

## PATIENT INFORMATION LEAFLET

### SEDEVER 5 mg/5 mL I.V./I.M./Rectal ampoule for injection and infusion

For intramuscular, intravenous or rectal administration.

Sterile

- **Active Ingredient:** Each 5 mL ampoule contains 5 mg midazolam.
- **Excipients:** Sodium chloride, hydrochloric acid, sodium hydroxide, water for injection.

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.*
- *Tell your doctor that you are taking this medicine when you go to the doctor or hospital during the use of this medicine.*
- *Follow exactly what is written in this instruction. Do not use **high or low doses** other than the recommended dosage.*

### **What is in this leaflet:**

1. ***SEDEVER is and what it is used for?***
2. ***What you need to know before you use SEDEVER***
3. ***How to use SEDEVER?***
4. ***Possible side effects***
5. ***How to store SEDEVER***

#### **1. What SEDEVER is and what it is used for?**

- SEDEVER is a benzodiazepine of the imidazobenzodiazepine group. It is a fast-acting drug used to induce sleep (calming down, lethargy or sleepy state) and to reduce excitement, muscle contractions and spasms. The drug is administered by intravenous injection, drip injection (infusion), intramuscular injection or rectal administration.
- SEDEVER is a clear, colorless, particle-free sterile solution whose active ingredient is midazolam. Each ampoule contains 5 mg of midazolam in 5 mL of solution. Each box contains 5 or 10 transparent, Type I self-contained glass ampoules of 5 mL.
- This drug is used for drowsiness and numbness in adults and children during examinations and treatment. It is used as a drug given before the intervention, to soothe patients before treatment and to put patients in the intensive care unit to sleep. Midazolam

can be used alone or in combination with other drugs used in anesthesia.

## **2.What you need to know before you use SEDEVER**

### **DO NOT USE SEDEVER;**

If;

- You are allergic (hypersensitive) to the group of drugs known as benzodiazepines or to any of the excipients contained in the drug.
- You have severe breathing difficulties or respiratory failure and are consciously drowsy (drowsiness and calmness).

### **USE SEDEVER CAREFULLY;**

If;

- You are over 60 years old,
- You have persistent breathing problems,
- You have myasthenia gravis (a disease caused by muscle weakness),
- You have liver, kidney or heart functions,
- You are addicted to alcohol or drugs,
- You are using any medication other than those prescribed by your doctor (See Section Using with other medicines),
- You are pregnant or possibly pregnant,

Inform your doctor in all these cases.

The use of SEDEVER in children and infants requires special attention. If your child has a heart problem, inform your doctor. Thus, your doctor will know that you or your child need careful observation and will adjust the dose specifically.

When SEDEVER is administered intravenously, it can reduce your breathing and heart rate. In rare cases, it may cause your breathing or heart to stop. To prevent this from happening, doses are given slowly and in as low amounts as possible.

Patients response to midazolam is highly variable when SEDEVER is given prior to intervention. Therefore, you will be very tightly controlled to make sure you get the correct dose.

If these warnings are valid for you, even at any time in the past, please consult your doctor.

### **Use of SEDEVER with food and drink**

- Alcohol can increase the sleep-inducing effects of SEDEVER and therefore its use should be avoided. Do not drink alcohol until your doctor gives permission.

## **Pregnancy**

*Consult your doctor or pharmacist before using this medication.*

- If you are pregnant, think you may be pregnant, or are planning to become pregnant, please consult your doctor. Your doctor will decide whether to take the medicine or not.
- If your doctor decides to prescribe the drug, your baby may have irregular heartbeats, low body temperature, breathing, feeding, and sucking difficulties in late pregnancy, delivery or cesarean section. You may be at risk of pulling vomit into your lungs.
- There is not enough information about the safety of SEDEVER during pregnancy. Benzodiazepines should not be used during pregnancy unless there is a safer alternative.

*If you notice that you are pregnant during treatment, consult your doctor or pharmacist.*

## **Breast-feeding**

*Consult your doctor or pharmacist before using this medication.*

- SEDEVER can pass into breast milk, so you should not breast-feed for 24 hours after taking the medicine.

## **Driving and using machines**

The medication may make you drowsy, forgetful, or affect your concentration and coordination.

This can affect your performance in skilled jobs (eg using or driving).

Your doctor will decide when to start this type of work again. After the administration (always) you must be accompanied by a responsible adult until you get home.

## **Important information about some of the excipients in SEDEVER**

SEDEVER contains less than 23 mg of sodium, but due to the dose it contains, no adverse effects related to sodium are expected at this dose.

## **Using other medicines**

More than one drug used at the same time can increase or decrease the effect of drugs taken.

For example; sedatives, hypnotics (sleeping pills), sedatives, antidepressants, narcotic analgesics (very strong painkillers), antiepileptics (for epilepsy treatment), anesthetics and some antihistamines (for allergy treatment) can aggravate the effects of SEDEVER.

In addition, antifungals, antibiotics, drugs used in the treatment of blood pressure and digestive problems, and some drugs used in the treatment of AIDS and HIV can increase the effects of midazolam.

*If you are currently using any prescription or non-prescription medicine or have used it recently, please inform your doctor or pharmacist about them.*

### **3.How to use SEDEVER**

#### **Instructions for use and dose/administration frequency:**

Your doctor will decide the appropriate dose for you. Doses may differ depending on the planned treatment and sedation required. Your age, weight, general health condition, response to medication and other medicines used at the same time will affect the dose taken.

If you are using strong pain relievers, you should use them first and then take the SEDEVER dose specifically adjusted for you.

#### **Method of administration**

SEDEVER is administered slowly by intravenous injection, drip injection (infusion), intramuscular injection or rectal administration.

#### **Various age groups**

##### **Use in children and elderly:**

Your doctor will decide the appropriate dosage for you and your child.

##### **Special cases of use:**

##### **Renal failure**

No dose adjustment is required.

##### **Hepatic failure**

In case of liver failure, your doctor may need to reduce the dose.

*If you have an impression that the effect of SEDEVER is too strong or too weak, talk to your doctor or pharmacist.*

##### **If you use more SEDEVER than you should**

Your medicine will be administered by a doctor. If you think you have been given too much medication, you should tell your doctor.

*Talk to a physician or pharmacist if you have used more SEDEVER than you should use.*

##### **If you forget to use SEDEVER**

It is not valid as it will be administered by your doctor.

*Do not take double doses to make up for forgotten doses.*

#### **Effects that may occur when treatment with SEDEVER is terminated**

##### **Long Term Treatment**

Patients on long-term treatment with SEDEVER may develop intolerance (drugs may be less effective) or vary by medication.

