fentanyl has to be adjusted individually, depending on the course of pain and on concomitant medication. Normally the initial doses are in the range of 50 to 100 microgram i.v. (0.7-1.4 microgram/kg), but can be titrated higher if necessary. The initial dose normally is followed by repeated injections, of totally up to 25 to 125 microgram fentanyl per hour (0.35-1.8 microgram/kg/h).

Dosage in elderly and weak patients

The initial dose in elderly and weak patients should be reduced. The effect of the initial dose should be taken into account for the determination of supplemental doses.

Dosage in patients with chronic opioid medication

In patients with chronic opioid medication or with a known history of opioid abuse a higher dosage of fentanyl may be necessary.

Dosage in patients with additional diseases

In patients with one of the following diseases the intended dosage of fentanyl should be titrated very carefully:
- uncompensated hypothyreosis
- lung diseases, especially those with reduced vital capacity
- alcohol abuse
- impaired hepatic function
- impaired renal function

Caution is also required if fentanyl is to be administered to patients with adrenal insufficiency, prostatic hypertrophy, porphyria and bradyarrhythmia.

In all these conditions, except alcohol abuse, the dose may have to be reduced. In alcohol abuse, the dose may have

to be either reduced or increased.

In these patients a prolonged postoperative monitoring period is recommended.

Method and duration of administration

Fentanyl should be administered slowly (1-2 minutes) by intravenous injection (see also “Special warnings and precautions for use”), if applicable in combination with a neuroleptic (preferably Droperidol).
In anaesthesia the duration of administration depends on the time course of the surgical procedure. In pain management of intensive care patients the physician has to determine the duration of administration according to the intensity and the time course of pain.

4.3 Contraindications

Fentanyl should not be used in patient with:

- Known hypersensitivity to fentanyl, other morphinomimetics or to any of the excipients.
- Respiratory depression without artificial ventilation.
- A co-medication of MAO inhibitors or within two weeks after cessation of administration of MAO inhibitors.
- Increased intracranial pressure and brain trauma
- Hypovolaemia and hypotension
- Myasthenia gravis

4.4 Special warnings and special precautions for use

Intravenous fentanyl should only be used by a trained anaesthetist in hospitals or other locations with facilities for intubation and assisted ventilation.

The vital functions of the patient have to be monitored routinely. This also applies to the postoperative period. Fentanyl has a strong dose-dependent depressing effect on respiration which may be prolonged especially in the elderly. In neonates, respiratory depression is to be expected already after small doses. Generally, the risk of a delayed respiratory depression has to be considered. In cases of emergency appropriate instruments and medicinal product have to be available.

In isolated cases, in epileptic patients after a rapid and high dosage fentanyl application (19-36 microgram/kg) of 2 to 5 minutes duration, an electrical seizure activity was recorded electrocorticographically even in healthy brain regions. An impact on the intraoperative electrocorticographic focus localisation after lower fentanyl doses is not known until now.

Muscle rigidity may occur which may also lead to respiratory depression. The incidence of this rigidity may be decreased by slow intravenous administration. The reaction can be treated by controlled ventilation and when necessary by administration of a muscle relaxant.
Non-epileptic (myo)clonic reactions may occur.

After fentanyl an increase of the bile duct pressure and in isolated cases a spasm of the Sphincter of Oddi can be observed: This has to be taken into account during intraoperative diagnostic procedure in bile duct surgery and in pain management of intensive care patients.

As all other opioids, fentanyl can have an inhibitory effect on intestinal motility. This should be considered in the pain management of intensive care patients with inflammatory or obstructive intestinal diseases.

Bradycardia and asystolia may occur when the patient has received an insufficient dose of an antimuscarinic agent or when fentanyl is combined with non-vagolytic muscle-relaxants. Bradycardia is treated with atropine.

Opioids may cause hypotension, especially in hypovolaemic patients and in patients with decompensated heart

failure. Induction doses should be adapted and administered slowly, in order to prevent cardiovascular depression. Appropriate measures should be taken to maintain a stable arterial pressure.

In neonates, there is a sufficient likelihood of developing a withdrawal syndrome after treatment of more than 5 days or a total dose of >1.6mg/kg.

The use of fast bolus injections of fentanyl should be avoided.

Patients with hepatic failure should be dosed carefully because of the probably disturbed metabolism.

Patients with renal insufficiency should be carefully checked on the symptoms of fentanyl toxicity. As a result of dialysis the volume of distribution of fentanyl may be altered, which can influence the serum concentrations.

When fentanyl is given together with droperidol, the user should be familiar with the specific properties and undesirable effects of both medications.

4.5 Interaction with other medicinal products and other forms of interaction

Agents like barbiturates, benzodiazepines, neuroleptics, volatile anaesthetics containing halogens or other medicaments that have a non-selective depressant effect on the central nervous system (i.e. alcohol), may augment the respiratory depression caused by opioids. When such medicaments have been administered to patients, the required dose of fentanyl will be lower than usual. This should also result in lowering the dose of other medicaments which have a depressant effect on the central nervous system, when these agents are administered after fentanyl is given.

