DATA SHEET

1. PRODUCT NAME

FENTANYL INJECTION
Fentanyl citrate 50 µg/mL, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2ml ampoule contains 100 micrograms of Fentanyl as Fentanyl citrate.
Each 10ml ampoule contains 500 micrograms of Fentanyl as Fentanyl citrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Injection: a clear, colourless, particle-free solution, pH 4.0-7.5, and containing fentanyl 50µg/mL (as citrate).

Fentanyl is chemically identified as N-(1-phenethyl-4-piperidyl) propionanilide citrate, MW 528.61.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short duration analgesia during pre-medication, induction and maintenance of anaesthesia, and in the immediate post-operative period.

Opioid analgesic supplement to general and regional anaesthesia.

Combination with a neuroleptic as an anaesthetic pre-medication for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage should be individualised according to age, bodyweight, physical status, underlying pathological condition, use of other medicines, type of anaesthesia to be used and the surgical procedure involved (see also section 4.4 Special Warnings and Precautions for Use). FENTANYL INJECTION contains no antimicrobial agent. It should be used only once and any residue discarded.

ADULTS

Premedication

(To be appropriately modified in the elderly, debilitated and those who receive other depressant medicines): 50 to 100 µg (1 to 2 mL) may be administered intramuscularly 30 to 60 minutes prior to surgery.

Adjunct to general anaesthesia

Induction: 50 to 100 µg (1 to 2 mL) IV initially, repeat at two to three minute intervals until desired effect is achieved. A reduced dose of 25 to 50 µg (0.5 to 1 mL) is recommended in elderly and poor risk patients.

Maintenance

25 to 50 µg (0.5 to 1 mL) IV or IM when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

Adjunct to regional anaesthesia

50 to 100 µg (1 to 2 mL) may be administered IM or slowly IV when additional analgesia is required.

Post-operatively (recovery room)

50 to 100 µg (1 to 2 mL) may be administered IM for the control of pain, tachypnoea and emergence delirium. The dose may be repeated in one or two hours as needed.

CHILDREN

For induction and maintenance in children 2 to 12 years of age, a reduced dose of 20 to 30 µg (0.4 to 0.6 mL) per 10 kg is recommended.

IMPAIRED RENAL FUNCTION

Fentanyl should be used with caution.

IMPAIRED HEPATIC FUNCTION

Fentanyl should be used with caution.

INCOMPATIBILITIES:

Fentanyl is incompatible with thiopentone sodium and methohexitone sodium.

4.3 CONTRAINDICATIONS

1. Known hypersensitivity or intolerance to fentanyl, other opioid analgesics, or to any of the excipients.

2. Bronchial asthma.

(See also section 4.4 Special Warnings and Precautions for Use).

3. Head injuries and increased intracranial pressure

As for any opioid analgesic, Fentanyl should not be used in patients susceptible to respiratory depression, such as comatose patients who may have head injuries or a brain tumour. (See also section 4.4 Special Warnings and Precautions for Use). Fentanyl may obscure the clinical course of patients with head injury.

4. Concomitant MAO inhibitors

Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics and the use of Fentanyl in patients who have received MAO inhibitors within 14 days is not recommended. (See section 4.5 Interactions).

5. Myasthenia gravis

Fentanyl may cause muscle rigidity upon IV administration. Therefore, the need for reversal and muscle relaxants contraindicates its use in patients with a history of myasthenia gravis.

6. Children two years of age or younger

Safe conditions for use have not been established.

7. Use in patient after operative interventions in the biliary tract.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Adequate facilities should be available for post-operative monitoring and ventilation. Resuscitative equipment, oxygen and an opioid antagonist should be readily available to manage apnoea. Fentanyl should only be used by experienced doctors and in patients who are under constant supervision.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Fentanyl with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, medicines with antihistamine-sedating actions such as antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of medicine-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see section 4.5 Interactions with other medicines and other forms of interaction).

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Fentanyl is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see section 4.5 Interactions with other medicines and other forms of interaction).

Concomitant Neuroleptics

If Fentanyl is administered with neuroleptics, the user should be familiar with the special properties of each medicine, particularly with regard to durations of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available.