The following withdrawal symptoms may occur after prolonged treatment (such as in the intensive care unit): Headache, muscle aches, restlessness, tension, discomfort, confusion, irritability, inability to sleep, mood changes, hallucinations and convulsions. If you have these

effects, your doctor will gradually reduce the dose.

*If you have any further questions about the use of this medication, please consult your doctor or pharmacist.*

#### **4. Possible side effects**

As with all medicines, there may be side effects in people who are sensitive to the ingredients of SEDEVER.

**If you notice any of the following, stop using SEDEVER and inform your doctor IMMEDIATELY, or apply to the emergency service of the nearest hospital:**

- Temporary memory loss. How long this will take depends on the SEDEVER dose you take, and you may experience this after treatment. It has been reported in some specific cases.
- Respiratory complications (sometimes causing heart or respiratory arrest)
- Blood and circulatory system disorders
- Low blood pressure
- Changes in heart rate and pressure
- Fainting
- Shortness of breath
- Obstruction of the windpipe
- Anaphylactic shock (life-threatening allergic reaction)

Life-threatening events are more common in the elderly with pre-existing respiratory failure or heart problems, especially when the injection is given too quickly or in high doses.

Respiratory problems are likely to develop in patients younger than 6 months, so they will be given a dose-by-little dose to monitor their breathing and oxygen levels.

**If you notice any of the following, inform your doctor immediately or contact the emergency department of your nearest hospital:**

- Rash
- Allergic reaction
- Difficulty managing muscles
- Agitation
- Muscle spasms and muscle tremors
- Feeling sick
- Vomiting
- Constipation

These are all serious side effects. Emergency medical attention may be required.

**If you notice any of the following, tell your doctor:**

- Itching
- Prolonged calming
- Drowsiness
- Reduced attention
- Mind blur
- Intense happiness
- Hallucinations
- Fatigue
- Headache
- Dizziness
- Unrest, excitement
- Feeling of grudge, violence, fighting, aggression
- Hiccups
- Dry mouth
- Wheezing
- Redness and pain at the injection site
- Swelling and redness in the veins
- Blood clotting

These are mild side effects of SEDEVER.

These have mostly been observed when high doses were given or when the drug was administered too quickly. Children and elderly people are more susceptible to these reactions. Contractions have been reported more frequently in preterm and newborn babies.

After long-term intravenous use, it may become dependent on midazolam. To avoid withdrawal symptoms, including withdrawal spasms, it is important that you taper off the medication dose gradually.

*If you experience any side effect not mentioned in this patient information leaflet, inform your doctor or your pharmacist.*

**Reporting of the side effects:**

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.

**5.How to store SEDEVER**

*Keep SEDEVER out of the reach and sight of children and within its packaging.*

- Store at room temperature below 25 ° C.
- Protect from light.
- SEDEVER ampoules should not be frozen due to the possibility of explosion. At room temperature, a precipitation may be seen which dissolves with agitation.
- SEDEVER ampoules are for single use only.
- Before use, the solution should be inspected visually. Only clear solutions without particles should be used

**Use in compliance with the expiry date.**

*Do not use SEDEVER after the expiry date which is stated on the packaging.*

***Marketing Authorization Holder:***

HAYER FARMA İlaç A.Ş.

Akbaba Mah. Maraş Cad. No:52/1/2

34820 Beykoz / İSTANBUL

***Manufacturer:***

Osel İlaç Sanayi ve Ticaret A.Ş.

Akbaba Mah. Maraş Cad. No: 52

Beykoz / İSTANBUL

*This patient information leaflet approved in 09/10/2015*

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

SEDEVER 5 mg/5 mL I.V./I.M./Rectal ampoule solution for injection and infusion

**Sterile**

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### Active Substance:

Each 5 mL ampoule contains 5 mg of midazolam.

#### Excipients:

Sodium chloride 45 mg

Sodium hydroxide q.s. (for pH adjustment)

See section 6.1 for excipients.

### 3. PHARMACEUTICAL FORM

Solution for injection

Clear, colorless and sterile solution

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutical indications

SEDEVER as a sedative drug acting in a short time has the following indications:

##### *In adults*

- Conscious sedation with or without local anesthesia before and during diagnostic or surgical procedures.
- Anesthesia:
  - Premedication before anesthesia induction
  - Anesthesia induction
  - As sedative in combined anesthesia
- Creating sedation in intensive care units.

##### *In children*

- Conscious sedation before and during diagnostic or surgical procedures, with or without local anesthesia
- Anesthesia
  - Premedication before anesthesia induction
- It can be used for creating sedation in intensive care units.

#### 4.2. Posology and method of administration

**ONLY FOR CLINICAL USE.**



### Standard dose

Midazolam is a potent sedative agent that requires slow administration and individual dosing in each patient.

The dose should be adjusted individually for each individual, and depending on the patient's clinical needs, physical condition, age, and drugs being used, dose titration is highly recommended to safely achieve the desired level of sedation.

In adults over 60 years of age, critically ill, high-risk patients and pediatric patients, the dose should be carefully determined and risk factors for each patient should be considered.

After intravenous injection, the drug takes effect within 2 minutes. The maximum effect is achieved after 5 to 10 minutes.

Standard doses are given in the table below. Details are in the text after the table.

**Table 1. Standard doses**

Indication	Adults over 60 years	Adults over 60 years of age, critically ill, high risk patients	Pediatric patients
<b>Conscious sedation</b>	<b>I.V.</b> Initial dose: 2-2.5 mg Titration dose: 1 mg Total dose: 3.5-7.5 mg	<b>I.V.</b> Initial dose: 0.5-1 mg Titration dose: 0.5-1 mg Total dose: <3.5 mg	<b>I.V. 6 months-5 years</b> Initial dose: 0.05-0.1 mg/kg Total dose: <6 mg <b>IV 6-12 years</b> Initial dose: 0.025-0.05 mg/kg Total dose: <10 mg <b>13-16 years</b> As adults <b>Rectal &gt; 6 months</b> 0.3-0.5 mg/kg <b>I.M. 1-15 years</b> 0.05-0.15 mg/kg
<b>Anesthesia premedication</b>	<b>I.V.</b> repeatable 1-2 mg <b>I.M.</b> 0.07-0.1 mg/kg	<b>I.V.</b> Initial dose: 0.5 mg Slow titration needed <b>I.M.</b> 0.025-0.05 mg/kg	<b>Rectal older than 6 months</b> 0.3-0.5 mg/kg <b>I.M. 1-15 years</b> 0.08-0.2 mg /kg
<b>Anesthesia induction</b>	<b>I.V.</b> 0.15-0.2 mg/kg (0.3-0.35 mg/kg without premedication)	<b>IV</b> 0.05-0.15 mg/kg (0.15-0.3 mg/kg without premedication)	Not indicated in pediatric patients
<b>Sedatively in combined anesthesia</b>	<b>I.V.</b> Intermittent 0.03-0.1 mg/kg doses or 0.03-0.1 mg/kg/hr continuous infusion	<b>I.V.</b> Less than recommended dose for adults <60 years	Not indicated in pediatric patients

