SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FENTAVER 0.5 mg/10 mL I.V./I.M. Solution for Injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Each 1 mL solution contains 0.0785 mg fentanyl citrate equivalent to 0.05 milligram fentanyl.

Excipients:

Each 1 mL solution

Sodium chloride…….. 9 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Solution for intravenous / intramuscular injection.

Sterile, preservative-free, isotonic, clear solution for intravenous / intramuscular use.

4. CLINICAL PARTICULARS

4.1. Therapeutical indications

FENTAVER is indicated in the following situations:

- As a narcotic analgesic additive in general or regional anesthesia,
- In low doses to provide analgesia during short surgical procedures
- In combination with a neuroleptic in the technique of neuroleptanalgesia.
- As an anesthetic agent with oxygen for "opioid-based anesthesia" in high risk patients undergoing major surgery.

4.2. Posology and method of administration

Posology / administration frequency and duration

FENTAVER should be administered only in an environment where the airway can be controlled, and by a person who can control the airway (See Section 4.4.).

In order to prevent bradycardia, it is recommended to administer intravenous anticholinergic at a low dose immediately before induction.

It is recommended to wear gloves when opening the ampoule (See Section 6.6).

Posology

The dose of FENTAVER should be individualized according to age, body weight, physical condition,

underlying pathological conditions, use of other drugs, type of surgery, and anesthesia.
The starting dose should be reduced in elderly (> 65 years of age) and debilitated patients. When determining complementary (additional) doses, the effect of the starting dose should be taken into account.
Use as analgesic support in general anesthesia
Low dose: 2 micrograms / kg
FENTAVER at low doses is more useful in minor but painful surgical procedures.
Intermediate dose: 2-20 micrograms / kg
When surgery is more complicated, higher doses may be required.
The duration of action depends on the dose.
High dose: 20-50 micrograms / kg

It has been shown that 20-50 micrograms / kg FENTAVER together with nitrous oxide / oxygen has a mitigating effect in major surgical applications that take longer and the stress response may harm the well-being of the patient. When doses in this range are used during surgery, post-operative ventilation and monitoring is essential, considering the possibility of prolonged post-operative respiratory depression.
Additional doses of 25-250 micrograms/kg (0.5-5 mL) can be administered according to the patient's requirements and the estimated time required to complete the operation.

Use as an anesthetic agent
When alleviating the response to surgical stress is particularly important, doses of 50-100 micrograms / kg can be administered together with oxygen and muscle relaxants. This technique provides anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 micrograms / kg may be required to achieve this anesthetic effect. FENTAVER has been particularly used in this way in open heart surgery and certain other major surgical procedures in patients in which the myocardium must be protected from excessive oxygen demand.

Method of Administration:
It is administered by intravenous/intramuscular injection.

Additional information on special populations

Renal/Hepatic Impairment:
Opioids should be titrated carefully in patients with impaired renal and hepatic function. The use of low doses of FENTAVER in patients with renal failure should be evaluated and these patients should be carefully observed for signs of fentanyl toxicity (See section 5.2.).

Obese patients:
If the dose is determined by body weight, there is a risk of high doses being given in obese patients. In obese patients, the dose estimate should be calculated based on lean body weights.

Pediatric population:
A dose of 2-3 micrograms/kg is recommended for induction and maintenance in children aged 2-11 years. Dosage regimen in children is usually as follows:

	Age	Initial	Support
Natural breathing	2-11 years	1 -3 microgram /kg	1-1.25 microgram /kg
Assisted breathing	2-11 years	1-3 microgram /kg	1-1.25 microgram /kg

Adult doses can be administered in children aged 12-17 years.

Geriatric population:
As with other opioids, the starting dose should be reduced in elderly (> 65 years of age) or debilitated persons. The effect of the starting dose should be taken into account in determining the maintenance doses.

4.3. Contraindications

Contraindicated in the following situations:

- Hypersensitivity to the active ingredient of the drug or any of the excipients,
- Respiratory depression
- Obstructive respiratory disease
- Concomitant use with monoamine oxidase inhibitors or use within two weeks after discontinuation of these drugs

4.4. Special warnings and precautions for use

Tolerance development and dependence can occur. Following intravenous administration of FENTAVER, a temporary decrease in blood pressure may develop, especially in hypovolemic patients.
Appropriate measures must be taken to maintain a stable arterial pressure.

