Midathetic® ampoules

Midazolam

1 NAME OF THE MEDICINAL PRODUCT
Midathetic® 5 mg/ml solution for IM or slow IV injection or infusion.
2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml* Midathetic®** ***contains:
Active ingredient:
Midazolam hydrochloride 5.56 mg eq. to 5 mg Midazolam.
Inactive ingredients:
Sodium Chloride, Disodium Edetate, Concentrated hydrochloric acid, water for injection
3 PHARMACEUTICAL FORM
Solution for IM or slow IV injection or infusion
4 CLINICAL PARTICULARIS
4.1 Therapeutic indications
Midathetic® is a short-acting sleep-inducing drug that is indicated:
In adults
• CONSCIOUS SEDATION, before and during diagnostic or therapeutic procedures with or without local anesthesia
• ANAESTHESIA :
– Premedication before induction of anesthesia.
– Induction of anesthesia.
– As a sedative component in combined anesthesia.
• SEDATION IN INTENSIVE CARE UNITS
In children
• CONSCIOUS SEDATION before and during diagnostic or therapeutic procedures with or without local anesthesia
• ANAESTHESIA
– Premedication before induction of anesthesia
• SEDATION IN INTENSIVE CARE UNITS
4.2 Posology and method of administration
STANDARD DOSAGE
Midathetic® is a potent sedative agent that requires titration and slow administration. Titration is strongly recommended to safely obtain the desired level of sedation according to the clinical need, physical status, age and concomitant medication. In adults over 60 years, debilitated or chronically ill patients and pediatric patients, dose should be determined with caution and risk factors related to each patient should be taken into account. Standard dosages are provided in the table below. Additional details are provided in the text following the table.

Indication	Adults <60 years	Adults ≥ 60 years / debilitated or chronically ill	Children
Conscious sedation	**i.v.** Initial dose: 2-2.5 mg Titration doses: 1 mg Total dose : 3.5-7.5 mg	**i.v.** Initial dose : 0.5-1 mg Titration doses : 0.5-1 mg Total dose : <3.5 mg	**i.v. in patients 6 months- 5 years** Initial dose: 0.05-0.1 mg/kg Total dose: <6 mg **i.v. in patients 6-12 years** Initial dose: 0.025-0.05 mg/kg Total dose: < 10 mg **i.m 1-15 years** 0.05-0.15mg/kg
Anaesthesia premedication	**i.v.** 1-2 mg repeated **i.m.** 0.07-0.1 mg/kg	**i.v.** Initial dose: 0.5mg Slow up titration as needed **i.m.** 0.025-0.05 mg/kg	**i.m. 1-15 years** 0.08-0.2 mg/kg
Anaesthesia induction	**i.v.** 0.15-0.2 mg/kg (0.3-0.35 without premedication)	**i.v.** 0.05-0.15 mg/kg (0.15-0.3 without premedication)	
Sedative component in combined anaesthesia	**i.v.** intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h	**i.v.** lower doses than recommended for adults <60 years	
Sedation in ICU	**i.v.** Loading dose: 0.03-0.3 mg/ kg in increments of 1-2.5 mg Maintenance dose: 0.03-0.2 mg/kg/h		**i.v. in neonates <32 Weeks gestational age** 0.03 mg/kg/h **i.v in neonates >32 weeks and children up to 6 months** 0.06 mg/kg/h **i.v. in patients >6 months of age:** Loading dose: 0.05-0.2 mg/kg Maintenance dose: 0.06-0.12 mg/kg/h