<b>Sedation in intensive care units</b>	<b>I.V.</b> Loading dose: 0.03-0.3 mg / kg in 1-2.5 mg increments Maintenance dose: 0.03-0.2 mg / kg / hour	<b>IV in neonates less than 32 weeks</b> 0.03 mg / kg / hour <b>IV born older than 32 weeks newborn (up to 6 months)</b> 0.06 mg / kg / hour <b>IV older than 6 months</b> Loading dose: 0.05-0.2 mg / kg Maintenance dose: 0.06-0.12 mg / kg / hour
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### **Conscious sedation**

SEDEVER is administered intravenously for basal (conscious) sedation before diagnostic or surgical intervention. The dose should be adjusted individually for each patient, titrated, and not administered by rapid or single bolus injection. The onset of sedation can be different in each patient, depending on the physical condition of the patient and the details of dosing (administration rate, dose amount). If necessary, subsequent doses can be applied according to the needs of the individual. Special attention should be paid to signs of conscious sedation in patients with impaired respiratory function (See section 4.4. Special warnings and precautions for use).

#### *Adults*

SEDEVER should be administered slowly at a rate of IV injection of approximately 1 mg / 30 seconds.

In adults under 60 years of age, the first dose is 2-2.5 mg administered 5-10 minutes before the start of the procedure. If necessary, it can be continued with 1 mg doses. It was determined that the total doses ranged from 3.5 to 7.5 mg on average. Doses above 5.0 mg are generally not required.

In adults over 60 years of age, critically ill patients and high-risk patients, the first dose should be administered 5-10 minutes before the start of the procedure and reduced to around 0.5-1.0 mg. If necessary, it can be continued with doses of 0.5-1 mg. Since the maximum effect is reached more slowly in these patients, the overdose of SEDEVER should be titrated very slowly and carefully. Generally, a total dose of more than 3.5 mg is not required.

#### *Pediatric patients*

##### *IV administration:*

SEDEVER should be titrated slowly until the desired clinical effect is achieved. The first dose of SEDEVER should be administered within 2-3 minutes. It is recommended to wait 2-5 minutes after the dose is administered for the sedative effect to be fully evaluated before starting the procedure or repeating the dose. If further sedation is required, continue titration in small increments until the desired level of sedation is reached. Significantly higher doses may be required in infants and children under 5 years of age compared to older children and adolescents.

1) *Children under six months of age:* Children under six months of age are more susceptible to respiratory tract obstruction and hypoventilation, therefore the use of conscious sedation is not recommended in children under six months of age. In such cases, titration in small increments and careful monitoring are essential until clinical effect is achieved.

2) *Pediatric patients between the ages of six months and 5 years:* The first dose is 0.05-0.1 mg / kg.

A total dose of 0.6 mg / kg may be required to achieve the desired endpoint, but the total dose should not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with high doses (See section 4.4. Special warnings and precautions for use).

3) *Children between the ages of 6-12*: The first dose is 0.025-0.05 mg / kg. A total dose of 0.4 mg / kg can be used with a maximum dose of 10 mg. Prolonged sedation and risk of hypoventilation may be associated with high doses (See section 4.4. Special warnings and precautions for use).

4) *Children between the ages of 13-16*: The same dose as adults.

*Rectal administration (pediatric patients older than six months)*

The total dose of SEDEVER should be between 0.3-0.5 mg/kg. The total dose should be administered at once and repeated rectal administration avoided. Due to the limited data available in this population, its use is not recommended in children younger than six months (See Section 4.2. Special Dosing Instructions).

*I.M. administration (1-16 years old children)*

The recommended dose range is 0.05-0.15 mg/kg 5-10 minutes before the start of the procedure. Generally, a total dose of more than 10.0 mg is not required. Only in exceptional cases i.m. administration should be done. Rectal administration should be preferred as IM injection can be painful.

In children less than 15 kg body weight, midazolam concentrations above 1 mg/mL are not recommended. Higher concentrations should be diluted to 1 mg/mL.

**Anesthesia - Premedication**

SEDEVER premedication applied just before the procedure provides sedation (induction of sleep or drowsiness and decreased comprehension) and weakens memory before surgery. SEDEVER can also be used with anticholinergic agents. For this indication, SEDEVER should be administered IV or IM (deep into a large muscle mass 20-60 minutes before the induction of anesthesia) or rectally, preferably in children. Since the sensitivity between patients varies and overdose symptoms may occur, the patient should be observed for a sufficient period of time after administration.

*Adults*

The recommended dose for adults with ASA Physical Status I and II and under 60 years of age is 1-2 mg IV or 0.07-0.1 mg/kg IM, repeatedly as necessary, to ensure preoperative sedation and to weaken memory prior to surgery.

When SEDEVER is administered to adults over the age of 60, critically ill, high risk patients, the dose should be reduced and adjusted individually for each patient. The recommended initial IV dose is 0.5 mg, and the dose should be increased gradually by titration as needed. It is necessary to wait 2-3 minutes to fully evaluate the effect between doses. If narcotics are not used at the same time, an IM dose of 0.025-0.05 mg/kg is recommended. The usual dose is 2-3 mg.

*Pediatric patients*

*Rectal administration (older than six months)*

Generally, a total dose of SEDEVER 0.4 mg / kg (ranging from 0.3-0.5 mg/kg) should be administered 20-30 minutes before induction of anesthesia. Use is not recommended in children younger than six months as the available data are limited.

### *I.M. administration (1-15 years old)*

This route should only be used in exceptional cases, as IM injection can be painful. Rectal administration should be preferred. However, IM SEDEVER given in dose ranges of 0.08-0.2 mg/kg has been shown to be effective and safe. In children 1-15 years of age, proportionately higher doses should be administered in relation to body weight than in adults. It is recommended that SEDEVER be applied deep into a large muscle mass 30-60 minutes before induction of anesthesia. In children less than 15 kg body weight, midazolam concentrations above 1 mg/mL are not recommended. Higher concentrations should be diluted to 1 mg/mL.