Respiratory depression
As with other potential opioids, deep analgesia may be accompanied by marked respiratory depression, which may persist or recur during the post-operative period. When FENTAVER is administered in high doses or by infusion, it is imperative to ensure that adequate natural breathing

has been established and maintained before leaving the post-anesthesia care / recovery room.

Severe respiratory depression may occur after administration of FENTAVER at doses higher than 200 micrograms. These and other pharmacological effects of FENTAVER can be reversed by specific opioid antagonists. Additional doses may be required later, as respiratory depression may last longer than the opioid effect. Resuscitation equipment and opioid antagonists should be available. Hyperventilation during anesthesia can alter the patient's response to CO2, which affects post-operative breathing.
Administration of FENTAVER during delivery may cause neonatal respiratory depression.

Cardiac disease
Bradycardia and possibly cardiac arrest may occur in patients who have not received sufficient anticholinergics, or in cases where FENTAVER is combined with non-vagolytic novelistic muscle relaxants. Bradycardia can be antagonized with atropine.

Muscle rigidity
Muscle rigidity (morphine-like effect) may occur.

Muscle rigidity, including the thoracic muscles, can be avoided by the following measures:
- Slow intravenous injection (low doses are usually sufficient)
- Premedication with benzodiazepines,
- Use of muscle relaxants.

Non-epileptic (Myo)clonic movements may occur.

Precautions:
FENTAVER should be administered only in an environment where the airway can be controlled and by a staff who can control the airway.

Special dosage cases:
Rapid bolus injections of opioids should be avoided in patients with impaired intracerebral compliance; In such patients, the transient decrease in mean arterial pressure was sometimes accompanied by a temporary decrease in cerebral perfusion pressure.

Dose reduction is recommended in elderly or debilitated patients.
Dosage should be carefully titrated in patients with any of the following conditions: uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism, or insufficient renal or hepatic function. For this type of patients, longer - term post-operative monitoring is required.

A higher dose may be required in patients who are in chronic opioid therapy or have a history of opioid addiction.

Myasthenia gravis
In patients with myasthenia gravis, careful consideration should be given to the use of certain anticholinergic agents and neuromuscular blocking pharmaceutical agents before or during the administration of general anesthesia regimens, including intravenous administration of FENTAVER.

Interaction with neuroleptics
When FENTAVER is administered in conjunction with a neuroleptic, the patient should be aware of the specific properties of each drug, especially the duration of action may differ. The incidence of hypotension is higher when such a combination is used. Neuroleptics can induce extrapyramidal symptoms, but this can be controlled with anti-parkinson agents.

Bile duct
As with other opioids, administration of FENTAVER may cause increased pressure in the bile duct due to its anticholinergic effects and spasms may be observed in the Oddi sphincter in isolated cases.

Serotonin syndrome:
Caution is required when using FENTAVER in conjunction with drugs that affect the serotonergic neurotransmitter system.

When used in combination with serotonergic drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and drugs that reduce serotonin metabolism (including Monoamine Oxidase Inhibitors [MAOIs]) serotonin syndrome may develop. This situation can be seen at the recommended doses.

Symptoms of serotonin syndrome include changes in mental status (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, diarrhea).
If serotonin syndrome is suspected, FENTAVER should be discontinued immediately.

Pediatric population:
It should only be used as part of an anesthetic technique for analgesia in children with spontaneous breathing. It can be used as part of sedation / analgesia techniques only by an experienced physician and in an environment where sudden chest wall rigidity requiring intubation or apnea situations requiring airway support can be intervened.

Important information about some excipients in the composition of FENTAVER:
Since FENTAVER contains less than 23 mg of sodium in each dose, no negative effects due to sodium are expected.

4.5. Interactions with other medical products and other forms of interaction

Effect of other drugs on FENTAVER:
The use of opioid premedication, barbiturates, benzodiazepines, neuroleptics, halogenic gases, and other non-selective central nervous system (CNS) depressants (e.g. alcohol) can strengthen or prolong respiratory depression caused by FENTAVER.
When patients take other CNS depressants, the dose of FENTAVER needed will be less than normal.

FENTAVER is a drug with high clearance and is extensively and rapidly metabolized mainly by cytochrome P4503A4 (CYP3A4).

Itraconazole (a potent CYP3A4 inhibitor) at a dose of 200 mg/day administered orally for four days had no significant effect on the pharmacokinetics of intravenous fentanyl.

Oral ritonavir (one of the strongest CYP3A4 inhibitors) reduced the clearance of intravenous fentanyl by two thirds; however, the maximum plasma concentration achieved after a single intravenous dose of fentanyl was not affected.