Total Opioid dose

As with other potent opioids, the respiratory depressant effect of Fentanyl persists longer than the measured analgesic effect. The total dose of all opioid analgesics should be considered before additional opioid analgesics are given during recovery from anaesthesia. It is recommended that post-operative opioids, when required, should be used initially in reduced doses, as low as 1/4 to 1/3 of those usually recommended.

Muscle Rigidity

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the dose and speed of injection and may be reduced by slow intravenous injection. If this effect occurs, it may be managed by the use of assisted or controlled respiration and, if necessary, by administration of a neuromuscular blocking agent compatible with the patient's condition.

Nonepileptic myoclonic movements can occur.

Drug Dependence

Fentanyl can produce drug 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 to achieve an adequate therapeutic effect.

Respiratory Depression

Depression of respiration is the most marked and dangerous side effect of Fentanyl. In the post-operative period, patients may exhibit delayed depression of respiration. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary. (See Impaired Respiration below).

Impaired Respiration

Fentanyl should be used with caution in patients with severe impairment of pulmonary function because of the possibility of respiratory depression (e.g. chronic obstructive pulmonary disease, patients with decreased respiratory reserve, or any patient with potentially compromised respiration).

In such patients, opioids may further decrease respiratory drive and increase airway resistance. During anaesthesia, this can be managed by assisted or controlled respiration.

Use of Opioid Antagonists for Respiratory Depression

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists.

However, appropriate surveillance should be maintained because the duration of respiratory depression of doses of Fentanyl employed during anaesthesia is usually longer than the duration of opioid antagonist action. Consult individual product information (nalorphine or naloxone) before employing opioid antagonists.

Impaired Liver and Kidney Function

Fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of medicines.

Bradycardia

Fentanyl may produce bradycardia and possibly asystole. Bradycardia may be treated with atropine; however, Fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

Sphincter of Oddi Spasm

As has been observed with all opioid analgesics, episodes suggestive of Sphincter of Oddi Spasm may occur with Fentanyl.

Adjunct to Conduction Anaesthesia; Nitrous Oxide

Certain forms of conduction anaesthesia, such as spinal anaesthesia and some peridural anaesthetics, can alter respiration by blocking intercostal nerves.

Through other mechanisms Fentanyl can also alter respiration. Therefore, when Fentanyl is used to supplement these forms of anaesthesia, the anaesthetist should be familiar with the physiological alterations involved and be prepared to manage them in patients selected for these forms of anaesthesia.

Monitoring

Vital signs should be monitored routinely.

Elderly, Debilitated Patients

The initial Fentanyl dose should be reduced in elderly and debilitated patients. Elderly patients may be more susceptible to adverse effects, such as respiratory depression and cardiovascular effects. They may also have age related kidney function impairment, resulting in lower clearance rates of Fentanyl. Opioids should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism, impaired hepatic or renal function. Such patients also require prolonged postoperative monitoring.

Hypotension

Opioids may induce hypotension, particularly in hypovolaemic patients. Appropriate measures should be taken to maintain stable arterial pressure.

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 Reuptake 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. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).

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

USE IN CHILDREN

The safety of Fentanyl in children younger than two years of age has not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Coadministration of the following medicines may enhance or prolong the effects of Fentanyl: azole antifungals, macrolide antibiotics and protease inhibitors such as Ritonavir.

Coadministration of the following medicines may decrease the plasma concentration of fentanyl: phenytoin.

The concurrent administration of Fentanyl and naltrexone precipitates opioid withdrawal symptoms.

OTHER CNS DEPRESSANTS

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including barbiturates, tranquilizers, alcohol, neuroleptics, opioids and general anaesthetics increases the risk of respiratory depression, profound sedation, coma and death. Reserve concomitant prescribing of these medicines for use in patients for whom alternative treatment options are inadequate. When patients have received such medicines, the dose of fentanyl required will be less than usual. Likewise, following the administration of Fentanyl the dose of other CNS depressant medicines should be reduced. Follow patients closely for signs of respiratory depression and sedation. (See section 4.4 Special Warnings and Precautions for Use).

FENTANYL/NEUROLEPTIC COMBINATION

When a neuroleptic such as droperidol is used with Fentanyl, pulmonary arterial pressure may be decreased. Hypotension can occur and, possibly, hypovolaemia (which should be managed with appropriate parenteral fluids).