With higher doses of fentanyl the concomitant application of nitrous oxide or even small doses of diazepam can lead to an impairment of cardiovascular function.

The combined application of fentanyl and midazolam can lead to a decrease in blood pressure.

Simultaneous application of droperidol can lead to a fall in blood pressure, but in some cases also a rise in blood pressure was observed. The pulmonary arterial pressure can be decreased. Furthermore, shivering, restlessness and postoperative episodes of hallucinations may occur.

In patients with preceding medication with MAO inhibitors within the last 14 days before opioid administration life-threatening interactions with pethidine on the central nervous system (i.e. agitation, muscle rigidity, hyperpyrexia, convulsions), and the respiratory and circulatory system (i.e. circulatory depression, hypotension, haemodynamic instability and coma) have been observed and cannot be ruled out with fentanyl.

MAO-inhibitors also block the enzymes which metabolise centrally active substances (sedatives, antihistamines, opioids, etc.). As a consequence an intensive and prolonged effect of fentanyl may occur, including respiratory depression.

A preceding administration of cimetidine may lead to increased plasma levels of fentanyl.

Co-administration of clonidine may enhance fentanyl effects and especially prolong fentanyl-induced ventilatory depression.

Vecuronium can cause haemodynamic depression when combined with fentanyl. Significant decreases in heart rate, mean arterial pressure, and cardiac output may occur which are not dependent on the dose of vecuronium.

Bradycardia may develop during the combined application of atracurium and fentanyl.

Fentanyl effects are enhanced and prolonged when combined with baclofen.

Anticonvulsants like carbamazepine, phenytoin, primidone are potent enzyme inducing agents which increase the

metabolism of fentanyl by the liver so that fentanyl is cleared from the body more quickly. A marked increase in the fentanyl requirements should be anticipated in any patient on long-term treatment with these anticonvulsants, but not with sodium valproate.

4.6 Pregnancy and lactation

There are no sufficient clinical data available to evaluate possible risks of the use of fentanyl during pregnancy. For this reason fentanyl should not be used in this period.

It is advised not to use fentanyl during delivery, because fentanyl passes the placenta and may cause respiratory depression in the neonate. In obstetrics, fentanyl may only be used intravenously after clamping the umbilical cord. The placental transfer (fetal: maternal ratio) amounts to 0.44 (1.00:2.27).

Fentanyl passes into breast milk. After the application of fentanyl breast feeding should be stopped for at least 24 hours.

4.7 Effects on ability to drive and use machines

The use of fentanyl may cause a decreased level of reactiveness and concentration.
Patients should be advised that the performance of skilled tasks such as driving or operating machinery may be impaired for a considerable time after administration of fentanyl.

Patients should be accompanied on their way home after discharge and should be instructed to avoid alcohol.

4.8 Undesirable effects

Very common:	>1/10
Common:	>1/100 and <1/10
Uncommon:	>1/1000 and <1/100
Rare:	>1/10 000 and <1/1000
Very rare:	<1/10 000 including isolated cases

Blood and lymphatic system disorders

Rare:	Methaemoglobinemia

Immune system disorders

Rare:	Anaphylaxis

Psychiatric disorders

Very rare:	Administration of fentanyl over a longer period of time may cause the development of tolerance. The development of drug dependence cannot be ruled out.

Nervous system disorders

Very common:	Sedation
Common:	Vertigo, euphoria, nausea, vomiting
Rare:	Cerebral seizures. After infusions of fentanyl of long duration in children movement disturbances, increased sensitiveness.

Eye disorders

Rare:	Miosis, vision disturbances

Cardiac disorders

Common:	Bradycardia
Very rare:	Cardiac arrest

Vascular disorders
Common: Hypotension, especially in hypovolaemic patients
Rare: Orthostatic regulatory disturbances

Respiratory, thoracic and mediastinal disorders
Very common: Respiratory depression
Depending on dosage fentanyl causes respiratory depression up to apnoea lasting normally only a few minutes at low doses, but many hours at high doses. The respiratory depressant effect may last longer than the analgesic effect and may re-occur in the postoperative period. Postoperative monitoring is therefore compulsory.
Common: Thoracic stiffness, possibly resulting in impaired ventilation
Rare: Laryngospasm
Very rare: Pulmonary oedema, bronchospasm

Gastrointestinal disorders
Rare: Constipation, singultus

Hepato-biliary disorders
Rare: Spasm of the sphincter of Oddi.

Skin and subcutaneous tissue disorders
Rare: Pruritus, urticaria

Musculoskeletal, connective tissue and bone disorders
Common: Muscle rigidity, myoclonic movements

Renal and urinary system disorders
Rare: Increased muscle tone of the ureter, urinary retention especially in patients with prostatic hypertrophy.

General disorders and administration site conditions
Rare: Opioid withdrawal symptoms, sweating.