Co-administration of fluconazole or voriconazole (moderate CYP3A4 inhibitors) with FENTAVER may result in increased exposure to FENTAVER. When FENTAVER is used as a single dose, the concomitant use of strong CYP3A4 inhibitors such as ritonavir requires special patient care and monitoring.

Continuous treatment using FENTAVER in combination with CYP3A4 inhibitors may require a dose reduction to avoid accumulation of FENTAVER, which may cause prolonged or delayed respiratory depression.

In combination with non-vagolytic muscle relaxants, bradycardia and possibly cardiac arrest may occur.

Simultaneous use of FENTAVER with droperidol may result in a higher incidence of hypotension.

Serotonergic drugs:
Serotonin syndrome with a life-threatening risk may develop when used in combination with serotonergic drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and drugs that reduce serotonin metabolism (including Monoamine Oxidase Inhibitors [MAOI]).

The effect of FENTAVER on other drugs:
Following the administration of FENTAVER, the dose of other central nervous system depressant drugs should be reduced.

When used with FENTAVER, the plasma concentration of etomidate is significantly increased (2-3-fold). When co-administered with FENTAVER, the total plasma clearance and volume of distribution are significantly (by 2 to 3-fold) reduced, with no change in the half-life of etomidate.

The terminal half-life of intravenous midazolam administered in combination with FENTAVER is prolonged and plasma clearance is reduced. If these drugs are used in combination with FENTAVER, their dose may need to be reduced.

Additional information on special populations:
No interaction studies have been conducted on specific populations.

Pediatric population:
No interaction studies have been conducted on pediatric population.

4.6. Pregnancy and lactation

General advice
Pregnancy category: C

Women with childbearing potential/Contraception
During the period when FENTAVER should be used, if necessary, it should be protected from pregnancy using an appropriate method of contraception.

Pregnancy
Studies in animals have shown reproductive toxicity (See section 5.3). The potential risk for humans is unknown. There is not enough data regarding the use of FENTAVER in pregnant women. FENTAVER can cross the placenta early in pregnancy. Studies on animals have shown reproductive toxicity (See section 5.3). The potential risk for humans is unknown.

FENTAVER is not recommended to be administered (intramuscular or intravenous) during delivery (including cesarean section) as it may cross the placenta and suppress natural respiration in the neonatal period. If FENTAVER is to be used, supported breathing equipment should be available for use when required by both mother and baby. An antidote should be available for the child at all times.

Lactation
Fentanyl passes into breast milk. For this reason, breastfeeding and the use of milked breast milk are not recommended within 24 hours of administration of the drug. The risk/ benefit ratio of breastfeeding following FENTAVER should be taken into account.

Fertility
There are no clinical data on the effects of fentanyl on male and female fertility. In animal studies, some tests with rats showed reduced female fertility at maternally toxic doses (See section 5.3).

4.7. Effects on ability to drive and use machines

Patients should be warned that if they are discharged early, they should not drive or use machinery and do anything that requires attention within 24 hours after the administration. This drug may impair cognitive functions and affect the patient's ability to drive safely.
When prescribing this medicine, patients should be told the following:

- The medicine may affect your ability to drive.
- Do not drive before learning how the drug will affect you,
- Driving while under the influence of this drug is a traffic offense,

But if the following applies to you, it does not knowingly commit a crime:

- If this medicine is prescribed for the treatment of a medical condition or dental treatment,
- If you are taking the medicine as the prescribing doctor told you and as directed in the instructions for use of this medicine,
- If it does not affect your ability to drive safely.

4.8. Undesirable effects

Clinical trial data
Data on the safety of IV fentanyl were obtained from 376 patients participating in 20 clinical trials in which IV fentanyl was used as an anesthetic agent. These patients received at least one dose of IV fentanyl and provided safety information.

The most frequently reported adverse drug reactions in these clinical trials (incidence 5% or more) were: nausea (26.1%), vomiting (18.6%), muscle rigidity (10.4%), hypotension (8.8%), hypertension (8.8%), bradycardia (6.1%) and sedation (5.3%).

Adverse drug reactions reported in clinical trials or post-marketing experience, including the above, are listed below:
Adverse drug reactions are listed by system organ class and frequency (SOC):
Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000) and unknown (estimation based on the existing data is impossible).

