PROFESSIONAL INFORMATION

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

Pharma-Q Fentanyl 500 µg/10 ml Injection solution for injection

Pharma-Q Fentanyl 100 µg/2 ml Injection solution for injection

Pharma-Q Fentanyl Injection should only be used in facilities where immediate access to life support is available.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pharma-Q Fentanyl 500 µg/10 ml Injection: Each 10 ml contains the equivalent of 500 µg fentanyl base as fentanyl citrate.

Pharma-Q Fentanyl 100 µg/2 ml Injection: Each 2 ml contains the equivalent of 100 µg fentanyl base as fentanyl citrate.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for intravenous injection.

A clear, colourless solution in amber glass ampoules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pharma-Q Fentanyl Injection is indicated:

- for use as an opioid analgesic supplement during intravenous,
- inhalation or regional anaesthesia.
- as a co-induction anaesthetic for intravenous or inhalation anaesthesia.

4.2 Posology and method of administration

Posology

The dosage of Pharma-Q Fentanyl Injection should be individualised according to age, body weight, physical status, underlying pathological conditions, use of other medicines, and type of surgery and anaesthesia.

The effects of the initial dose should be taken into account in determining supplemental doses.

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

USE AS AN ANALGESIC SUPPLEMENT TO INTRAVENOUS OR INHALATION ANAESTHESIA:

Analgesia during anaesthetic induction

1 – 10 µg/kg.

Analgesia during maintenance of anaesthesia

For both balanced anaesthesia and total intravenous anaesthesia (TIVA), dose amounts and the intervals between doses should be adjusted to account for the duration and severity of the surgical procedure.

Bolus administration

0,5 – 10 µg/kg.

Continuous infusion

0,5 – 5 µg/kg/h.

USE AS AN ANAESTHETIC MEDICINE:

When attenuation of the response to surgical stress is especially important, doses of 50 - 100 µg/kg may be administered with oxygen and a muscle relaxant. This technique provides anaesthesia without necessitating the use of additional anaesthetic medicines. In certain

cases, doses of up to 150 µg/kg may be required to produce this anaesthetic effect. Pharma-Q Fentanyl Injection has been used in this fashion for open heart surgery and certain other major surgical procedures for which protection of the myocardium from excess oxygen demand is particularly indicated.

Special populations

Use in the elderly and debilitated patients

The dose should be reduced in the elderly (> 65 years of age) and in 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 the body mass. Obese patients should be dosed based on estimated lean body mass rather than on body mass only.

Renal impairment

In patients with renal impairment reduced dosing of Pharma-Q Fentanyl Injection should be considered and these patients should be observed carefully for signs of fentanyl toxicity (see section 5.2).

Paediatric population

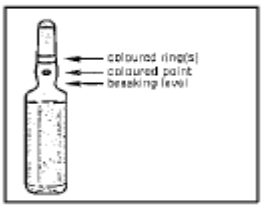
For the induction and maintenance in children aged 2 – 12 years, a reduced dose as low as 1 – 3 µg/kg in divided doses is recommended.

Method of administration

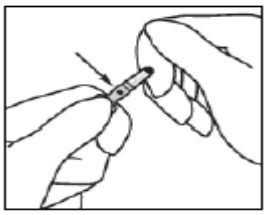
Pharma-Q Fentanyl Injection is administered by the intravenous route.

Instructions for use and handling

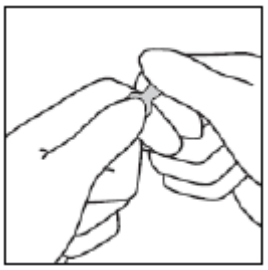
Wear gloves while opening the ampoule.



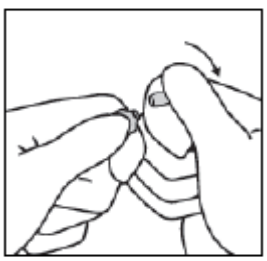
1. Hold the ampoule between thumb and index, leaving the tip of the ampoule free.



2. With the other hand, hold the tip of the ampoule by putting the index finger against the neck of ampoule, and the thumb on the coloured point in parallel to the identification ring(s).



3. Keeping the thumb on the point, sharply break the tip of the ampoule while firmly holding the other part of the ampoule in the hand.