CONSCIOUS SEDATION DOSAGE
For conscious sedation prior to diagnostic or surgical intervention, **Midathetic**® is administered i.v. The dose must be individualized and titrated, and should not be administered by rapid or single bolus injection. The onset of sedation may vary individually depending on the physical status of the patient and the detailed circumstances of dosing (e.g. speed of administration, amount of dose). If necessary, subsequent doses may be administered according to the individual need. The onset of action is about 2 minutes after the injection. Maximum effect is obtained in about 5 to 10 minutes.
Adults
The IV injection of **Midathetic**® should be given slowly at a rate of approximately 1 mg in 30 seconds.
• *In adults below the age of 60,* the initial dose is 2 to 2.5 mg given 5 to 10 minutes before the beginning of the procedure. Further doses of 1 mg may be given as necessary. Mean total doses have been found to range from 3.5 to 7.5 mg. A total dose greater than 5 mg is usually not necessary.
• *In adults over 60 years of age,* debilitated or chronically ill patients, the initial dose must be reduced to 0.5–1.0 mg and given 5–10 minutes before the beginning of the procedure. Further doses of 0.5 to 1 mg may be given as necessary. Since in these patients the peak effect may be reached less rapidly, additional Midathetic should be titrated very slowly and carefully. A total dose greater than 3.5 mg is usually not necessary.
Children
I.V. administration: **Midathetic**® should be titrated slowly to the desired clinical effect. The initial dose of **Midathetic**® should be administered over 2 to 3 minutes. One must wait an additional 2 to 5 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. Infants and young children less than 5 years of age may require substantially higher doses (mg/kg) than older children and adolescents.
• *Pediatric patients less than 6 months of age:* pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation. For this reason, the use in conscious sedation in children less than 6 months of age is not recommended.
• *Pediatric patients 6 months to 5 years of age:* initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint, but the total dose should not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
• *Pediatric patients 6 to 12 years of age:* initial dose 0.025 to 0.05 mg/kg. A total dose of up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
• *Pediatric patients 12 to 16 years of age:* should be dosed as adults.
Pediatric Patients
Neonates and children up to 6 months of age
The use in children less than 6 months of age is not recommended as available data are limited.
Children over 6 months of age
I.M. administration: As IM injection is painful, this route should only be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08 to 0.2 mg / Kg of **Midathetic** administered IM has been shown to be effective and safe. In children between ages 1 and 15 years, proportionally higher doses are required than in adults in relation to body-weight.
In children, less than 15 kg of body weight, **Midathetic** solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.
INDUCTION
Adults
If **Midathetic** is used for induction of anesthesia before other anesthetic agents have been administered, the individual response is variable. The dose should be titrated to the desired effect according to the patient's age and clinical status. When **Midathetic** is used before or in combination with other IV or inhalation agents for induction of anesthesia, the initial dose of each agent should be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents. The desired level of anesthesia is reached by stepwise titration. The IV induction dose of **Midathetic** should be given slowly in increments.
Each increment of not more than 5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments.
• *In Premedicated adults below the age of 60 years,* an IV dose of 0.15 to 0.2 mg/kg will usually suffice.
• *In Non-premedicated adults below the age of* 60 the dose may be higher (0.3 to 0.35 mg/kg i.v.). If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used. Induction may instead be completed with inhalational anesthetics. In resistant cases, a total dose of up to 0.6 mg/kg may be used for induction, but such larger doses may prolong recovery.
• *In Premedicated adults over 60 years of age, debilitated or chronically ill patients,* the dose should significantly be reduced, e.g., down to 0.05- 0.15 mg/kg administered i.v. over 20-30 seconds and allowing 2 minutes for effect.
• *Non-premedicated adults over 60 years of age usually* require more **Midathetic** for induction; an initial dose of 0.15 to 0.3 mg/kg is recommended. Nonpremedicated patients with severe systemic disease or other debilitation usually require less **Midathetic** for induction. An initial dose of 0.15 to 0.25 mg/kg will usually suffice.
SEDATIVE COMPONENT IN COMBINED ANAESTHESIA
Adults
Midathetic can be given as a sedative component in combined anesthesia by either further intermittent small i.v. doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of i.v. **Midathetic** (range between 0.03 and 0.1 mg/kg/h) typically in combination with analgesics. The dose and the intervals between doses vary according to the patient's individual reaction.