Immune system disorders

Unknown: Hypersensitivity (such as anaphylactic shock, anaphylactic reaction and urticaria)

Psychiatric disorders
Common: Agitation
Uncommon: Euphoric state

Nervous system disorders
Very common: Muscle rigidity (including thoracic muscles)
Common: Dyskinesia, sedation, dizziness / lightheadedness
Uncommon: Headache
Unknown: Convulsions, loss of consciousness, myoclonus

Eye disorders
Common: Visual disturbances

Cardiac disorders
Common: Bradycardia, tachycardia, arrhythmia
Unknown: Cardiac arrest

Vascular disorders
Common: Hypotension, hypertension, venous pain
Uncommon: Phlebitis, blood pressure fluctuations

Respiratory, thoracic and mediastinal disorders
Common: Laryngospasm, bronchospasm, apnea
Uncommon: Hyperventilation, hiccups
Unknown: Respiratory depression

Gastrointestinal disorders
Very common: Nausea, vomiting

Skin and subcutaneous tissue disorders
Common: Allergic dermatitis
Unknown: Pruritus

General disorders and administration site conditions

Uncommon: Chills, hypothermia

Injury and poisoning, surgical and medical procedures

Common: Post-operative confusion

Uncommon: Respiratory complication of anesthesia

When a neuroleptic is used in combination with FENTAVER, the following adverse reactions may be observed: chills and / or tremors; restlessness, post-operative hallucinatory episodes and extrapyramidal symptoms (See section 4.4).

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose and treatment

Symptoms and signs:

Symptoms of FENTAVER overdose are generally in the form of increased pharmacological effects. Depending on the individual sensitivity, the clinical picture is primarily defined by the degrees of respiratory depression ranging from bradypnea to apnea.

Treatment:

If hypoventilation or apnea occurs:

- Oxygen should be administered and breathing assisted or controlled as needed.

In case of respiratory depression:

- The use of a narcotic antagonist is indicated. This does not make more urgent countermeasures unnecessary.
- Respiratory depression may last longer than the effect of the antagonist; therefore, additional doses of the antagonist may be required later.

In case of muscle rigidity:

- An intravenous neuromuscular blocking agent may be required to facilitate assisted or controlled breathing.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Opioid anesthetics
ATC Code: N01AH01

General properties

Fentanyl is a synthetic opioid that is 50 to 100 times stronger than morphine.
Its effect starts quickly and its duration of action is short. In humans, surgical analgesia, respiratory depression, bradycardia and other typical morphine-like effects develop rapidly with a single IV dose of 0.5-1 mg/70kg. The maximum duration of action is approximately 30 minutes. All potent morphine-like drugs develop pain relief, respiratory depression, nausea, constipation, physical dependence, some vagus effects, and varying degrees of sedation. Fentanyl differs from morphine not only in its short duration of action, but also in the absence of vomiting in animals and minimal hypotensive activity.
All the effects of fentanyl can be rapidly and completely reversed by a specific narcotic antagonist.

5.2. Pharmacokinetic properties

Distribution:
Plasma concentrations of fentanyl decrease rapidly after intravenous injection, with sequential distribution half-lives of approximately 1 minute and 18 minutes, and terminal elimination half-life of 475 minutes. The V_c (central compartment distribution volume) of fentanyl is 13 L and its total V_{dss} (distribution volume at steady state) is 339 L. Plasma protein binding of fentanyl is approximately 84%.

Biotransformation:
Fentanyl is rapidly metabolized by the enzyme CYP3A4, mainly in the liver. Its major metabolite is norfentanyl. Clearance of fentanyl is 574 mL/min.

Elimination:
About 75% of the administered dose is excreted within 24 hours, and only 10% is excreted in urine as an unchanged drug.

Characteristics in patients

Children:
The rate at which fentanyl binds to plasma proteins in newborn babies is about 62%, lower than in adults. The volume of clearance and distribution is higher in dairy children and children. This may result in a further dose requirement for fentanyl.

Adult patients with burns:
A larger volume of distribution with up to 44% increase in clearance of fentanyl results in decreased plasma concentrations of the drug. This may require increasing the fentanyl dose.

Renal failure:
Data from a study using intravenous fentanyl in renal transplant patients suggest that clearance may be reduced in this patient population. If patients with renal insufficiency will use fentanyl, they should be carefully observed for signs of fentanyl toxicity and the dose should be reduced if necessary (See section 4.2).

Obese patients:
Increased fentanyl clearance was seen with increased body mass. In patients with a Body Mass Index of more than 30, fentanyl clearance increases by approximately 10% with every 10 kg increase in lean body mass.

