SUMMARY OF PRODUCT CHARACTERISTICS

hameln

Fentanyl 50 micrograms/ml solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Fentanyl 50 micrograms/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COM-POSITION

1 ampoule with 10 ml solution for injection contains

Fentanyl citrate 0.785 mg

equivalent to fentanyl 0.50 mg.

Excipient with known effect:

Fentanyl 50 micrograms/ml solution for injection contains 3.5 mg sodium per millilitre solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

The product is a clear, colourless solution with a pH of 5.0 - 7.5.

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 administration

Posology

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).

The dosage 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.

Adults

The usual dosage regimen for adults by intravenous injection is as follows:

	Initial	Supplemental
Spontaneous Respiration	50-200* micrograms	50 micrograms
Assisted Ventilation	300-3500 micrograms (up to 50 micrograms/kg)	100-200 micrograms

*Doses in excess of 200 micrograms are for use in anaesthesia only as significant respiratory depression develops.

Fentanyl 50 micrograms/ml solution for injection may also be given as an infusion.

In ventilated patients, a loading dose of 1 microgram/kg/minute for the first 10 minutes is followed by an infusion of approximately 0.1 microgram/kg/minute.

Alternatively, the loading dose may be given as a bolus. Infusion rates should be titrated to individual patient response and rates of up to 3 microgram/kg/minute have been used in cardiac surgery. Infusion should be stopped about 40 minutes before the end of surgery unless artificial ventilation is to be continued post-operatively.

For spontaneously respirating patients, lower infusion rates of 0.05 0.08 microgram/kg/minute are necessary.

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 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.

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 Paediatric population

Children aged 12 to 17 years should follow the recommended adult dose schedule.

For children aged 2 to 11 years the usual dosage regimen is recommended as follows:

	Age in years	Initial dose in micrograms/kg body weight	Supplemental dose in micrograms/kg body weight
Spontaneous Respiration	2-11	1-3	1-1.25
Assisted Ventilation	2-11	1-3	1-1.25

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).

Dosage in elderly and debilitated patients

As with other opioids, the initial dose should be reduced in the elderly (>65 years of age) and debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.

Obese patients

In obese patients there is a risk of overdosing if the dose is calculated based on body weight. Obese patients should have dosage calculated according to their estimated lean body mass.

Renal Impairment

In patients with renal impairment reduced dosing of fentanyl should be considered and these patients should be observed carefully for signs of fentanyl toxicity.

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

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 of administration

Intravenous administration either as a bolus injection or by infusion.

For instructions on dilution of the medicinal product before administration, see section 6.6.

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

By intravenous injection, Fentanyl should be administered slowly over 1 - 2 minutes (see also section 4.4), 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 patients with

- hypersensitivity to the active substance, other morphino-mimetics or to any of the excipients listed in section 6.1.
- 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 precautions for use

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

Respiratory depression

As with all potent opioids, respiratory depression is dose related and can be reversed by a specific narcotic antagonist such as naloxone, but additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist. Profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the postoperative period. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and narcotic antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's responses to CO_2, thus affecting respiration postoperatively.

The effect on respiration may be prolonged especially in the elderly. In neonates, respiratory depression is to be expected after small doses.

In isolated cases, in epileptic patients after a rapid and high dosage fentanyl application (19 - 36 microgram/kg) of 2 to 5 minutes duration, 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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs

Concomitant use of Fentanyl and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Fentanyl concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Nervous system disorders

- Induction of muscle rigidity, which may also involve the thoracic muscles, can occur, but can be avoided by the following measures: slow IV injection (ordinarily sufficient for lower doses), premedication with benzodiazepines and the use of muscle relaxants.
- Non-epileptic (myo)clonic movements can occur.

Biliary disorders

As with other opioids, due to anti-cholinergic effects, administration of fentanyl may lead to an increase of the bile duct pressure and, in isolated cases, spasm of the Sphincter of Oddi might be observed. This has to be taken into account during intraoperative diagnostic procedures in bile duct surgery and in pain management of intensive care patients.

Intestinal motility

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.

Cardiovascular disorders

Bradycardia, and possibly cardiac arrest can occur if the patient has received an insufficient amount of anti-cholinergic, or when fentanyl is combined with non-vagolytic muscle-relaxants. Bradycardia can be treated with atropine.

Opioids may induce 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 to maintain a stable arterial pressure should be taken.

The use of rapid bolus injections of fentanyl 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 short-lasting reduction of the cerebral perfusion pressure.