Repositioning of 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 together with other countermeasures do not correct hypotension, the administration of pressor agents other than adrenaline should be considered. Because of the alpha-adrenergic blocking action of droperidol, adrenaline may paradoxically decrease the blood pressure in patients treated with droperidol.

When droperidol is used with Fentanyl and the EEG is used for post-operative monitoring, it may be found that the EEG pattern returns to normal slowly.

MAO INHIBITORS

Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. Since the safety of Fentanyl in this regard has not been established, the use of Fentanyl in patients who have received MAO inhibitors within 14 days is not recommended. (See section 4.3 Contraindications).

NITROUS OXIDE

Nitrous oxide has been reported to produce cardiovascular depression when given with high doses of Fentanyl.

AMIODARONE

Profound bradycardia, sinus arrest and hypotension have occurred when patients receiving amiodarone have been given Fentanyl for anaesthesia.

ADRENERGIC BLOCKERS AND CALCIUM CHANNEL BLOCKERS

The combination of calcium channel blockers and beta-adrenergic blockers during Fentanyl anaesthesia should be used with caution since severe hypotension has been reported to occur.

SEROTONIN SYNDROME

Opioids can interact with antidepressants and migraine medicines to cause a serious central nervous system reaction called serotonin syndrome in which high levels of the chemical serotonin build up in the brain and cause toxicity.

Coadministration of sibutramine hydrochloride with Fentanyl may increase the risk of serotonin syndrome (hypertension, hypothermia, myoclonus and mental status changes).

4.6 FERTILITY, PREGNANCY AND LACTATION

PREGNANCY

Category C

Opioid analgesics may cause respiratory depression in the newborn infant. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus. If Fentanyl is nevertheless administered, an antidote should always be at hand for the child. The safe use of Fentanyl has not been established with respect to possible adverse effects upon foetal development. Therefore it should be used in women of childbearing potential only when in the judgement of the physician the potential benefits outweigh the possible hazards.

Withdrawal symptoms in newborn infants have been reported with prolonged use of opioids.

BREAST-FEEDING

Fentanyl may enter the maternal milk. Therefore, breastfeeding is not recommended for 24 hours following the administration of the medicine.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

MORE COMMON

Respiratory depression, apnoea, muscular rigidity, myoclonic movements, bradycardia, tachycardia, vein pain and allergic dermatitis. If these remain untreated, respiratory arrest, circulatory depression, or cardiac arrest could occur.

Respiratory depression is more likely to occur with intravenous administration if a dose is given too rapidly; it rarely occurs with intramuscular administration. If respiratory depression occurs during anaesthesia, assisted or controlled respiration will provide adequate ventilation without reversing analgesia. Respiratory depression can be immediately reversed by opioid antagonists (e.g. nalorphine or naloxone) which, it should be noted, will also reverse analgesia. Secondary rebound respiratory depression has been observed after the operation in rare instances.

Muscular rigidity may be associated with reduced pulmonary compliance and/or apnoea, laryngospasm or bronchospasm. Prompt reversal of this effect can be achieved with the intravenous administration of an appropriate single dose of a muscle relaxant such as suxamethonium**.** Assisted or controlled respiration is required to provide ventilation after the use of muscle relaxants.

Bradycardia and other cholinergic effects may occur and can be controlled with the appropriate dose of atropine. The inclusion of atropine or other anticholinergic agents in the pre-anaesthetic regimen tends to reduce the occurrence of such effects.

LESS COMMON

Hypotension, hypertension, dizziness, blurred vision, miosis, nausea, emesis, constipation, laryngospasm, diaphoresis, itching, euphoria, seizures, spasm of the sphincter of Oddi, anaphylaxis, headache, loss of consciousness, myoclonus, phlebitis, hyperventilation, hiccups, cough, hypothermia, airway complications of anaesthesia, agitation postoperative. Motor stimulation and bronchospasm may occur with high doses of Fentanyl. Less frequently, cardiac arrhythmias, postoperative mental depression, paradoxical CNS excitation or delirium may occur.