### **Anesthesia induction**

#### *Adults*

Patient responses may vary when SEDEVER is used for anesthesia induction before other anesthetic agents are administered. The dose should be titrated to the desired effect, based on the age and clinical condition of the patient. When SEDEVER is used for the induction of anesthesia before other IV or inhalation agents are administered, or in combination, the initial dose of each agent can be significantly reduced (up to 25% of the overall starting dose). The desired level of anesthesia is achieved by gradual titration. The induction dose of iv SEDEVER should be administered slowly in small increments. Each increment of not more than 5 mg should be given over 20-30 seconds, leaving 2 minutes between each successive increment.

#### *In adults under 60*

Within 20-30 seconds, A dose of 0.2 mg / kg, which is administered by the i.v. route and is expected for 2 minutes, is sufficient for its effect. The dose may be higher (0.3-0.35 mg/kg) in non-premedicated patients; This dose is administered intravenously within 20-30 seconds and 2 minutes is waited for the effect to be seen. If it is desired to complete induction, increments of approximately 25% of the patient's starting dose can be made. Induction can also be completed with volatile, liquid anesthetic agents taken by inhalation. In resistant cases, a total dose of 0.6 mg/kg can be used for induction, but such large doses may prolong the recovery period.

#### *Adults over 60 years of age (critically ill and high-risk patients)*

1. *In non-premedicated patients*, the minimum starting dose is 0.15-0.2 mg/kg recommended.
2. *In patients who have been premedicated*, a dose of 0.05-0.15 mg/kg administered intravenously within 20-30 seconds and expected for 2 minutes is sufficient.

#### *Pediatric patients*

Since their experience in children is very limited, the use of SEDEVER for induction of anesthesia is limited to adults only.

### **Sedative component in combined anesthesia**

#### *Adults*

For sedation in combined anesthesia, SEDEVER is administered either as intermittent small IV doses (ranging from 0.03-0.1 mg/kg) or as a continuous IV infusion of SEDEVER (ranging from 0.03-0.1

mg/kg per hour), typically in combination with analgesics. Dosage and dose ranges vary according to the individual patient's response. Lower maintenance doses will be required in adults over 60, critically ill and / or high risk patients.

#### *Pediatric patients*

Since their experience in children is very limited, the use of SEDEVER as a sedative in combined anesthesia is limited to adults only.

#### **Sedation in intensive care units**

To achieve the desired level of sedation, the dose of SEDEVER should be titrated gradually after continuous infusion or intermittent bolus, based on the patient's clinical need, physical condition, age, and medications (See section 4.5 Interactions with other medicinal products and other forms of interaction).

#### *Adults*

I.V. loading dose; 0.03-0.3 mg/ kg should be administered slowly in increments. Increments of 1-2.5 mg should be injected within 20-30 seconds, allowing 2 minutes between successive increments. In hypovolemic, vasoconstricted, or hypothermic patients the loading dose should be reduced or omitted. If SEDEVER is to be given together with potent analgesics, the analgesic agent should be given beforehand in order to safely titrate the effects of SEDEVER after sedation caused by analgesics.

I.V. maintenance dose; It varies between 0.03-0.2 mg / kg / hour. In hypovolemic, vasoconstricted, or hypothermic patients, the maintenance dose should be reduced. The level of sedation should be monitored regularly, if the patient's condition allows. With prolonged sedation, tolerance may develop and the dose may have to be increased.

#### *Pediatric patients*

Midazolam concentrations above 1 mg/mL are not recommended in preterm infants and newborns or pediatric patients below 15 kg body weight. Higher concentrations should be diluted to 1 mg/mL.

#### *Children up to six months*

SEDEVER should be given as a continuous IV infusion:

- In newborns younger than 32 weeks: starting dose 0.03 mg/kg/hr (0.5 µg/kg/min)
- In neonates older than 32 weeks to six months: starting dose 0.06 mg/kg/hr (1 µg/kg/min)

Intravenous loading doses should not be administered in newborns, instead infusion can be made faster in the first few hours to reach therapeutic plasma levels. The rate of infusion should be carefully and frequently monitored, especially after the first 24 hours, to administer the lowest possible effective dose and to reduce the potential for drug accumulation. Patients should be carefully monitored for respiratory rate and oxygen saturation.

#### *Children over six months old*

In intubated and ventilated patients, 0.05-0.2 mg/kg loading the i.v. dose of SEDEVER should be administered slowly over at least 2-3 minutes. SEDEVER should not be given as a rapid intravenous dose. The loading dose is followed by a continuous IV infusion of 0.06-0.12 mg/kg per hour (1-2 µg /kg/min). The infusion rate can be increased or decreased if necessary (usually 25% of the first or next infusion rate), or supplemental IV SEDEVER doses can be administered to increase or maintain

the desired effect. When starting SEDEVER infusion in patients with impaired hemodynamic balance, the classical loading dose should be titrated in small increments and the patient should be monitored for hemodynamic imbalances (e.g., hypotension). These patients are also sensitive to the respiratory depressant effect of SEDEVER and should be carefully monitored in terms of respiratory rate and oxygen saturation.

### **Additional information on special populations**

#### *Renal Impairment*

In patients with renal impairment (creatinine clearance <10 mL/min), the pharmacokinetics of unbound midazolam were similar to those reported in healthy volunteers. It has been shown that in those with chronic kidney disease the accumulation of  $\alpha$ -hydroxy midazolam and midazolam may contribute to its clinical effects resulting in prolonged sedation.

**Table 2. Recovery period after discontinuation of midazolam infusion**

		Sobering time (min)	
	Patient count	Average $\pm$ SD	Interval
All patients	37	27.8 $\pm$ 37.2	0- 140
Patients without renal or hepatic failure	24	13.6 $\pm$ 16.4	0- 58
Patients with renal failure without hepatic failure	9	44.6 $\pm$ 42.5	2-120
Patients with renal and hepatic failure	2	-	124- 140

#### *Renal Impairment*

Liver failure decreases IV midazolam clearance, increasing the elimination half-life. Therefore, clinical effects may be stronger and longer lasting. The required dose of midazolam can be reduced and regular monitoring of vital signs should be ensured (See section 4.2. Posology and method of administration and 4.4 Special warnings and precautions for use).

