SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SEDEVER 15 mg / 3 mL I.V./I.M./Rectal ampoule solution for injection and infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
Each 3 mL ampoule contains 15 mg of midazolam.

Excipients:

Sodium chloride	15 mg
Sodium hydroxide	q.s. (for pH adjustment)

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Injectable solution containing ampoule
Clear, colorless and particle-free solution

4. CLINICAL PARTICULARS

4.1. Therapeutical indications

SEDEVER as a short acting sedative drug 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
- Sedatively in combined anesthesia
• 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 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**
Conscious sedation	**I.V.** Initial dose: 2-2,5 mg Titration dose: 1 mg Total dose: 3.5-7,5 mg	**I.V.** Initial dose: 0-5-1 mg Titration dose: 0.5-1 mg Total dose: <3,5 mg	**I.V. 6 months-5 years** Initial dose: 0.05-0,1 mg/kg Total dose: <6 mg **IV 6-12 years** Initial dose: 0.025-0.05 mg/kg Total dose: <10 mg **13-16 years** As adults **Rectal> 6 months** 0.3-0,5 mg/kg **I.M. 1-15 yaş** 0.05-0.15 mg/kg
Anesthesia premedication	**I.V.** repeatable 1-2 mg **I.M.** 0.07-0,1 mg/kg	**I.V.** Initial dose: 0,5 mg Slow titration needed **I.M.** 0.025-0.05 mg/kg	**Rectal older than 6 months** 0.3-0,5 mg/kg **I.M. 1-15 years** 0.08-0,2 mg /kg
Anesthesia induction	**I.V.** 0.15-0,2 mg/kg (0.3-0.35 mg/kg without premedication)	**IV** 0.05-0.15 mg/kg (0.15-0,3 mg/kg without premedication)	Not indicated in pediatric patients
Sedatively in combined anesthesia	**I.V.** Intermittent 0.03-0.1 mg/kg doses or 0.03-0.1 mg/kg/hr continuous infusion	**I.V.** Less than recommended dose for adults <60 years	Not indicated in pediatric patients

Sedation in intensive care units	**I.V.** Loading dose: 0.03-0,3 mg / kg in 1-2,5 mg increments Maintenance dose: 0.03-0,2 mg / kg / hour	**IV in neonates less than 32 weeks** 0.03 mg / kg / hour **IV born older than 32 weeks newborn (up to 6 months)** 0.06 mg / kg / hour **IV older than 6 months** Loading dose: 0.05-0.2 mg / kg Maintenance dose: 0.06-0.12 mg / kg / hour

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 α-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 ± SD	Interval
All patients	37	27.8 ± 37.2	0- 140
Patients without kidney or liver failure	24	13.6 ±16.4	0- 5 8
Patients with kidney failure without liver failure	9	44.6 ±42.5	2-120
Patients with kidney and liver 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
- Kidney function impairment
- Liver 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> 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 15 mg / 3 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 CYP3A 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-fold and fluconazole 1.5-fold, while intravenously increasing the plasma concentrations of midazolam 2-3-fold.

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

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

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

H IVprotease inhibitors: Sacinavir and other H I V protease inhibitors: Upon co-administration with lopinavir and ritonavir, plasma concentrations of intravenous midazolam increased 5.4-fold 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-fold 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, 250mg 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 (≥ 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).

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, vasodilatative 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 areas
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
The 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 package 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:

Absorbation:

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 α-hydroxyimidazolam. The plasma concentration of α-hydroxyimidazolam is 12% of the parent compound. α-hydroxyimidazolam 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 gluuroconjugated α-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 (t1 / 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 precipitates in bicarbonate-containing precipitates. Theoretically, the solution for injection of midazolam may not be stable at neutral or alkaline pH. Midazolam, albumin, amoxicillin sodium, ampicillin sodium, bumetanide, dexamethasone sodium phosphate, dimenhydrinate, floxacillin sodium, furosemide, hydrocortisone sodium succinate, pentobarbital sodium, perphenazine, prochlorperazine edicylate, ranitidine or thiopental sodium or trimethoprimase-white precipitate sodium immediately mixed with .

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; It should not be mixed with acyclovir, albumin, alteplase, acetazolam disodium, diazepam, enoxyimone, 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.

After dilution, it is stable for 24 hours at 2-8 ° C for 3 days at room temperature.

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 is presented in a colorless 3 ml Type I autopul glass ampoule in a 5-piece package.

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

2015/676

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

First Authorization Date: 31.08.2015
License renewal date:

10. DATE OF REVISION OF THE TEXT