5.3. Preclinical safety data

As with other opioid analgesics, in vitro fentanyl has shown mutagenic effects in mammalian cell culture experiment only at cytotoxic concentrations and in combination with metabolic activation. In in vivo rodent experiments and bacterial studies, fentanyl showed no signs of mutagenicity.

In a two-year study conducted in rats, fentanyl was not found to be carcinogenic.

Some tests in female rats have shown reduced fertility and embryo mortality. These findings are associated with maternal toxicity and are not related to the drug's direct effect on the developing embryo. No evidence of teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Water for injection

6.2. Incompatibilities

This medicinal product should not be mixed with other products.
FENTAVER is stable for 24 hours at 2-8 ° C when diluted with 0.9% NaCl and 5% Dextrose solution.

6.3. Shelf life
24 months

6.4. Special precautions for storage
Store at room temperature below 25°C.
Store the ampoules in their original outer carton to protect from light.

6.5. Nature and contents of container
10 mL x 1 glass ampoule.

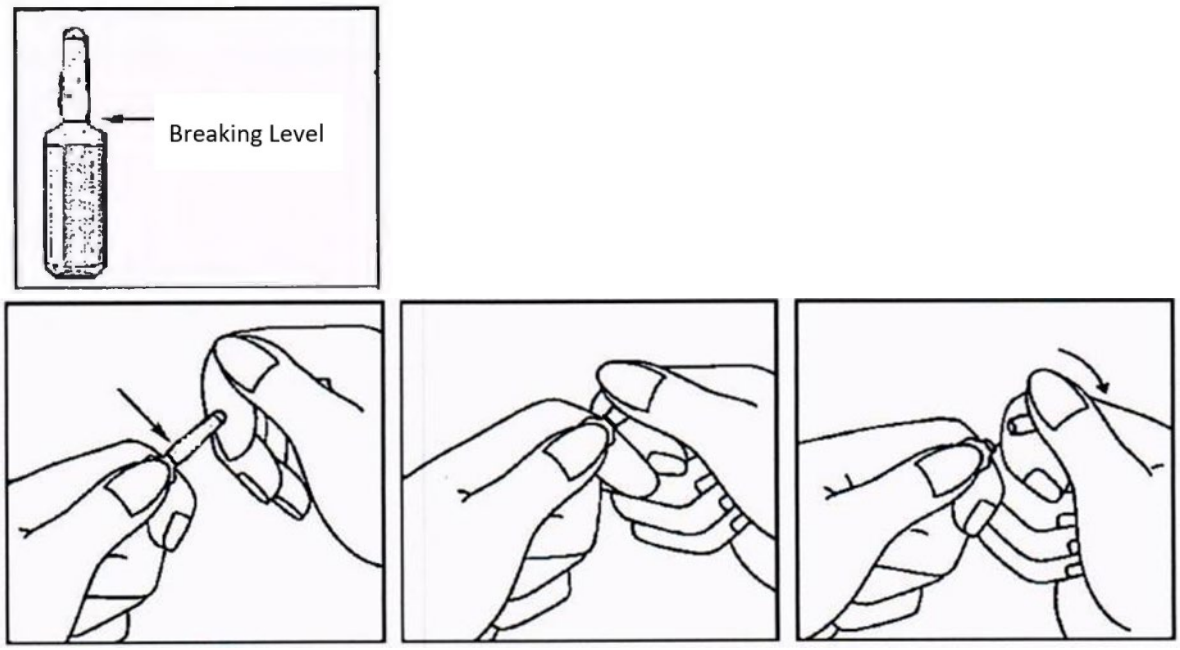
6.6. Special precautions for disposal and other handling

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

Method of Administration:
FENTAVER dosage should be individualized according to age, body weight, physical condition, underlying pathological conditions, use of other drugs, type of surgery and anesthesia.
The starting dose should be reduced in elderly (> 65 years of age) and debilitated patients. When determining complementary (additional) doses, the effect of the starting dose should be taken into account.

Considerations in use

1. Hold the ampoule between thumb and index fingers, release the tip of the ampoule.
2. Hold the tip of the ampoule with the other hand so that the index finger is on the neck of the ampoule and the thumb parallel to the colored lines on the colored dot.
3. Quickly break the tip of the ampoule with the thumb above the point, while the body of the ampoule should be held firmly with the other hand.



7. MARKETING AUTHORIZATION HOLDER
HAVER FARMA İlaç A.Ş.
Akbaba Mah. Maraş Cad.
No:52/2/1 34820
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