Accidental dermal exposure should be treated by rinsing the affected area with water. Avoid use of soap, alcohol, and other cleaning materials that may cause chemical or physical abrasions to the skin.

4.3 Contraindications

- Pharma-Q Fentanyl Injection is contraindicated in patients with hypersensitivity to fentanyl, or to other opioids, or to any of the excipients (see section 6.1).
- Pharma-Q Fentanyl Injection should not be administered to patients with uncontrolled bronchial asthma or heart failure secondary to chronic lung disease, due to the potential for histamine release.
- It should not be used in patients who may be susceptible to respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion, or comatose patients who may have a head injury or brain tumour and conditions in which increased intracranial pressure occurs; and after an operation on the biliary tract.
- The administration of Pharma-Q Fentanyl Injection is contraindicated in patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment, and in alcoholism.

4.4 Special warnings and precautions for use

Secondary respiratory depression after the operation may occur.

Pharma-Q Fentanyl Injection should be administered only by healthcare providers specifically trained in the use of intravenous anaesthetics and management of the respiratory effects of potent opioids.

Safety has not been demonstrated in children younger than 2 years of age.

Respiratory depression

Respiratory depression may result with intravenous administration of Pharma-Q Fentanyl Injection. The risk of respiratory depression is increased if Pharma-Q Fentanyl Injection is administered in high dose or too rapidly.

Respiratory depression is related to the dose and rate of administration and can be reversed by specific antagonists (naloxone), but additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of the action of the opioid antagonist.

Profound analgesia is accompanied by marked respiratory depression and diminished sensitivity to CO_2 stimulation, which can persist or recur in the postoperative period. Respiratory depression secondary to chest wall rigidity has been reported in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2.

Patients who have received Pharma-Q Fentanyl Injection should remain under appropriate surveillance.

Resuscitation equipment, oxygen and a narcotic antagonist should be readily available to manage apnoea. Care should be taken after infusion of large doses of Pharma-Q Fentanyl Injection to ensure adequate spontaneous breathing has been established and maintained before the patient is released from the recovery area.

Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anaesthetic doses of Pharma-Q Fentanyl Injection, in particular where doses above 10 µg/kg are used. These facilities should be fully equipped to handle all degrees of respiratory depression.

If respiratory depression does occur during anaesthesia, assisted or controlled ventilation will provide adequate respiratory support without reversing analgesia. Respiratory depression can be reversed by administration of the narcotic antagonist, naloxone, which may also reverse analgesia.

Risk from concomitant use of central nervous system (CNS) depressants, especially benzodiazepines or related medicines

Concomitant use of Pharma-Q Fentanyl Injection and CNS depressants, especially benzodiazepines or related medicines, in spontaneously breathing patients, may increase

the risk of profound sedation, respiratory depression, coma and death. If a decision is made to administer Pharma-Q Fentanyl Injection concomitantly with a CNS depressant, especially a benzodiazepine or a related medicine, the lowest effective dose of both medicines should be administered, for the shortest period of concomitant use. Patients should be carefully monitored for signs and symptoms of respiratory depression and profound sedation.

In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Muscle rigidity

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

Cardiac disease

Pharma-Q Fentanyl Injection has weak cholinergic activity and should be used with caution in patients with cardiac dysrhythmias. [1] Bradycardia and possibly cardiac arrest with asystole can occur if the patient has received an insufficient amount of anticholinergic medicine, or when Pharma-Q Fentanyl Injection is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine. [1, 2]

Nitrous oxide has been reported to produce cardiovascular depression when given with Pharma-Q Fentanyl Injection.

In the supine position, therapeutic doses of opioids such as Pharma-Q Fentanyl Injection have minimal effect on blood pressure or cardiac rate and rhythm. [1] Pharma-Q Fentanyl Injection may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Special dosing conditions

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 short-lasting reduction of the cerebral perfusion pressure.

Pharma-Q Fentanyl Injection can produce dependence of the morphine type and therefore has the potential for being abused. Patients on chronic opioid therapy or with a history of opioid abuse, may require higher doses.

It is recommended to reduce the dosage in the elderly and in debilitated patients. Pharma-Q Fentanyl Injection should be titrated with caution in patients with the following conditions:

- uncontrolled hypothyroidism,
- pulmonary disease,
- decreased respiratory reserve,
- alcoholism,
- adrenocortical insufficiency,
- impaired renal or hepatic function,
- prostatic hypertrophy, or
- shock.