In Adults over 60 years of age, debilitated or chronically ill patients, lower maintenance doses will be required.
SEDATION IN INTENSIVE CARE UNITS
The desired level of sedation is reached by stepwise titration of **Midathetic** followed by either continuous infusion or intermittent bolus, according to the clinical need, physical status, age and concomitant medication.
Adults
I.V. loading dose: 0.03 to 0.3 mg/kg should be given slowly in increments. Each increment of 1 to 2.5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments. In hypovolaemic, vasoconstricted, or hypothermic patients the loading dose should be reduced or omitted.
When Midathetic is given with potent analgesics, the latter should be administered first so that the sedative effects of Midathetic can be safely titrated on top of any sedation caused by the analgesic.
I.V. maintenance dose: doses can range from 0.03 to 0.2 mg/kg/h. In hypovolaemic, vasoconstricted, or hypothermic patients the maintenance dose should be reduced. The level of sedation should be assessed regularly. With long-term sedation, tolerance may develop and the dose may have to be increased.
Neonates and children up to 6 months of age:
Midathetic® should be given as a continuous i.v. infusion, starting at 0.03 mg/kg/h (0.5 µg/kg/min) in neonates with a gestational age < 32 weeks, or 0.06 mg/kg/h (1 µg/kg/min) in neonates with a gestational age > 32 weeks and children up to 6 months.
Intravenous loading doses is not recommended in premature infants, neonates and children up to 6 months, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation.
Careful monitoring of respiratory rate and oxygen saturation is required.
Children over 6 months of age:
In intubated and ventilated pediatric patients, a loading dose of 0.05 to 0.2 mg/kg. i.v. should be administered slowly over at least 2 to 3 minutes to establish the desired clinical effect. **Midathetic**® should not be administered as a rapid intravenous dose. The loading dose is followed by a continuous i.v. infusion at 0.06 to 0.12 mg/kg/h (1 to 2 µg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental i.v. doses of **Midathetic**® can be administered to increase or maintain the desired effect.
When initiating an infusion with **Midathetic**® in hemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient monitored for hemodynamic instability, e.g. hypotension. These patients are also vulnerable to the respiratory depressant effects of **Midathetic**® and require careful monitoring of respiratory rate and oxygen saturation.
In premature infants, neonates and children less than 15 kg of body weight, **Midathetic**® solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.
Special Populations
Renal Impairment
In patients with renal impairment (creatinine clearance <10ml/min) the pharmacokinetics of unbound Midazolam following a single IV dose is similar to that reported in healthy volunteers. However, after prolonged infusion in intensive care unit (ICU) patients, the mean duration of the sedative effect in the renal failure population (shown after prolonged infusion in intensive care unit (ICU) patients) was considerably increased most likely due to accumulation of α-hydroxy Midazolam glucuronide.
There is no specific data in patients with severe renal impairment (creatinine clearance below 30 ml/min) receiving Midazolam for induction of anesthesia.
Hepatic Impairment
Hepatic impairment reduces the clearance of i.v. Midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged. The required dose of Midazolam may be reduced and proper monitoring of vital signs should be established.
4.3 Contraindications
Hypersensitivity to benzodiazepines or to any of the excipients listed in section.
Use of this drug for conscious sedation in patients with severe respiratory failure or acute respiratory depression.
4.4 Special warnings and precautions for use
Midazolam should be administered only by experienced physicians in a setting fully equipped for the monitoring and support of respiratory and cardiovascular function and by persons specifically trained in the recognition and management of expected adverse events including respiratory and cardiac resuscitation.
Severe cardiorespiratory adverse events have been reported. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered. Special caution is required for the indication of conscious sedation in patients with impaired respiratory function.
Pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential.
When Midazolam is used for premedication, adequate observation of the patient after administration is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.
Special caution should be exercised when administering Midazolam to high-risk patients:
• adults over 60 years of age
• chronically ill or debilitated patients, e.g.
• patients with chronic respiratory insufficiency
• patients with chronic renal failure, impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment) or with impaired cardiac function
• pediatric patients especially those with cardiovascular instability.
These high-risk patients require lower dosages and should be continuously monitored for early signs of alterations of vital functions. As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering Midazolam to a patient with myasthenia gravis.
Tolerance
Some loss of efficacy has been reported when Midazolam was used as long-term sedation in intensive care units (ICU).