4.9 Overdose

Symptoms
Overdosage of fentanyl expresses itself by prolongation of the duration of the pharmacological effects. Dependent on the individual sensitiveness, the clinical picture is respiratory depression ranging from bradypnoea to apnoea, bradycardia up to asystole, decrease in blood pressure, circulatory failure, coma, seizure-like activity, muscle rigidity of the chest wall, trunk and extremities, and pulmonary oedema.

Treatment of overdose
Hypoventilation should be treated by administration of oxygen and the patient should be ventilated. Respiratory depression should be treated by administration of an opioid antagonist like naloxone. The usual initial naloxone dose amounts 0.4 to 2mg. If no effect can be seen, this dose may be repeated every 2 to 3 minutes up to reversal of respiratory depression or awakening. Since the respiratory depressant effect of fentanyl may last longer than the antagonistic effect, repeated doses of naloxone may be appropriate.

Ventilatory problems caused by muscle rigidity can be diminished or abolished by application of a peripherally acting muscle relaxant. The patient should be monitored carefully. Normal body temperature and balanced fluid volumes should be ensured. In the case of severe and persistent hypotension, hypovolaemia should be considered, which can be compensated by parenteral fluid therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid analgesics
ATC- code: N01AH01

Fentanyl is a potent opioid analgesic which may be used as an analgesic supplement with general anaesthesia or as an anaesthetic agent alone.
Fentanyl possesses μ-agonistic properties. The agonistic behaviour to δ- and κ-receptors is comparable to morphine. A dose of 100 microgram (2ml) has an analgesic action which is comparable with 10 mg morphine.

Fentanyl has a rapid onset of action. The maximum analgesic effect and the depressant action on the respiration take place within a few minutes.
The average duration of action of the analgesic effect is about 30 minutes after a single bolus injection of 100 microgram. The level of analgesia is dose related and may be adjusted to the pain level of the surgical procedure.

Fentanyl exhibits relatively small cardio circulatory effects but has a strong depressive effect on respiration. Stress induced hormonal changes are not reliably suppressed by fentanyl. An increase in blood pressure due to intraoperative pain stimuli may occur in spite of high dose fentanyl treatment.

Depending on dosage and rate of injection fentanyl may cause muscle rigidity, euphoria, miosis and bradycardia. Intradermal tests and serum determinations of histamine in humans, as well as in-vivo tests in dogs, showed that clinically significant histamine release after fentanyl application is rarely observed.

All effects of fentanyl can be antagonised by specific opioid-antagonists like naloxone.

5.2 Pharmacokinetic properties

After intravenous injection the fentanyl plasma concentrations decrease rapidly. The disposition of fentanyl is triphasic with half-lifes of about 1 minute, 15 minutes and 6 hours. Fentanyl has a volume of distribution of the central compartment of about 15 litres and a total volume of distribution of about 400 litres.

Especially in elderly patients or after repeated administration, half-lifes may be prolonged. Secondary peak plasma levels may occur.
Fentanyl is bound to plasma proteins for 80 – 85%.

Fentanyl is metabolised rapidly, mainly in the liver, mainly by oxidative N-desalkylation. The clearance is about 0.5 1/hour/kg. About 75% of the administered dose is eliminated within 24 hours. Only 10% of the dose is excreted as intact substance.

5.3 Preclinical safety data

Similar effects as previously described for other opioids were observed in repeated dose toxicity studies up to 4 weeks.

Animal studies have revealed a reduced fertility in female rats as well as embryomortality, although no signs of teratogenicity have occurred.

Mutagenicity studies in bacteria and rodents revealed no mutagenic potential of fentanyl. As well as other opioids fentanyl showed mutagenic effects in vitro in mammalian cells. These effects were induced only in very high concentrations. Therefore fentanyl is not considered to pose a genotoxic hazard to patients.
Long-term carcinogenicity studies were not performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection
Hydrochloric acid or sodium hydroxide for pH adjustment

6.2 Incompatibilities

This medicinal product must not be diluted with other solutions for parenteral use than those mentioned in section 6.6 Instructions for use and handling.

Compatibility must be checked before administration, if intended to be mixed with other drugs.

Fentanyl citrate is reportedly physically incompatible with pentobarbital sodium, methohexital sodium, thiopental sodium and nafcillin.

6.3 Shelf Life

Shelf-life before first opening:
3 years.

Shelf-life after first opening and/or dilution:
From the microbiological point of view, the solutions or dilutions 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 normally 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

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

6.5 Nature and contents of container

5 (10) ampoules made of colourless glass, type I, containing 2 or 10ml solution.

6.6 Instructions for use and handling

Use finger protection when opening an ampoule.

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

The product can be used either undiluted or diluted. Dilution ranges tested with 0.9% sodium chloride and 5% glucose solutions are 1:1 and 1:25. Hence the maximal dilution must not exceed 1 part fentanyl with 25 parts 0.9% sodium chloride or 5% glucose solutions.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 971/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th September 2000
Date of last renewal: 16th February 2004

10 DATE OF REVISION OF THE TEXT

May 2004