Such patients also require prolonged post-operative monitoring.

Interaction with neuroleptics

If Pharma-Q Fentanyl Injection is administered with a neuroleptic medicine, such as droperidol, the user should be familiar with the special properties of each medicine, particularly the difference in duration of action. When such a combination is used, there is a higher incidence of hypotension and fluids and other countermeasures should be

available to manage hypotension. Neuroleptic medicines, such as droperidol, can induce extrapyramidal symptoms that can be controlled with anti-Parkinson medicines.

Vital signs of patients should be monitored routinely.

When Pharma-Q Fentanyl Injection is used with a tranquilliser such as droperidol, hypotension may occur. If it occurs, the possibility of hypovolaemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor medicines other than epinephrine (adrenaline) should be considered. Because of the alpha-adrenergic blocking action of droperidol, epinephrine (adrenaline) may paradoxically decrease the blood pressure in patients treated with droperidol.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of Pharma-Q Fentanyl Injection combined with droperidol. This might be due to alterations in sympathetic activity following large doses of droperidol; however, it is also frequently attributed to anaesthetic and surgical stimulation during light anaesthesia.

It is imperative to discontinue MAO inhibitors 2 weeks prior to any surgical or anaesthetic procedure.

Serotonin syndrome

Caution is advised when Pharma-Q Fentanyl Injection is co-administered with medicines that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs) and serotonin norepinephrine re-uptake inhibitors (SNRIs), and with medicines

which impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]). This may occur within the recommended dose (see sections 4.3 and 4.5).
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. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).
If serotonin syndrome is suspected, rapid discontinuation of Pharma-Q Fentanyl Injection should be considered (see sections 4.3 and 4.5).

When a tranquilliser is used with Pharma-Q Fentanyl Injection, pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

When high dose or anaesthetic doses of Pharma-Q Fentanyl Injection are used, even relatively small dosages of diazepam may cause cardiovascular depression.

The use of Pharma-Q Fentanyl Injection should be avoided in patients with raised intracranial pressure. An antidiuretic effect and hypothermia may occur.

Pharma-Q Fentanyl Injection increases tone in smooth muscle, especially the sphincters of the gastrointestinal tract. Contact dermatitis has been reported and pain and irritation may occur on injection. It should be used with caution in patients with inflammatory or obstructive bowel disease.

Care should be taken when Pharma-Q Fentanyl Injection is given to patients with myasthenia gravis.

Tolerance and Opioid use disorder (abuse and dependence)

For all patients, prolonged use of Pharma-Q Fentanyl Injection may lead to drug dependence (addiction), even at therapeutic doses.

Repeated use of opioids may lead to Opioid use disorder (OUD). Abuse or intentional misuse of opioids may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance.

The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with Pharma-Q Fentanyl Injection.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women use Pharma-Q Fentanyl Injection during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on Pharma-Q Fentanyl Injection:

Central nervous system (CNS) depressants:

Medicines such as barbiturates, benzodiazepines, tricyclic antidepressants, phenothiazines, hypnotics, opioid premedication, neuroleptics, general anaesthetics, halogenic gases and other non-selective central nervous system depressants (e.g. alcohol) may potentiate the respiratory depression of narcotics. When patients have received such medicines, the dose of Pharma-Q Fentanyl Injection required will be less than usual.

Concomitant use with Pharma-Q Fentanyl Injection in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma and death (see section 4.4).

Cytochrome P450 3A4 inhibitors:

Pharma-Q Fentanyl Injection, a high clearance medicine, is rapidly and extensively metabolised by hepatic microsomal enzymes, mainly by CYP3A4.

When Pharma-Q Fentanyl Injection is used, the concomitant use of a CYP3A4 inhibitor may result in a decrease in fentanyl clearance.

With single-dose Pharma-Q Fentanyl Injection administration, the period of risk for respiratory depression may be prolonged, which may require special patient care and longer observation.

Itraconazole (a potent CYP3A4 inhibitor) has no significant effect on the pharmacokinetics of IV Pharma-Q Fentanyl Injection.

Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduces the clearance of IV Pharma-Q Fentanyl Injection by two thirds; however peak plasma concentrations after a single IV dose are not affected.