#### *Pediatric patients*

- Midazolam concentrations above 1 mg/mL are not recommended for preterm infants and newborns or pediatric patients less than 15 kg body weight. Higher concentrations should be diluted to 1 mg/mL.
- In pediatric patients younger than 6 months of age, except intensive care units, i.v. and rectal administration is not recommended.
- SEDEVER is not indicated as a sedative for anesthesia induction and combined anesthesia in children due to limited data.

### *Geriatric population*

For geriatric patients over 60 years of age, the required doses are lower and should be continuously monitored for early signs of vital function changes (See section 4.2. Posology and method of administration and 4.4 Special warnings and precautions for use).

### **Special dosage instructions**

*For use with infusion solutions:* SEDEVER can be diluted with 0.9% sodium chloride, 5% and 10% dextrose, 5% levulose, Ringer and Hartmann solutions in a ratio of 15 mg midazolam in 100-1000 mL infusion solution. These solutions remain physically and chemically stable for 24 hours at room temperature or 3 days at 2-8°C.

To avoid potential incompatibilities with other solutions, SEDEVER should not be mixed with solutions other than those mentioned above. The product should be used immediately from a microbiological point of view. If not used immediately, it is the user's responsibility to store it in the proper storage time and conditions, and normally this period should not be longer than 24 hours at 2-8°C, unless dilution is performed under controlled and validated aseptic conditions. SEDEVER is for single use only. Unused solution should be discarded. Before use, the solution should be inspected visually. Only clear solutions without particles should be used.

*Rectal administration:* The rectal administration of the ampoule solution is made with the plastic administration tool at the tip of the syringe. If the volume to be applied is too small, water can be added until the total volume is 10 mL.

### **4.3. Contraindications**

The use of SEDEVER is contraindicated in patients with known hypersensitivity to benzodiazepines or any of the excipients contained in the drug.

Its use for conscious sedation is contraindicated in patients with severe respiratory insufficiency or acute respiratory depression.

### **4.4. Special warnings and precautions for use**

Midazolam should be administered by an experienced physician and where full respiratory and cardiovascular support and monitoring can be performed, and by persons trained in recognizing and correcting respiratory and cardiac adverse events, where only age and size appropriate resuscitation can be performed, because IV administration of midazolam can depress myocardial contraction and lead to apnea. In rare instances, serious cardiorespiratory adverse events have been observed. These are respiratory depression, apnea, respiratory arrest and / or heart arrest. Such life-threatening events are more common when the injection is given too quickly or when high doses are administered (See section 4.8 Undesirable effects). It requires special attention when used in conscious sedation in patients with impaired respiratory function.

#### *Premedication*

When midazolam is used for premedication, the patient should be observed for a sufficient period of time after administration, as sensitivity varies between patients and overdose symptoms may occur.

### *Patients in the high-risk group*

Special care should be taken when administering midazolam to patients in the high risk group:

- Adults over the age of 60
- Patients with impaired organ functions
- Respiratory function impairment
- Renal function impairment
- Hepatic function impairment
- Heart function impairment
- Pediatric patients especially with cardiovascular instability

These high-risk patients should receive lower doses (See section 4.2. Posology and method of administration) and should be constantly monitored for early signs of changes in vital functions. Benzodiazepines should be used with caution in patients with alcohol and drug addiction.

Special precautions should be taken when administering a substance with CNS depressant and / or muscle relaxant properties to a patient with myasthenia gravis together with midazolam.

### *Discharge criteria*

After taking SEDEVER, patients may be discharged from the hospital when recommended by the treating physician and accompanied by them. It is recommended to accompany the patient while going home after the administration.

### *Tolerance*

Loss of efficacy has been reported when SEDEVER is used for long-term sedation in intensive care units (ICU).

### *Deprivation symptoms*

Since the risk of drug withdrawal symptoms will increase after abrupt cessation of treatment, it is recommended to taper the dose slowly, especially after prolonged sedation (eg:  $\geq 2$ -3 days). The following withdrawal symptoms may occur; headache, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood swings, hallucinations, and convulsions.

### *Amnesia*

Midazolam causes anterograde amnesia. Long-term amnesia can cause problems in patients who are discharged after the intervention and are followed up outside the hospital.

### *Paradoxical reactions*

Paradoxical reactions such as agitation, involuntary movements (including tonic / clonic convulsions and muscle tremor), hyperactivity, hostility, anger reaction, aggression, paroxysmal excitability and attack have been reported after administration of midazolam. These reactions can occur when the injection is given too quickly or when a high dose is administered. The incidence of susceptibility to such reactions has been rarely reported in children and the elderly receiving high dose IV administration.

### *Altered elimination of midazolam*

In patients using compounds that inhibit or stimulate CYP3A4, midazolam elimination may vary and the dose of midazolam may need to be adjusted (see 4.5 Interaction with other medicinal products and other forms of interaction) In patients with hepatic impairment, low cardiac output and neonates,



midazolam elimination may be delayed (See section 4.2. Posology and method of administration; Additional information on special populations).

#### *Preterm babies*

While sedation is applied to preterm babies whose tracheas are not intubated and born before 36 weeks of gestation, extreme caution is recommended due to the increased risk of apnea. Rapid injection should be avoided in preterm babies born before 36 weeks of gestation. Patients should be carefully monitored for respiratory rate and oxygen saturation.

#### *Children under six months*

Since children younger than six months of age are more susceptible to airway obstruction and hypoventilation, titration in small increments until clinical effect is achieved and careful monitoring for respiratory rate and oxygen saturation (See also section 4.4. Special warnings and precautions for use; Premature birth) (preterm babies).

#### *Use of alcohol and CNS depressants together*

The use of SEDEVER in combination with alcohol and / or CNS depressants should be avoided. Such concomitant use has the potential to increase the possible clinical effects of SEDEVER, such as severe sedation, clinically related respiratory and / or cardio-vascular depression. (See section 4.5. Interactions with other medicinal products and other forms of interaction)

#### *Medical history of alcohol or drug addiction*

The use of SEDEVER should be avoided in patients with a medical history of alcohol or drug addiction.

#### *Others*

As with other substances with CNS depressant and / or muscle relaxant properties, special care should be taken when administering midazolam to patients with myasthenia gravis.

#### *Addiction*

Physical dependence may develop as a result of prolonged sedation of midazolam. The risk of addiction may increase with dose and duration of treatment; It is also more common in patients with a medical history of alcohol or drug addiction.

#### *Sodium chloride*

SEDEVER contains less than 23 mg sodium at a dose of 5 mg/5 mL. No sodium-related side effects are expected at this dose.

