1.4.1. PRESCRIBING INFORMATION (SUMMARY OF PRODUCTS CHARACTERISTICS)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

VERFEN (Fentanyl citrate injection USP, 50mcg/ml, 2ml)

2. Qualitative and Quantitative composition

2.1 Qualitative composition

Each ml contains

Fentanyl citrate USP

Eq. to Fentanyl

Water for Injection USP

2.2 Quantitative composition

Each ml contains

Fentanyl citrate USP

Eq. to Fentanyl 50mcg/ml

Water for Injection USP qs

2.3 Salts and hydrates

Fentanyl citrate 78.5 micrograms equivalent to 50 micrograms per ml fentanyl.

2.4 Esters and pro-drugs

Not Applicable

2.5 Oral powders for solution or suspension

Not Applicable

2.6 Parenterals excluding powders for reconstitution

Each ml contains: Fentanyl citrate 50mcg/ml,

2.7 Powders for reconstitution prior to parenteral administration

Not Applicable

2.8 Concentrates

Not Applicable

2.9 Transdermal patches

Not Applicable

2.10 Multi dose solid or semi-solid products

Not Applicable

2.11 Biological medicinal products

2.11.1 Expression of strength

Not Applicable

2.11.2 The biological origin of the active substance

Not Applicable

2.11.3 Special provisions for normal immunoglobulins

Not Applicable

2.11.4 Herbal pharmaceutical products

Not Applicable

3. Pharmaceutical form

Solution for Injection

A clear, colorless solution filled in 2 ml clear glass ampoules.

4. Clinical particulars

4.1 Therapeutic indications

Fentanyl is an Opioid analgesic used:

- In low doses to provide analgesia during short surgical procedures

- In high doses as an analgesic/respiratory depressant in patients requiring assisted ventilation

- In combination with a neuroleptic drug as part of the technique of neuroleptanalgesia

- In the treatment of severe pain, such as the pain of myocardial infarction

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with fentanyl in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Route of administration

Intravenous administration either as a bolus or by infusion.

Intramuscular administration.

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 Special warnings and precautions for use).

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

It is recommended to wear gloves while opening the ampoule (see section 6.6).

Posology

Fentanyl, by the intravenous route, can be administered to both adults and children. The dose 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 in adults is as follows:

	Initial	Supplemental
Spontaneous Respiration	50-200 micrograms	50 micrograms
Assisted Ventilation	300-3500 micrograms	100-200 micrograms

Doses in excess of 200 micrograms are for use in anaesthesia only. As a premedicant, 1-2 ml fentanyl may be given intramuscularly 45 minutes before induction of anaesthesia.

After intravenous administration in unpremedicated adult patients, 2 ml fentanyl may be expected to provide sufficient analgesia for 10-20 minutes in surgical procedures involving low pain intensity. 10 ml fentanyl injected as a bolus gives analgesia lasting about one hour. The analgesia produced is sufficient for surgery involving moderately painful procedures. Giving a dose of 50 micrograms/kg fentanyl will provide intense analgesia for some four to six hours, for intensely stimulating surgery.

Fentanyl may also be given as an infusion. In ventilated patients, a loading dose of fentanyl may be given as a fast infusion of approximately 1 microgram/kg/min for the first 10 minutes followed by an infusion of approximately 0.1 micrograms/kg/min. Alternatively the loading dose of fentanyl may be given as a bolus. Infusion rates should be titrated to individual patient

response; lower infusion rates may be adequate. Unless it is planned to ventilate post-operatively, the infusion should be terminated at about 40 minutes before the end of surgery.

Lower infusion rates, e.g. 0.05-0.08 micrograms/kg/minute are necessary if spontaneous ventilation is to be maintained. Higher infusion rates (up to 3 micrograms/kg/minute) have been used in cardiac surgery.

Fentanyl is chemically incompatible with the induction agents pentobarbital sodium, thiopentone and methohexitone because of wide differences in pH (see section 6.2 Incompatibilities).

Paediatric population

Children aged 12 to 17 years old:

Follow adult dosage.

Children aged 2 to 11 years old:

The usual dosage regimen in children is as follows:

	Age	Initial	Supplemental
Spontaneous Respiration	2-11 yrs	1-3 micrograms/kg	1-1.25 micrograms/kg
Assisted Ventilation	2-11 yrs	1-3 micrograms/kg	1-1.25 micrograms/kg

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).

Use in elderly and debilitated patients:

As with other opioids, the initial 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 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 (see section 5.2 Pharmacokinetic properties).

4.3 Method of administration

By intramuscular, intravenous injection.

The epidural or intrathecal routes must not be used as the product contains a preservative.

4.4 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or other opioids.

- Respiratory depression, obstructive airways disease.

- Concurrent administration with monoamine oxidase inhibitors or within 2 weeks of their discontinuation.