When Pharma-Q Fentanyl Injection is used as a single dose, the concomitant use of potent CYP3A4 inhibitors such as ritonavir requires special patient care and observation.

Co-administration with fluconazole or voriconazole may result in an increased exposure to Pharma-Q Fentanyl Injection. With continuous treatment, dose reduction may be required to avoid accumulation, which may increase the risk of prolonged or delayed respiratory depression.

In-vitro data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. fluconazole, ketoconazole, erythromycin, diltiazem and cimetidine) may inhibit the metabolism of Pharma-Q Fentanyl Injection.

Serotonergic medicines

Co-administration of fentanyl with a serotonergic agent, such as a selective serotonin re-uptake inhibitor (SSRI) or a serotonin norepinephrine re-uptake inhibitor (SNRI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Effects of Pharma-Q Fentanyl Injection on other medicines:

Following the administration of Pharma-Q Fentanyl Injection, the dose of other CNS-depressant medicines should be reduced. This is particularly important after surgery, because profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the post-operative period. Administration of a CNS depressant, such as a benzodiazepine or related medicines, during this period may disproportionally increase the risk for respiratory depression (see section 4.4).

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 Pharma-Q Fentanyl Injection.

Simultaneous administration with intravenous midazolam results in an increase in the terminal plasma half-life and a reduction in the plasma clearance of midazolam.

When these medicines are co-administered with Pharma-Q Fentanyl Injection their dose may need to be reduced.

When Pharma-Q Fentanyl Injection is used with a neuroleptic such as droperidol, chills and/or shivering, restlessness, post-operative hallucinatory episodes and extrapyramidal symptoms may be observed. Extrapyramidal symptoms may be controlled with anti-Parkinson medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Pharma-Q Fentanyl Injection in pregnant women. Pharma-Q Fentanyl Injection crosses the placenta. Studies in animals have shown

some reproductive toxicity. The potential risk for humans is unknown.

Administration during childbirth (including caesarean section) is not recommended prior to delivery because Pharma-Q Fentanyl Injection crosses the placenta and because the neonatal respiratory centre is particularly sensitive to opiates.

If Pharma-Q Fentanyl Injection is nevertheless administered, assisted ventilation equipment must be immediately available for the mother and infant, if required. An antidote (opioid antagonist) for the newborn ~~child~~ should always be at hand.

Breastfeeding

Pharma-Q Fentanyl Injection is excreted into human milk. Therefore, breastfeeding is not recommended for 24 hours following the administration of Pharma-Q Fentanyl Injection.

Fertility

There are no clinical data on the effects of fentanyl on male or female fertility. In animal studies, some tests on rats showed reduced female fertility at maternal toxic doses.

4.7 Effects on ability to drive and use machines

Patients should only drive or operate a machine if 24 hours has elapsed after the administration of Pharma-Q Fentanyl Injection.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported Adverse Drug Reactions (ADRs) were nausea, vomiting, muscle rigidity, hypotension, hypertension, bradycardia and sedation. [(2)]

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.

b. Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Frequency unknown	Hypersensitivity reactions such as anaphylactic shock, anaphylactic reaction and urticaria.
Psychiatric disorders	Less frequent	Euphoric mood.
	Frequency unknown	Delirium Drug dependence (see section 4.4).
Nervous system disorders	Frequent	Sedation, dizziness and dyskinesia.
	Less frequent	Headache.
	Frequency unknown	Convulsions, loss of consciousness, confusion, restlessness, change of mood, sweating, facial flushing and myoclonus. Hyperalgesia.
Eye disorders	Frequent	Visual disturbance (e.g. miosis).
Cardiac disorders	Frequent	Bradycardia, tachycardia and arrhythmia.
	Frequency unknown	Cardiac arrest.
Vascular disorders	Frequent	Hypotension, hypertension and vein pain.
	Less frequent	Blood pressure fluctuation and phlebitis.
	Frequency unknown	Orthostatic hypotension and raised intracranial pressure. These effects occur more commonly in ambulant patients than in those at rest in bed.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Respiratory, thoracic and mediastinal disorders	Frequent	Apnoea, bronchospasm and laryngospasm.
	Less frequent	Hiccups and hyperventilation.
	Frequency unknown	Respiratory depression. Cough.
Gastrointestinal disorders	Frequent	Nausea and vomiting.
	Frequency unknown	Constipation and dry mouth. Increased risk of abdominal pain, including pancreatitis.
Skin and subcutaneous tissue disorders	Frequent	Allergic dermatitis.
	Frequency unknown	Pruritus.
Musculoskeletal and connective tissue disorders	Frequent	Muscle rigidity (which may also involve the thoracic muscles).
Renal and urinary disorders	Frequency unknown	Passing of urine may be difficult, uretic or biliary spasm and antidiuretic effect.
General disorders and administration site conditions	Less frequent	Chills and hypothermia. Drug withdrawal syndrome (see section 4.4).
Injury, poisoning and procedural complications	Frequent	Postoperative confusion and neurological anaesthetic complications.
	Less frequent	Postoperative agitation, procedural