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

#### *Pharmacokinetic Drug-Drug Interactions*

Midazolam is mostly metabolized by cytochrome P450 3A4 (CYP3A4). CYP3A4 inhibitors and stimulants have the potential to increase and decrease plasma concentrations and consequently the pharmacodynamic properties of midazolam. No mechanism other than modulation of CYP3A4 activity has been demonstrated as a source for clinically relevant pharmacokinetic drug-drug interactions with midazolam. However, acute protein displacement from albumin is the theoretical possibility of drug interaction with drugs, preferably with high therapeutic serum concentrations, as has always been assumed (eg for valproic acid). Midazolam is not known to alter the pharmacokinetics of other drugs.

Considering the possibility of increased clinical effect and prolonged duration of midazolam after co-administration with CYP3A inhibiting drugs, it is recommended to monitor clinical effects and vital signs during the use of midazolam. Depending on the magnitude of CYP3A inhibition, the dose of midazolam may be reduced. On the contrary, administration of CYP3A stimulant drug may require high doses of midazolam to achieve the desired effect.

In the case of CYP3A stimulation and irreversible inhibition (mechanism-based inhibition), the effect on midazolam pharmacokinetics may last for several days to several weeks after the administration of the CYP3A inhibitor. Examples of mechanism-based CYP3A inhibitors: antibacterials (eg clarithromycin, erythromycin, isoniazid), anti HIV agents (eg HIV protease inhibitors, delavirdine), antihypertensives (eg verapamil, diltiazem), sex steroids and their receptor modulators (eg gestodene, raloxifene) and several herbal items (eg bergamot (grapefruit)). Compared to other mechanism-based inhibitors, ethinylestradiol / norgestrel and grapefruit juice (200 ml) used for oral contraception do not alter the plasma concentrations of IV midazolam.

The range of inhibiting / stimulating effects of drugs is wide. Antifungal ketoconazole, a very potent CYP3A inhibitor, increased the plasma concentration of IV midazolam by 5-fold. Co-administration with the tuberculostatic drug rifampicin, one of the strongest CYP3A stimulants, resulted in a 60% decrease in the plasma concentration of intravenous midazolam.

The mode of use of midazolam determines the magnitude of the pharmacokinetic changes in CYP3A modulation: (i) Intravenous use is expected to cause little change in plasma concentration, (ii) There are no studies showing the effect of CYP3A modulation on midazolam pharmacokinetics after rectal and intramuscular administration. After rectal administration, part of the drug passes through the liver and less CYP3A is expressed in the colon compared to the upper part of the gastrointestinal tract, and the change in plasma concentration of midazolam due to CYP3A modulation is expected to be small with rectal administration. After intramuscular administration, the drug enters the systemic circulation directly, although the duration of action may be prolonged, the CYP3A modulation effect is expected to be similar to intravenous midazolam. (iii) In line with the pharmacokinetic guidelines, clinical studies show that the clinical effect on CYP3A modulation will be minor, although the duration of action may be prolonged after a single IV dose of midazolam. However, after prolonged administration of midazolam, both the magnitude and persistence of the effect will increase in the presence of CYP3A inhibition.

The following list shows clinical pharmacokinetic drug interactions after intravenous administration of midazolam. Any drug that exhibits CYP3A modulating action in-vivo and in-vitro has the potential to alter midazolam plasma concentrations and associated effects. However, as stated above, the change in plasma concentrations of intravenous midazolam is expected to be slight.

#### *CYP3A inhibiting drugs*

*Azole antifungals:* Ketoconazole increases the plasma concentrations of intravenous midazolam 5-fold and the elimination half-life 3-fold. If parenteral midazolam is to be co-administered with the strong CYP3A inhibitor ketoconazole, it should be administered in an intensive care unit or in an environment where clinical observation and appropriate medical intervention can be performed against respiratory depression and / or prolonged sedation. Midazolam, especially more than one i.v. If the dose is to be administered, care should be taken to give the drug at intervals and to adjust the

dose.

Fluconazole, itraconazole and voriconazole: Itraconazole increases the elimination half-life 2.4 times and fluconazole 1.5 times, while intravenously increasing the plasma concentrations of midazolam 2-3-times.

Posaconazole: It increases the plasma concentrations of intravenous midazolam 2 times.

Macrolide antibiotics: Erythromycin increased the plasma concentrations of intravenous midazolam 1.6-2 times, increasing the elimination half-life of midazolam 1.5-1.8 times.

Clarithromycin increased the plasma concentrations of midazolam 2.5 times, increasing the elimination half-life 1.5-2 times.

HIV protease inhibitors: Sacinavir and other HIV protease inhibitors: Upon co-administration with lopinavir and ritonavir, plasma concentrations of intravenous midazolam increased 5.4 times due to the increased elimination half-life. If parenteral midazolam is to be used in combination with HIV protease inhibitors, the treatment conditions should be as described in the section on the use of azole antifungals with ketoconazole.

Histamine receptor 2 antagonist: Cimetidine increased the fixed plasma concentration of midazolam by 26%.

Calcium channel blockers: A single dose of diltiazem increased the plasma concentration of intravenous midazolam by 25% and prolonged the elimination half-life by approximately 43%.

Various drugs / Plants: Atorvastatin showed an approximately 1.4 times increase in plasma concentrations of IV midazolam compared to the control group.

#### CYP3A stimulating drugs

Rifampicin reduced the plasma concentrations of intravenous midazolam by approximately 60% after 7 days of rifampicin 600 mg use. Excretion half-life is shortened by 50-60%.

Plants and foods: Extract of Echinacea purpurea root shortened the half-life time by about 42%, i.v. midazolam reduced its plasma concentration by 20%. St John's wort reduced plasma concentrations of midazolam by about 20-40%, shortening the elimination half-life by about 15-17%.

Acute protein displacement: Valproic acid: In one study, midazolam's protein made by valproic acid was mentioned as a potential drug interaction mechanism. Due to methodological concerns, little mention has been made of the clinical relevance of this study. However, due to the high therapeutic plasma concentrations of valproic acid, the protein displacement of midazolam cannot be ruled out in acute dosage adjustments resulting in the noticeable clinical effect of midazolam.

#### Pharmacodynamic Drug-Drug Interactions

Co-administration of midazolam with other sedative / hypnotic agents, including alcohol, is likely to result in increased sedative / hypnotic effects. Examples are as follows; opiates / opioids (when used as analgesic, antitussive or adjunct therapy), antipsychotics, other benzodiazepines used as anxiolytic or hypnotic, barbiturates, propofol, ketamine, etomidate, sedative antidepressants, antihistamines and centrally acting antihypertensive drugs.