4.5 Special warnings and precautions for use

Warnings:

Following intravenous administration of fentanyl, a transient fall in blood pressure may occur, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Tolerance and Opioid use disorder (abuse and dependence)

For all patients, prolonged use of this product 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 fentanyl.

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 receive this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Respiratory Depression

As with all potent opioids, profound analgesia is accompanied by marked respiratory depression, which may persist into or recur in the early postoperative period. Care should be taken after large doses or infusions of fentanyl to ensure that adequate spontaneous breathing has been established and maintained before discharging the patient from the recovery area.

Significant respiratory depression will occur following the administration of fentanyl in doses in excess of 200 micrograms. This, and the other pharmacological effects of fentanyl, can be reversed by specific opioid antagonists, but additional doses may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.

Resuscitation equipment and opioid antagonists should be readily available.

Hyperventilation during anaesthesia may alter the patient's response to CO_2, thus affecting respiration postoperatively.

Administration in labour may cause respiratory depression in the new-born infant.

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.

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).

Cardiac disease

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

Muscle rigidity

Muscular rigidity (morphine-like effect) may occur.

Rigidity, which may also involve the thoracic muscles, can be avoided by the following measures:

− slow IV injection (usually sufficient for lower doses);

− premedication with benzodiazepines;

− use of muscle relaxants.

Non-epileptic (myo)clonic movements can occur.

Precautions:

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

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 transient reduction of the cerebral perfusion pressure.

It is recommended to reduce dosage in the elderly and debilitated patients. In uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism and hepatic or renal impairment the dosage should be titrated with care and prolonged post-operative monitoring is required.

Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses.

Myasthenia gravis

In patients with myasthenia gravis, careful consideration should be applied in the use of certain anticholinergic agents and neuromuscular-blocking pharmaceutical agents prior to, and during, the administration of a general anaesthetic regimen which includes administering intravenous fentanyl.

Interaction with neuroleptics

If fentanyl is administered with a neuroleptic, 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.

Bile duct

As with other opioids, due to the anticholinergic effects administration of fentanyl may lead to increases of bile duct pressure and in isolated cases spasms of the Sphincter of Oddi might be observed.

Intestinal motility

As with 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.

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.

4.6 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.

4.7 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

The use of other CNS depressants such as opioid premedication, barbiturates, neuroleptics, general anaesthetics, gabapentinoids (gabapentin and pregabalin), and other non-selective CNS depressants (e.g. alcohol) may enhance or prolong the respiratory depression of fentanyl.

When patients have received other CNS-depressants, the dose of fentanyl required may be less than usual. Concomitant use with fentanyl in spontaneously breathing patients may increase the risk of respiratory depression, profound sedation, coma, and death.

The pharmacological effects of fentanyl citrate can be reversed by naloxone.

Antipsychotics

Droperidol: The concomitant use of droperidol can result in a higher incidence of hypotension.

Antihypertensive

Clonidine: Co-administration of clonidine may enhance fentanyl effects and especially prolong fentanyl-induced respiratory depression.

Cytochrome P450 3A4 (CYP3A4) inhibitors

Fentanyl, a high clearance drug, is rapidly and extensively metabolised mainly by CYP3A4. When IV fentanyl is used, the concomitant use of a CYP3A4 inhibitor may result in a decrease in fentanyl clearance. With single-dose IV 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 IV fentanyl dose by two thirds, although peak plasma concentrations of IV 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 dose of IV fentanyl.

Co-administration of fluconazole or voriconazole (moderate CYP3A4 inhibitors) and fentanyl may result in an increased exposure and/or prolonged exposure to fentanyl.

Bradycardia and possibly cardiac arrest can occur when fentanyl is combined with non-vagolytic muscle relaxants (e.g. vecuronium).

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 (see section 4.3 Contraindications)

Effect of fentanyl on other drugs

Following the administration of fentanyl, the dose of other CNS depressant drugs 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 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 is decreased by a factor of 2 to 3 without a change in half-life when administered with fentanyl.

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.

4.8 Additional information on special populations

4.9 Pediatric population

Techniques that involve analgesia in a spontaneously breathing child should only be used as part of an anesthetic 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.

4.10 Fertility, pregnancy and lactation

4.10.1Pregnancy

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

There are no adequate data from the use of fentanyl in pregnant women. Fentanyl can cross the placenta in early pregnancy. Studies in animals have shown some reproductive toxicity (see Section 5.3, Preclinical safety data). The potential risk for humans is unknown.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

4.10.2Breast-feeding

Administration to nursing women is not recommended as fentanyl may be secreted in breast milk and may cause respiratory depression in the infant. Therefore breast-feeding or use of expressed breast milk is not recommended within 24 hours of treatment. The risk/benefit of breast-feeding following fentanyl administration should be considered.

4.10.3Fertility

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 (see section 5.3 Preclinical safety data).