MedDRA system organ class	Frequency	Adverse reactions
		complication and airway complication of anaesthesia.

c. Description of selected adverse reactions

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).

Extrapyramidal symptoms may be controlled with anti-Parkinson medicines (see section 4.3).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms:

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

Treatment:

In the presence of hypoventilation or apnoea, oxygen should be administered and lung ventilation should be assisted or controlled as indicated. A specific opioid antagonist, such as naloxone, should be used as indicated to control respiratory depression. This does not

preclude the use of more immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.

If impaired breathing is associated with muscular rigidity, an intravenous neuromuscular 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 hypovolaemia should be considered, and if present, it should be controlled with appropriate parenteral fluid administration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.2.9 Central nervous system depressants. Narcotic Analgesics.

Pharmacotherapeutic group: anaesthetics general, opioid anaesthetics

ATC code: N01AH01.

Fentanyl is a potent, opioid analgesic.

Fentanyl is a narcotic analgesic. Fentanyl obtunds stress-related hormonal changes at higher doses. The onset of action is within one arm-brain circulation time. However, the maximum analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is approximately 30 minutes after a single intravenous dose of up to 100 µg. Depth of analgesia is dose related and can be adjusted to the pain level of the surgical procedure.

Fentanyl, depending upon the dose and speed of administration, can cause muscle rigidity as well as euphoria, miosis and bradycardia. Histamine release may occur.

All actions of fentanyl are reversible by a specific narcotic antagonist, such as naloxone.

5.2 Pharmacokinetic properties

Fentanyl is a synthetic opioid with µ-agonist pharmacological effects.

Distribution

After intravenous injection in normal volunteers, fentanyl plasma concentrations have sequential distribution half-lives of about 1 minute and 18 minutes and a terminal elimination half-life of approximately 8 hours.

Fentanyl has a Vc (volume of distribution of the central compartment) of 13 L and a total Vdss (distribution volume at steady-state) of 339 L. The plasma-protein binding of fentanyl is about 84 %.

Metabolism

Fentanyl is rapidly metabolised, mainly in the liver by CYP3A4. The major metabolite is norfentanyl. Fentanyl clearance is 574 mL/min.

Elimination

Approximately 75 % of the administered dose is excreted in the urine within 24 hours and only 10 % of the dose eliminated in urine is present as unchanged medicine.

Special populations

Paediatric patients

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 result in an increased dose requirement for Pharma-Q Fentanyl Injection.

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 Pharma-Q Fentanyl Injection, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.2).

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 an increased dose of fentanyl.

Obese patients

An increase in clearance of fentanyl is observed with increased body mass. 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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

If desired, Pharma-Q Fentanyl Injection may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with plastic infusion sets. These should be used within 24 hours of preparation.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from light.

6.5 Nature and contents of container

Pharma-Q Fentanyl 500 µg/10 ml Injection: Amber 10 ml ampoules in boxes of 10.

Pharma-Q Fentanyl 100 µg/2 ml Injection: Amber 2 ml ampoules in boxes of 10.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMA-Q HOLDINGS (PTY) LTD

50 Commando Road

Industria West, 2093

Johannesburg

South Africa

8 REGISTRATION NUMBERS

Pharma-Q Fentanyl 500 µg/10 ml Injection: 29/2.7/0604

Pharma-Q Fentanyl 100 µg/2 ml Injection: 29/2.7/0605

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 1995

10 DATE OF REVISION OF THE TEXT

09 May 2024