Drug dependence and potential for abuse

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Risks are increased in patients with a personal history of substance abuse (including drug or alcohol abuse or addiction).

Withdrawal syndrome

Repeated administration at short term intervals for prolonged periods may result in the development of withdrawal syndrome after cessation of therapy, which may manifest by the occurrence of the following side effects: nausea, vomiting, diarrhoea, anxiety, chills, tremor, and sweating.

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

Neonatal withdrawal syndrome

If women receive long-term opioids during pregnancy, there is a risk that their newborns will develop neonatal withdrawal syndrome (see section 4.6).

Opioid-induced hyperalgesia

Opioid-induced hyperalgesia (OIH) is a paradoxical response to an opioid (especially in high doses or with chronic use) in which pain perception is increased despite stable or increased opioid exposure. It is different from tolerance, which requires higher doses of opioid to achieve the same analgesic effect or to treat recurrent pain. OIH may take the form of increased pain intensity, more generalised pain (i.e. less localised pain), or pain from normal (i.e. non-painful) stimuli (allodynia) with no evidence of disease progression. If OIH is suspected, the opioid dose should be reduced or tapered if possible.

Concomitant administration with neuroleptics

If fentanyl is administered with a neuroleptic, such as droperidol, the user should be familiar with the special properties of each drug, particularly the difference in duration of action. When such a combination is used, there is a higher incidence of hypotension. Neuroleptics can induce extrapyramidal symptoms that can be controlled with anti-Parkinson agents.

Use in special population groups

- It is recommended to reduce the dosage in the elderly and in debilitated patients. Opioids should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism; pulmonary disease; decreased respiratory reserve; alcoholism; or impaired hepatic or renal function. Such patients also require prolonged post-operative monitoring.
- 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.
- Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses (see also Drug dependence and potential for abuse, abuse).

Paediatric population

Techniques that involve analgesia in a spontaneously 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.

Serotonin Syndrome

Caution is advised when fentanyl is coadministered with drugs that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with drugs which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose.

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperoreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, rapid discontinuation of fentanyl should be considered.

Sodium content

This medicinal product contains 3.5 mg sodium per millilitre solution, equivalent to 0.2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Other Drugs on Fentanyl

Sedative medicines such as benzodiazepines or related drugs:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Other Central Nervous System (CNS) depressants

Drugs such as barbiturates, neuroleptics, general anaesthetics, and other, non-selective depressants (e.g. alcohol) may enhance or prolong the respiratory depression of fentanyl. When patients have received such drugs, the dose of fentanyl required will be less than usual. Concomitant use with fentanyl in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death.

Cytochrome P450 3A4 (CYP3A4) inhibitors

Fentanyl, a high clearance drug, is rapidly and extensively metabolized mainly by CYP3A4. When fentanyl is used, the concomitant use of a CYP3A4 inhibitor may result in a decrease in fentanyl clearance. With single-dose fentanyl administration, the period of risk for respiratory depression may be prolonged, which may require special patient care and longer observation. With multiple-dose fentanyl administration, the risk for acute and/or delayed respiratory depression may be increased, and a dose reduction of fentanyl may be required to avoid accumulation of fentanyl. Oral ritonavir (a potent CYP3A4 inhibitor) reduced the clearance of a single intravenous fentanyl dose by two thirds, although peak plasma concentrations of fentanyl were not affected. However, itraconazole (another potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of a single intravenous fentanyl dose. Co-administration of other potent or less potent CYP3A4 inhibitors, such as voriconazole or fluconazole, and fentanyl may also result in an increased and/or prolonged exposure to fentanyl.

Monoamine oxidase inhibitors (MAOIs)

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.

It is usually recommended to discontinue MAO-inhibitors 2 weeks prior to any surgical or anaesthetic procedure. However, several reports describe the uneventful use of fentanyl during surgical or anaesthetic procedures in patients on MAO-inhibitors.

Serotonergic Drugs

Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Other medications

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.

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.

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.

Effect of Fentanyl on Other Drugs

Following the administration of fentanyl, the dose of other CNS-depressant drugs should be reduced (see above). This is particularly important after surgery, because profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the postoperative period. Administration of a CNS depressant, such as a benzodiazepine, during this period may disproportionally increase the risk for respiratory depression (see above).

Plasma concentrations of etomidate increased considerably (by a factor 2-3) when combined with fentanyl. The total plasma clearance and volume of distribution of etomidate are decreased by a factor 2 to 3 without a change in half-life when administered with fentanyl.

