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SCHEDULING STATUS

S6

PROPRIETARY NAMES AND DOSAGE FORM

Fentanyl Fresenius 500 mcg/10 ml

Fentanyl Fresenius 100 mcg/2 ml

Injection

COMPOSITION

Active ingredients

Each 10 ml contains the equivalent of 500 µg fentanyl base as fentanyl citrate.

Each 2 ml contains the equivalent of 100 µg fentanyl base as fentanyl citrate.

Excipients: nitrogen, water for injection

Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A 2.7 Narcotic analgesics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Fentanyl is a narcotic analgesic of the phenylpiperidine class.

Following intravenous injection the effect begins almost immediately although maximum analgesia may not occur for several minutes, and the average duration of action is 30 to 60 minutes.

Fentanyl acts as an agonist, binding with stereospecific and saturable sites in the brain and other tissues. These binding sites are widely but unevenly distributed throughout the central nervous system with the highest concentration in the limbic system, thalamus, striatum, hypothalamus, midbrain and spinal cord.

Pharmacokinetic properties

Fentanyl is highly lipid-soluble such that following intravenous injection; it rapidly crosses the highly perfused organs such as the lungs, kidneys and blood-brain barrier.

Approximately 80 % of fentanyl is bound to plasma proteins. This is reflected in the half-life for equilibration between the plasma and cerebrospinal fluid of approximately 5 minutes for fentanyl. The levels in plasma and cerebrospinal fluid decline rapidly owing to redistribution of fentanyl from highly perfused tissue groups to other tissues, such as muscle and fat. As saturation of less well-perfused tissue occurs, the duration of effect of fentanyl approaches the length of the elimination half-lives of between 3 and 4 hours. Fentanyl undergoes hepatic metabolism and renal excretion. Therefore with the use of higher doses or prolonged infusion, fentanyl becomes longer acting.

Special populations:

Paediatrics

The plasma protein binding of fentanyl in newborns is approximately 62 % which is lower than in adults. The clearance and the volume of distribution are higher in infants and children. This may require dose adjustment for fentanyl.

Adult patients with burns

An increase in clearance up to 44 % together with a larger volume of distribution results in lower fentanyl plasma concentrations. This may require dose adjustment for fentanyl.

INDICATIONS

Fentanyl Fresenius is a narcotic analgesic, which is indicated for use in anaesthesia in combination with the following agents:

a) neuroleptic agents such as droperidol

b) inhalation anaesthetics

c) agents such as benzodiazepines

Fentanyl Fresenius is also indicated for the relief of pain during epidural anaesthesia and postoperative pain.

CONTRAINDICATIONS

Fentanyl Fresenius is contraindicated in the following conditions:

i) respiratory depression, (especially in the presence of cyanosis and excessive bronchial secretion)

and obstructive airway disease,

ii) after biliary tract operations,

iii) acute alcoholism,

iv) head injuries and conditions in which intracranial pressure is raised,

v) an attack of bronchial asthma,

vi) heart failure secondary to chronic lung disease,

vii) patients taking mono-amine oxidase inhibitors or within 14 days of stopping such treatment,

viii) pre-operative use in babies less than one year of age,

ix) convulsive disorders and

x) comatose patients.

WARNINGS AND SPECIAL PRECAUTIONS

Warnings:

A morphine-type drug dependence can occur after prolonged use of **Fentanyl Fresenius.**

Care should be taken when **Fentanyl Fresenius** is given to patients with myasthenia gravis. Opioid analgesics should be given with care to infants, especially neonates. The administration of **Fentanyl Fresenius** during labour may cause respiratory depression in neonates. Babies born to opioid-dependant mothers may suffer withdrawal symptoms.

Fentanyl Fresenius should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, asthma, impaired liver or kidney function, prostatic hyperplasia, shock or hypotension. It should be used with caution in patients with inflammatory or obstructive bowel disorders.

Dosage should be reduced in elderly or debilitated patients.

INTERACTIONS

The depressant effects of **Fentanyl Fresenius** are enhanced by central nervous system depressants such as alcohol, anaesthetics, hypnotics, sedatives, phenothiazine, meprobamate, anxiolytics, tricyclic antidepressants, and antipsychotics. Cyclizine may counteract the haemodynamic benefits of **Fentanyl Fresenius**. The actions of **Fentanyl Fresenius** may in turn affect the activities of other medicines. For instance, their gastrointestinal effects may delay absorption as with mexiletine or may be counteractive

as with cisapride, metoclopramide, or domperidone. Opioid premedicants have been reported to reduce serum concentrations of ciprofloxacin.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

Fentanyl Fresenius crosses the placenta and has been detected in breast milk.