Dependence
When Midazolam is used in long-term sedation in ICU, it should be borne in mind that physical dependence on Midazolam may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse.
Withdrawal Symptoms
During prolonged treatment with Midazolam in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.
Amnesia
Midazolam causes anterograde amnesia (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention. After receiving Midazolam parenterally, patients should be discharged from hospital or consulting room only if accompanied by an attendant.
Paradoxical reactions
Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported to occur with Midazolam. These reactions may occur with high doses and/or when the injection is given rapidly. The highest incidence to such reactions has been reported among children and the elderly. if these events occur, discontinuation of treatment should be considered.
Altered elimination of Midazolam
Midazolam elimination may be altered in patients receiving compounds that inhibit or induce CYP3A4 and the dose of Midazolam may need to be adjusted accordingly. Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates.
Sleep Apnea
Midazolam ampoules should be used with extreme caution in patients with sleep apnea syndrome and these patients should be monitored regularly.
Preterm infants and neonates:
Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm non-intubated patients. Careful monitoring of respiratory rate and oxygen saturation is required.
Rapid injection should be avoided in the neonatal population.
Neonates have reduced and/or immature organ function and are also vulnerable to profound and/or prolonged respiratory effects of Midazolam.
Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.
Pediatric patients less than 6 months:
In this population, Midazolam is indicated for sedation in ICU only. Pediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential (see also section 'Preterm infants' above).
Concomitant use of alcohol / CNS depressants:
The concomitant use of Midazolam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Midazolam possibly including severe sedation or clinically relevant respiratory depression.
Risk from concomitant use of opioids:
Concomitant use of **Midathetic**® 5 mg/ml solution for injection/infusion and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as **Midathetic**® 5 mg/ml solution for injection/infusion with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe **Midathetic**® 5 mg/ml solution for injection/infusion concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms.
Medical history of alcohol or drug abuse:
Midazolam as other benzodiazepines should be avoided in patients with a medical history of alcohol or drug abuse.
Discharging criteria
After receiving Midazolam, patients should be discharged from hospital or consulting room only when recommended by treating physician and if accompanied by an attendant. It is recommended that the patient is accompanied when returning home after discharge.
This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium free'.
4.5 Interaction with other medicinal products and other forms of interaction
Pharmacokinetic Interactions
Midazolam is metabolized by CYP3A4. Inhibitors and inducers of CYP3A have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of Midazolam thus requiring dose adjustments accordingly.
Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to i.v. Midazolam, since CYP3A4 also exists in the upper gastro-intestinal tract. This is because for the oral route both systemic clearance and availability will be altered while for the parenteral route only the change in the systemic clearance becomes effective.
After a single dose of i.v. Midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. However, after prolonged dosing of Midazolam, both the magnitude and duration of effect will be increased in the presence of CYP3A4 inhibition.
There are no available studies on CYP3A4 modulation on the pharmacokinetics of Midazolam after rectal and intramuscular administration. It is expected that these interactions will be less pronounced for the rectal than for the oral route because the gastro-intestinal tract is by-passed whereas after i.m. administration the effects of CYP3A4 modulation should not substantially differ from those seen with i.v.
Midazolam.
It is therefore recommended to carefully monitor the clinical effects and vital signs during the use of Midazolam, taking into account that they may be stronger and last longer after co-administration of a CYP3A4 inhibitor, be it given only once. Notably, administration of high doses or long-term infusions of Midazolam to patients receiving strong CYP3A4 inhibitors, e.g. during intensive care, may result in long lasting hypnotic effects, delayed recovery and respiratory depression, thus requiring dose adjustments.
With respect to induction, it should be considered that the inducing process needs several days to reach its maximum effect and also several days to dissipate. Contrary to a treatment of several days with an inducer, a short-term treatment is expected to result in less apparent DDI with Midazolam. However, for strong inducers a relevant induction even after short-term treatment cannot be excluded.
Midazolam is not known to change the pharmacokinetics of other drugs.