Midazolam lowers the minimum alveolar concentration (MAC) of inhalational anesthetics. When midazolam is administered with any centrally acting depressant, including alcohol, increased effects on sedation, respiratory and hemodynamic parameters may occur, so vital signs should be monitored. Alcohol should be avoided in patients receiving midazolam (See section 4.4. Special warnings and

precautions for use; Warning regarding overdose of other central nervous system depressants, including alcohol).

It has been shown that spinal anesthesia can increase the sedative effects of IV midazolam. Therefore, the dose of midazolam can be reduced. In addition, when lidocaine and bupivacaine were administered intramuscularly, the IV dose of midazolam required for sedation was reduced. Drugs that increase alertness / memory, such as the AchE inhibitor physostigmine, reverse the hypnotic effects of midazolam. Similarly, 250 mg of caffeine partially reverses the sedative effects of midazolam.

#### **4.6. Pregnancy and lactation**

##### **General advice**

Pregnancy category: D

##### **Women with childbearing potential/Contraception**

There is no warning.

##### **Pregnancy**

There is not enough information about the safety of midazolam during pregnancy. Benzodiazepines should not be used during pregnancy unless there is a safer alternative.

It has been reported that fetal heart rate irregularity, hypotonia, decreased sucking, hypothermia and moderate respiratory depression in the newborn occurs with the administration of midazolam in the last 3 months of pregnancy or at high doses during delivery. In addition, physical dependence may develop in babies of mothers who use benzodiazepines for a long time in the last stages of their pregnancy and the risk of symptoms due to discontinuation of the drug may increase in the postpartum period. Midazolam should not be used during pregnancy unless considered absolutely necessary. It is preferred to avoid its use for cesarean section.

##### **Lactation**

Midazolam passes into breast milk in small amounts. Nursing mothers should be warned that they should not breastfeed for 24 hours after administering midazolam.

##### **The reproductive capability/Fertility**

It has no effect on reproductive ability.

#### **4.7. Effects on ability to drive and use machines**

Sedation, amnesia, impaired concentration and muscle dysfunction impair the ability to drive vehicles and other machines. Before SEDEVER is administered, the patient should be cautioned not to drive or use machines until full recovery. The physician should decide when to resume these activities.

#### **4.8. Undesirable effects**

The frequency of undesirable effects associated with the use of midazolam is listed as follows.

Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10.000$  and  $< 1/1000$ ), very rare ( $< 1/10.000$ ) and unknown (estimation based on the existing data is impossible).

Post-marketing experience

The following undesirable effects have been reported after the injection of midazolam:

### **Immune system disorders**

Not known: General hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), anaphylactic shock.

### **Psychiatric disorders**

Not known: Paradoxical reactions such as confusion, euphoria, hallucinations, agitation, involuntary movements (tonic / clonic movements and muscle tremors), hyperactivity, hostility, anger reaction, aggression, paroxysmal excitement and aggression have been reported, particularly in children and the elderly.

### **Addiction**

The use of SEDEVER, even at therapeutic doses, may cause physical dependence. Discontinuation of the drug after prolonged i.v. administration, especially abrupt discontinuation of the drug, may cause withdrawal symptoms, including withdrawal convulsions.

### **Nervous system disorders**

Unknown: Prolonged sedation, decreased attention, headache, dizziness, ataxia, postoperative sedation; Anterograde amnesia in direct proportion to the administered dose. Anterograde amnesia may continue to be seen at the end of the procedure, and long-term amnesia has been reported in isolated cases.

Convulsions have been reported in premature infants and neonates.

### **Cardiac disorders**

Unknown: In rare cases, severe cardiorespiratory side effects have been observed. These are cardiac arrest, hypotension, bradycardia, vasodilative effects. Life-threatening events are more common in adults over 60 years of age, patients with pre-existing respiratory failure or impaired cardiac function, particularly when the injection is administered too quickly or when high doses are administered (See section 4.4 Special warnings and precautions for use).

### **Respiratory disorders**

Unknown: In rare cases, severe cardiorespiratory side effects have been observed. These are respiratory arrest, apnea, dyspnoea, laryngospasm. Life-threatening events are more common in adults over 60 years of age, pre-existing respiratory insufficiency or patients with impaired cardiac

function, especially when the injection is administered too quickly or when high doses are administered (See section 4.4. Special warnings and precautions for use). hiccups may occur.

#### **Gastrointestinal system disorders:**

Not known: Nausea, vomiting, constipation, dry mouth

#### **Skin and other regions**

Unknown: Skin rash, urticaria, pruritus.

#### **Disorders in the whole body and administration area**

Unknown: Erythema and pain at the injection site, thrombophlebitis, thrombosis.

#### **Injury, poisoning and procedural complications**

Unknown: An increased risk of falls and fractures has been noted in elderly benzodiazepine users.

#### 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*

Benzodiazepines generally cause drowsiness, ataxia, slurred speech, and nystagmus. If SEDEVER is used alone, overdose is rarely life-threatening but can lead to areflexia, apnea, hypotension, cardiorespiratory depression and in rare cases coma. Coma, if it occurs, usually resolves within a few hours, but may persist and recur, especially in older patients. The respiratory depression effects of benzodiazepines are more severe in patients with respiratory illness. Benzodiazepines increase the effects of CNS depressants, including alcohol.

#### *Treatment*

The patient's vital signs should be monitored and supportive measures initiated as required by the patient's clinical condition. In special cases, patients may require symptomatic treatment for cardiorespiratory effects and central nervous system effects.

If taken orally, further absorption should be prevented using an appropriate method, for example, it should be treated with activated charcoal within 1-2 hours. Airway protection is mandatory in drowsy patients if activated charcoal has been used. Although it is not a routine method, gastric lavage may be considered in mixed feeding situations.

In cases of severe CNS depression, the use of flumazenil, a benzodiazepine antagonist, may be considered. This should only be implemented under conditions of strict monitoring. Because it has a very short half-life (approximately 1 hour), patients treated with flumazenil should be observed for at

least 1 hour even if the effects have passed. Flumazenil should be administered with exceptional caution in the presence of drugs that lower the seizure threshold (eg tricyclic antidepressants). For more information on the correct use of this medication, see the Flumazenil patient information leaflet.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: Sedatives and hypnotics; benzodiazepine derivatives

ATC Code: N05CD08

*Mechanism of action:* Midazolam, the active substance of SEDEVER, is a derivative of imidazobenzodiazepine group. It is a free base and a lipophilic substance with low water solubility. The basic nitrogen atom in the 2nd position of the imidazobenzodiazepine ring enables midazolam to form water-soluble salts with acids. The pharmacological effect of midazolam starts fast and takes a short time since it is rapidly metabolized. Midazolam has a wide range of treatments due to its low toxicity. Midazolam is a very rapid sedative and sedating in significant intensity. It also has anxiolytic, anticonvulsant and muscle relaxant effects. It causes short-term anterograde amnesia after IM and IV administration (The patient cannot remember the events during the period when the drug's effect was strongest).