Fentanyl Fresenius is excreted into breast milk and may cause sedation or respiratory depression in breast-fed infants.

DOSAGE AND DIRECTIONS FOR USE

Epidural anaesthesia: 100 micrograms **Fentanyl Fresenius** diluted with 8 ml of 0,9 % sodium chloride injection, administered through an epidural catheter.

Postoperative pain: 50 to 100 micrograms of **Fentanyl Fresenius** may be given intramuscularly, repeated after 1 to 2 hours if necessary.

In anaesthesia where spontaneous respiration is maintained, an initial intravenous dose of the equivalent of 50 to 200 micrograms of **Fentanyl Fresenius** is given, with supplementary doses of 50 micrograms. The initial dose in children is 3 to 5 micrograms per kg body-mass. In anaesthesia with controlled respiration, the initial dose is 300 to 3 500 micrograms **Fentanyl Fresenius** with supplementary doses of 100 to 200 micrograms. The initial dose in children is 10 to 15 micrograms per kg body mass in anaesthesia with controlled respiration.

When **Fentanyl Fresenius** is combined with a neuroleptic agent such as droperidol, a state of neurolept-analgesia is established, during which a variety of diagnostic or minor surgical procedures can be accomplished. Neurolept-analgesia can be converted to neurolept anaesthesia by the concurrent administration of 65 % nitrous oxide in oxygen. Droperidol and **Fentanyl Fresenius** may be used alone or together, the dose of each being adjusted individually.

Droperidol has a prolonged duration of action (3 to 6 hours) whereas **Fentanyl Fresenius** exerts its analgesic effect for only 30 to 60 minutes. Following induction of neurolept anaesthesia, supplementary doses of **Fentanyl Fresenius** alone

(1 micrograms/kg) may be injected at intervals of approximately 20 minutes.

SIDE EFFECTS

General disorders

Frequency unknown: dry mouth, sweating, facial flushing, headache, hypothermia, decreased libido or potency, muscle rigidity (which can be alleviated by muscle relaxants).

Gastrointestinal disorders

Frequent: nausea, vomiting, constipation

Less frequent: abdominal pain (biliary spasm)

Neurological disorders

Frequent: dizziness, drowsiness, vertigo, respiratory depression

Less frequent: hallucinations, confusion, convulsions

Frequency unknown: restlessness, change of mood, raised intracranial pressure

Renal and urinary disorders

Less frequent: difficulty in micturition

Frequency unknown: ureteric spasm, antidiuretic effect.

Cardiac disorders

Frequent: bradycardia (can be prevented by administration of Atropine), hypotension

Less frequent: circulatory depression which may lead to cardiac arrest

Frequency unknown: tachycardia, palpitations.

Eye disorders

Frequent: miosis

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage produces respiratory depression and hypotension, with circulatory failure and deepening coma. Death may occur from respiratory failure. Toxic doses vary considerably between individuals whilst addicts may tolerate doses well above the average. Pulmonary oedema sometimes associated with opioid overdosage may be countered by positive-pressure respiration.

Rhabdomyolysis progressing to renal failure has been reported in overdosage. The triad of coma, pinpoint pupils and respiratory depression is considered indicative of opioid overdosage; dilatation of the pupils occurs as hypoxia develops.

Treatment:

In addition, the specific antagonist, naloxone hydrochloride is used to counteract, severe respiratory depression and coma. A dose of 400 µg is given intravenously, subcutaneously or intramuscularly, repeated at intervals of 2 to 3 minutes if necessary. In children, a dose of 5 to 10 µg per kg body-mass may be given, while in neonates a dose of 10 µg per kg may be given. Repeated doses may be necessary.

IDENTIFICATION

Fentanyl Fresenius 500 mcg/ 10 ml: Clear, colourless solution in amber glass ampoules.

Fentanyl Fresenius 100 mcg/ 2 ml: Clear, colourless solution in amber glass ampoules.

PRESENTATION

10 ml amber ampoules with a white ring above the neck and packed into blister trays into cardboard cartons in packs of 5.

2 ml amber ampoules with a white ring above the neck and packed into blister trays into cardboard cartons in packs of 10.

STORAGE INSTRUCTIONS

Protect from light.

Store at or below 25 ºC.

Keep out of reach of children.

REGISTRATION NUMBERS

Fentanyl Fresenius 500 mcg/10 ml: X/2.7/260

Fentanyl Fresenius 100 mcg/2 ml: W/2.9/123

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

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6020

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