Drugs that inhibit CYP3A

Azole Antifungals

• Ketoconazole increased the plasma concentrations of intravenous Midazolam by 5-fold while the terminal half-life increased by about 3-fold. If parenteral Midazolam is co-administered with the strong CYP3A inhibitor ketoconazole, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dosage adjustment should be considered, especially if more than a single i.v. dose of Midazolam is administered. The same recommendation may apply also for other azole antifungals (see further), since increased sedative effects of i.v. Midazolam, although lesser, are reported.

• Voriconazole increased the exposure of intravenous Midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.

• Fluconazole and itraconazole both increased the plasma concentrations of intravenous Midazolam by 2 – 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.

• Posaconazole increased the plasma concentrations of intravenous Midazolam by about 2-fold.

• It should be kept in mind that if Midazolam is given orally, its exposure will drastically be higher than the above-mentioned ones, notably with ketoconazole, itraconazole, voriconazole.

Midathetic® ampoules are not indicated for oral administration.

Macrolide antibiotics

• Erythromycin resulted in an increase in the plasma concentrations of intravenous Midazolam by about 1.6 – 2-fold associated with an increase of the terminal half-life of Midazolam by 1.5 – 1.8-fold.

• Clarithromycin increased the plasma concentrations of Midazolam by up to 2.5- fold associated with an increase in terminal half-life by 1.5 – 2-fold.

Additional information from oral Midazolam

• Roxithromycin: While no information on roxithromycin with i.v Midazolam is available, the mild effect on the terminal half-life of oral Midazolam tablet, increasing by 30%, indicates that the effects of roxithromycin on intravenous Midazolam may be minor.

HIV Protease inhibitors

• Saquinavir and other HIV protease inhibitors: Co-administration with protease inhibitors may cause a large increase in the concentration of Midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous Midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life. If parenteral Midazolam is coadministered with HIV protease inhibitors, treatment setting should follow the description in the above section for azole antifungals, ketoconazole.

Additional information from oral **Midathetic®**

Based on data for other CYP3A4 inhibitors, plasma concentrations of Midazolam are expected to be significantly higher when Midazolam is given orally. Therefore, protease inhibitors should not be co-administered with orally administered Midazolam.

Calcium channel blockers

• Diltiazem: A single dose of diltiazem administered to patients undergoing coronary artery bypass surgery increased the plasma concentrations of intravenous Midazolam by about 25% and the terminal half-life was prolonged by 43%.This is less than the 4-fold increase observed after oral administration of Midazolam.

Additional information from oral Midathetic

• Verapamil increased the plasma concentrations of oral Midazolam by 3- fold, respectively. The terminal- half-life of Midazolam was increased by 41% respectively.

Various drugs/Herbal preparations

• Atorvastatin showed a 1.4-fold increase in plasma concentrations of i.v. Midazolam compared to control group.

• Intravenous fentanyl is a weak inhibitor of Midazolam elimination: it increased by 1.5 times the AUC and half-life of Midazolam I.V.

Additional information from oral **Midathetic®**

• Nefazodone increased the plasma concentrations of oral Midazolam by 4.6-fold with an increase of its terminal half-life by 1.6-fold.

• Aprepitant dose dependently increased the plasma concentrations of oral Midazolam by 3.3-fold after 80 mg/day associated with an increase in terminal half-life by approximately. 2-fold.