4.11 Effects on ability to drive and use machines

Where early discharge is envisaged, patients should be advised not to drive or to operate machinery for at least 24 hours following administration.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• *The medicine is likely to affect your ability to drive*

• *Do not drive until you know how the medicine affects you*

• *It is an offence to drive while under the influence of this medicine*

• *However, you would not be committing an offence (called 'statutory defence') if:*

o *The medicine has been prescribed to treat a medical or dental problem and*

o *You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and*

o *It was not affecting your ability to drive safely*

4.12 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, Table 1 displays ADRs that have been reported with the use of fentanyl IV from either clinical trials or postmarketing experience.

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); and not known (cannot be estimated from the available clinical trial data).

Table 1: Adverse Drug Reactions

System Organ Class	**Adverse Drug Reactions**			
	Frequency Category			
	Very Common (≥ 1/10)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Not Known**
Immune System Disorders				Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric		Agitation	Euphoric mood	Delirium, Drug

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Disorders				dependence (see section 4.4)
Nervous System Disorders	Muscle rigidity (which may also involve the thoracic muscles)	Dyskinesia; Sedation; Dizziness	Headache	Convulsions; Loss of consciousness; Myoclonus
Eye Disorders		Visual disturbance		
Cardiac Disorders		Bradycardia; Tachycardia; Arrhythmia		Cardiac arrest
Vascular Disorders		Hypotension; Hypertension; Venous pain	Phlebitis; Blood pressure fluctuation	
Respiratory, Thoracic and Mediastinal Disorders		Laryngospasm; Bronchospasm; Apnoea	Hyperventilation; Hiccups	Respiratory depression
Gastrointestinal Disorders	Nausea; Vomiting			
Skin and Subcutaneous Tissue Disorders		Allergic dermatitis		Pruritus
General Disorders and Administration Site Conditions			Chills; Hypothermia; Drug withdrawal syndrome	Drug withdrawal syndrome (see section 4.4)
Injury, Poisoning and Procedural Complications		Postoperative confusion	Airway complication of anaesthesia	

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).

4.13 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms and signs:

The manifestations of fentanyl overdosage are generally an extension of its pharmacological action. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression which varies from bradypnoea to apnoea.

Treatment:

Hypoventilation or apnoea:	O_2 administration, assisted or controlled respiration.
Respiratory depression:	Specific opioid antagonist. This does not preclude the use of immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.
Muscular rigidity:	Intravenous neuromuscular blocking agent 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

Pharmacotherapeutic group: Anaesthetic general, opioid anaesthetic,ATC code: N01AH01

Fentanyl is a synthetic opiate with a clinical potency of 50 to 100 times that of morphine. Its onset of action is rapid and its duration of action is short. In man, a single IV dose of 0.5-1 mg/70 kg body weight immediately produces a pronounced state of surgical analgesia, respiratory depression, bradycardia and other typical morphine-like effects. The duration of action of the peak effects is about 30 minutes. All potent morphine-like drugs produce relief from pain, ventilatory depression, emesis, constipation, physical dependence, certain vagal effects and varying degrees of sedation. Fentanyl, however, differs from morphine not only by its short duration of action but also by its lack of emetic effect and minimal hypotensive activity in animals.

5.2 Pharmacokinetic properties

Some pharmacokinetic parameters for fentanyl are as follows:

Urinary excretion = 8%

Bound in plasma = 80%

Clearance (ml/min/kg) = 13±2

Volume of distribution (litres/kg) = 4.0±0.4

Estimates of terminal half-life range from 141 to 853 minutes.

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

In vitro fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in *in vivo* rodent studies and bacterial assays. In a two-year rat bioassay, fentanyl was not carcinogenic.

Some tests on female rats showed reduced fertility as well as embryo mortality. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. There was no evidence of teratogenic effects.

6. Pharmaceutical particulars

6.1 List of excipients

Tri sodium citrate Dihydrate, Citric Acid (anhydrous), water for injection

6.2 Incompatibilities

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

6.3 Shelf life

24 Months

Shelf-life after dilution:

Shelf-life after first opening: use immediately.

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6.4 Special precautions for storage

Keep the ampoules in the outer carton

Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C. From a microbiological point of view, the product 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 2-8°C, unless dilution has taken place in controlled validated aseptic conditions.

6.5 Nature and contents of container

2 ml clear glass ampoules, glass type I , packed in cardboard cartons and containing 10 x 10 x 2 ml ampoules.

6.6 Special precautions for disposal and other handling

Use finger protection when opening an ampoule.

The injection (both ampoules and vials) 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 AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation Holder

Verve Human Care Laboratories
15-A, Pharmacity,
Selaqui, Dehradun-248011
India

Manufacturing Site:

Verve Human Care Laboratories
15-A, Pharmacity,
Selaqui, Dehradun-248011

India

8. MARKETING AUTHORISATION NUMBER

Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Not Applicable

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY (IF APPLICABLE)

Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE

Not Applicable

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