### **5.2. Pharmacokinetic properties**

#### **General Particulars:**

#### Absorption:

*Absorption after intramuscular injection:* Absorption of midazolam from muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. Absolute bioavailability after IM injection is over 90%.

*Absorption after rectal administration:* After rectal administration, midazolam is rapidly absorbed and the maximum plasma concentration is reached after approximately 30 minutes. Absolute bioavailability is about 50%.

#### Distribution:

When midazolam IV is injected, one or two distinct phases of distribution are seen in the plasma concentration-time curve. The steady-state volume of distribution is 0.7-1.2 L/kg. The protein binding rate of midazolam is between 96-98%. The major fraction of plasma protein binding is albumin. There is a slow and insignificant midazolam transition into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and enter the fetal circulation. Midazolam has been found in small amounts in breast milk.

#### Biotransformation:

Midazolam is almost completely eliminated after biotransformation. Midazolam is hydroxylated by

the cytochrome P450 3A4 isozyme and its major urinary and plasma metabolite is  $\alpha$ -hydroxy midazolam. The plasma concentration of  $\alpha$ -hydroxy midazolam is 12% of the parent compound.  $\alpha$ -hydroxy midazolam is pharmacologically active, but the contribution of intravenous midazolam to its effects is only minimal (about 10%). There is no evidence that there is a genetic polymorphism in the oxidative metabolism of midazolam.

#### Elimination:

In healthy volunteers, the elimination half-life is 1.5-2.5 hours and plasma clearance ranges from 300-500 mL / min. Midazolam is mainly eliminated by the kidneys; 60-80% of the dose is excreted in the urine as glucuronide  $\alpha$ -hydroxy midazolam. Less than 1% of the dose is recovered from the urine unchanged. The elimination half-life of the metabolite is less than 1 hour. The elimination kinetics of midazolam do not differ when administered as an IV infusion or bolus injection.

### **Characteristics in patients**

#### Renal impairment:

The elimination half-life in patients with chronic renal failure is close to healthy volunteers (*See section 4.4. Special warnings and precautions for use and 4.2. Posology and method of administration; Additional information on special populations; Renal failure*).

#### Hepatic impairment:

The elimination half-life is longer in cirrhosis patients and its clearance is lower compared to healthy volunteers (*See section 4.4. Special warnings and precautions for use*).

#### Elderly:

The elimination half-life of the drug may be up to four times longer in adult patients over 60 years of age (*See section 4.4. Special warnings and precautions for use and Additional information on special populations: Geriatric use*).

#### Pediatric:

The rectal absorption rate in children is close to that in adults, but its bioavailability is lower (5–18%). However, in children 3-10 years of age, the elimination half-life ( $t_{1/2}$ ) after IV and rectal administration is shorter (1-1.5 hours) than in adults. This difference is consistent with the high metabolic clearance in children (*See Section 4.4. Special warnings and precautions for use*).

#### Newborns:

In preterm babies and term newborns, the elimination half-life is on average 6-12 hours and clearance is reduced, probably due to underdevelopment of the liver (*See section 4.4. Special warnings and precautions for use*).

#### Obese:

The mean half-life is higher in obese patients compared to non-obese patients (8.4-2.7 hours). This is



due to a 50% increase in the volume of distribution allocated to total body weight. There is no significant difference in clearance between obese and non-obese patients.

Critical patients:

The elimination half-life of midazolam is prolonged in critically ill patients (See section 4.4. Special warnings and precautions for use).

Heart failure:

The elimination half-life is longer in patients with congestive heart failure compared to healthy samples (See section 4.4. Special warnings and precautions for use).

### **5.3. Preclinical safety data**

Not applicable.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Sodium chloride  
Hydrochloric acid  
Sodium hydroxide  
Water for injection

### **6.2. Incompatibilities**

This medicinal product must not be diluted with solutions other than parenteral solutions specified in the special dosage instructions (see section 4.2. Posology and method of administration).

If it is applied by mixing with other drugs, it should be checked whether there is any incompatibility before the administration.

Midazolam collapses in sediments containing bicarbonate. Theoretically, the injection solution of midazolam may not be stable in neutral or alkaline pH's. Midazolam, albumin, amoxicillin sodium, ampicillin sodium, bumetanide, if dexamethasone is mixed with sodium phosphate, dimenhydrinate, floxacillin sodium, furosemide, hydrocortisone sodium succinate, pentobarbital sodium, perphenazine, prochlorperazine edisilate, ranitidine or thiopental sodium or trimetoprim-sulfamethoxazole, a white precipitate is immediately formed.

A white precipitate forms following turbidity with nafcillin sodium. Turbidity occurs with ceftazidime.

A yellow precipitate forms with methotrexate sodium. An orange discoloration occurs with clonidine hydrochloride. A brown precipitate forms followed by a brown color change with omeprazole sodium. With foscarnet sodium, a gas is released.

Midazolam also should not be mixed with acyclovir, albumin, alteplase, acetazolam disodium, diazepam, enoximone, flecainide acetate, fluorouracil, imipenem, mezlocillin sodium, phenobarbital sodium, phenytoin sodium, potassium canrenoate, sulbactam sodium, theophylline, trometamol, urokinase.

### **6.3. Shelf life**

24 months

### **6.4. Special precautions for storage**

It should be stored at room temperature below 25 ° C.

SEDEVER ampoules should not be frozen due to the possibility of explosion.

A precipitation may be seen that dissolves with shaking at room temperature. Protect from light.

### **6.5. Nature and contents of container**

SEDEVER 5 mg ampoule is in packages containing 5 or 10 glass ampoules of 5 mL.

### **6.6. Special precautions for disposal and other handling**

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

## **7. MARKETING AUTHORIZATION HOLDER**

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## **8. MARKETING AUTHORIZATION NUMBER**

2015/808

## **9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**

First Authorization Date: 09.10.2015

License renewal date:--

## **10. DATE OF REVISION OF THE TEXT**