FENTANYL/NEUROLEPTIC COMBINATION

When a neuroleptic such as droperidol is used with Fentanyl, the following adverse reactions can occur: chills and/or shivering, restlessness and postoperative hallucinatory episodes sometimes associated with transient periods of mental depression; extrapyramidal symptoms (dystonia, akathisia and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents.

Postoperative drowsiness is also frequently reported following the use of droperidol.

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

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSAGE

SYMPTOMS

Narcosis (which may be preceded by marked skeletal muscle rigidity), cardiorespiratory depression accompanied by cyanosis, followed by a fall in body temperature, circulatory collapse, coma and possibly death.

TREATMENT

In the presence of hypoventilation or apnoea, oxygen should be administered and respiration assisted or controlled as necessary. A patent airway must be maintained.

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 for 24 hours; body warmth and adequate fluid intake should be maintained.

If severe or persistent hypotension occurs, the possibility of hypovolaemia should be considered and managed with appropriate parenteral fluid therapy.

A specific opioid antagonist, such as nalorphine or naloxone, should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of Fentanyl is usually longer than the duration of opioid antagonist action.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Fentanyl is a opioid analgesic. A dose of 100 µg (0.1 mg or 2.0 mL) is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of pethidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation associated with opioid analgesics may last longer than the analgesic effect. As the dose of opioid is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnoea. Fentanyl appears to have less emetic activity than either morphine or pethidine. Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with Fentanyl. Recent assays in man show no clinically significant histamine release at doses up to 50 µg/kg (0.05 mg/kg or 1 mL/kg). Fentanyl preserves cardiac stability and blunts stress-related hormonal changes at higher doses.

Fentanyl produces minimal cortical depression and may act by filling receptor sites located in the thalamus, midbrain and spinal cord. A specific morphine antagonist (e.g. nalorphine or naloxone) produces reversal of respiratory, cardiovascular, miotic and motor inco-ordination effects and also produces reversal of analgesia, euphoria and sedation. Rigidity of the diaphragm and intercostal muscles can be eliminated by suxamethonium. Cholinergic effects such as bradycardia are reversed by atropine.

As with longer-acting opioid analgesics, the duration of the respiratory depressant effect of Fentanyl may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO_2 stimulation following administration of Fentanyl to man:

1. Diminished sensitivity to CO_2 stimulation may persist longer than depression of respiratory rate. Fentanyl frequently slows the respiratory rate (See section 4.4 Special Warnings and Precautions for Use).
2. Altered sensitivity to CO_2 stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 µg (12 mL) Fentanyl to healthy volunteers.
3. Duration and degree of respiratory depression is dose related.

4. The peak respiratory depressant effect of a single intravenous dose of Fentanyl is noted 5 to 15 minutes following injection. (See also section 4.4 Special Warnings and Precautions for Use concerning respiratory depression).

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of Fentanyl can be described by a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution for Fentanyl is 4 L/kg.

The onset of action is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single IV dose of up to 100 µg. Following intramuscular administration, the onset of action is from seven to eight minutes and the duration of action is one to two hours.

Fentanyl plasma protein binding capacity increases with increasing ionisation of the drug.

Alterations in pH may affect its distribution between plasma and the central nervous system. It accumulates in skeletal muscle and fat, and is released slowly into the blood.

Fentanyl is primarily transformed in the liver and demonstrates a high first pass clearance with approximately 75% of an intravenous dose excreted in urine, primarily as metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the faeces, primarily as metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Citric acid anhydrous
- Sodium chloride
- Sodium citrate
- Water for injection
- Sodium hydroxide

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

18 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

2mL : Store below 25°C
10 mL: Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

Polyamp Duofit 50 µg/mL, 10 x 2 mL and 10 x 10 mL.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

FENTANYL INJECTION contains no antimicrobial agent. It should be used once only and any residue discarded. Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Controlled Drug B3.

8. SPONSOR

AstraZeneca Limited
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Auckland 1142
Telephone: (09) 306 5650

9. DATE OF FIRST APPROVAL

17 October 1991

10. DATE OF REVISION OF THE TEXT

8 May 2017

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4 4.5	Warnings on use with benzodiazepines and other CNS depressants Section added regarding serotonin syndrome Section regarding other CNS depressants modified Section added regarding serotonin syndrome Update to new SPC format