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

Pregnancy

There are no adequate data from the use of fentanyl in pregnant women. Fentanyl can cross the placenta in early pregnancy. Therefore, fentanyl must only be used during pregnancy when considered necessary and following a careful assessment of the potential benefits and risks of treatment.

Chronic use of opioids during pregnancy can cause drug addiction in the newborn, which may lead to neonatal withdrawal syndrome.

Administration (IM or IV) during childbirth (including caesarean section) is not recommended because fentanyl crosses the placenta and because the foetal respiratory centre is particularly sensitive to opiates. However, if fentanyl is administered, assisted ventilation equipment for the mother and infant and an opioid antagonist for the child should always be at hand.

Breast-feeding

Fentanyl is excreted into human milk. Therefore, nursing is not recommended for 24 hours following the administration of this drug. The risk/benefit of breastfeeding following fentanyl administration should be considered.

Fertility

There are no clinical data on the effects of fentanyl on fertility. Studies in animals have shown some reproductive toxicity (see Section 5.3, Preclinical safety data). The potential risk for humans is unknown.

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 only drive or operate a machine if sufficient time has elapsed after the administration of fentanyl.

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

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 tables display 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
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data

System Organ Class	Very Common	Common	Uncommon	Not known
Blood and lymphatic system disorders				Methaemoglobinaemia
Immune system disorders				Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria
Psychiatric disorders			Euphoric Mood	Delirium, 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		Dyskinesia Sedation Dizziness	Headache	Convulsions, Loss of consciousness, Myoclonus, Vertigo, Horner's syndrome, Loss of gag reflex and swallowing ability
Eye disorders		Visual disturbance		
Cardiac disorders		Bradycardia, Tachycardia, Arrhythmia		Cardiac arrest
Vascular disorders		Hypotension, Hypertension, Vein pain	Phlebitis, Blood pressure fluctuation	
Respiratory, thoracic and mediastinal disorders		Laryngospasm, Bronchospasm, Apnoea	Hyperventilation, Hiccups	Respiratory depression, Pulmonary oedema
Gastrointestinal disorders	Nausea, Vomiting			
Hepatobiliary disorders				Spasm of the sphincter of Oddi
Skin and subcutaneous tissue disorders		Dermatitis allergic		Pruritus, Hyperhydrosis
Musculoskeletal and connective tissue disorders	Muscle rigidity including thoracic muscles			
Renal and urinary disorders				Increased muscle tone of the ureter, Urinary retention, especially in patients with prostatic hypertrophy
General disorders and administration site conditions			Chills, Hypothermia	Drug withdrawal syndrome (see section 4.4)
Injury, poisoning and procedural complications		Confusion postoperative	Airway complication of anaesthesia, Agitation postoperative	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Signs and Symptoms

An overdosage of fentanyl manifests itself as an extension of its pharmacologic actions. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies 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

In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific narcotic antagonist, such as naloxone, should be used as indicated to control respiratory depression. This does not preclude the use of more immediate countermeasures.

The usual initial naloxone dose amounts 0.4 to 2 mg. If no effect can be seen, this dose may be repeated every 2 to 3 minutes up to reversal of respiratory depression or awakening. The respiratory depression may last longer than the effect of antagonist; additional doses of the latter may therefore be required.

If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration.

The patient should be carefully observed; body warmth and adequate fluid intake should be maintained. If hypotension is severe or if it persists, the possibility of hypovolemia should be considered, and, if present, should be controlled with appropriate parenteral fluid administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioid anaesthetics

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 (2 ml) 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-life values 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-lives 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 l/hour/kg. About 75 % of the administered dose is eliminated within 24 hours. Only 10 % of the dose is excreted as intact substance.

Renal impairment

Data obtained from a study administering IV fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive fentanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.2 Posology and method of administration).

Obese Patients

An increase in clearance of fentanyl is observed with increased body weight. In patients with a BMI>30, clearance of fentanyl increases by approximately 10% per 10 kg increase of the fat free mass (lean body mass).

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 injections

Hydrochloric acid or sodium hydroxide for pH adjustment

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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 nafcilline.

6.3 Shelf life

Shelf life before first opening

3 years

Shelf life after dilution

Chemical and physical in-use stability of the dilutions (see section 6.6) has been demonstrated for 24 hours at 25°C.

From the microbiological point of view, the 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 the ampoules in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other 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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Inselstraße 1
31787 Hameln
Germany

8. MARKETING AUTHORISATION NUMBER

148203/03

9. DATE OF FIRST AUTHORISATION

12.08.2004

10. DATE OF REVISION OF THE TEXT

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