Drugs that induce CYP3A

• Rifampicin decreased the plasma concentrations of intravenous Midazolam by about 60% after 7 days of rifampicin 600mg o.d. The terminal half-life decreased by about 50-60%.

• Ticagrelor is a weak CYP3A inducer but has only a small effect on intravenous Midazolam (–12%) and 4-hydroxy-Midazolam (–23%) exposures.

Additional information from Oral **Midathetic®**

• Rifampicin decreased the plasma concentrations of oral Midazolam by 96% in healthy subjects and its psychomotor effects were almost totally lost.

• Carbamazepine / phenytoin: Repeat dosages of carbamezepine or phenytoin resulted in a decrease in plasma concentrations of oral Midazolam by up to 90% and a shortening of the terminal half-life by 60%.

• The very high induction of CYP3A4 observed after administration of mitotane or enzalutamide resulted in a significant and lasting decrease in Midazolam levels in cancer patients. AUC of oral Midazolam was reduced to 5% and 14%, respectively, of normal values.

• Clobazam and efavirenz are weak inducers of Midazolam metabolism and reduce the AUC of the parent compound by approximately 30%. This results in a 4–5fold increase in the active metabolite (α-hydroxy Midazolam) ratio on the parent molecule, but the clinical relevance of this increase is not known.

• Vemurafenib modulates CYP isoenzymes and slightly inhibits CYP3A4: repeated administration resulted in an average 32% decrease in oral Midazolam exposure (up to 80% in some individuals).

Herbs and food

• St John's Wort decreased plasma concentrations of Midazolam by about 30 - 40 % associated with a decrease in terminal half-life of about 15 - 17%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

Additional information obtained with oral **Midathetic®**

• Quercetin (also present in Gingko biloba) and Panax ginseng both have low enzyme-inducing effects and lead to a 20–30% reduction in Midazolam exposure after oral administration.

Acute displacement of proteins

• Valproic acid: An increase in the concentration of free Midazolam due to the displacement of plasma protein binding sites by valproic acid cannot be ruled out even if the clinical relevance of such interaction is not known.

Pharmacodynamic Drug–Drug Interactions (DDI)

The co-administration of Midathetic with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression. Examples include opiate derivatives (be they used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, non recent H1-antihistamines and centrally acting antihypertensive drugs. Alcohol may markedly enhance the sedative effect of **Midathetic®**. Alcohol intake should be strongly avoided in case of Midathetic administration.

Midazolam decreases the minimum alveolar concentration (MAC) of inhalational anesthetics.

Opioids:

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Midazolam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited.

4.6 Fertility, pregnancy and lactation

Pregnancy

Insufficient data are available on Midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but fetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

The administration of high doses of Midazolam in the last trimester of pregnancy, during labor or when used as an induction agent of anesthesia for caesarean section has been reported to produce maternal or fetal adverse effects (inhalation risk in mother, irregularities in the fetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate).

Moreover, infants born from mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Consequently, Midathetic may be used during pregnancy if clearly necessary but it is preferable to avoid using it for caesarean.

The risk for neonate should be taken into account in case of administration of Midathetic for any surgery near the term.

Breast-feeding

Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breast-feeding for 24 hours following administration of **Midathetic®**.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines. Prior to receiving **Midathetic®**, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge. In cases of insufficient sleep or alcohol consumption, the likelihood of impaired alertness may be increased.

4.8 Undesirable effects

The following undesirable effects have been reported (frequency not known, cannot be estimated from the available data) to occur when Midazolam is injected:

Frequency categories are as follows:

Very common: ≥ 1/10;
Common ≥ 1/100 to <1/10
Uncommon ≥ 1/1,000 to <1/100
Rare (≥ 1/10,000 to <1/1000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Immune system disorders	
Frequency not known	Hypersensitivity, angioedema, anaphylactic shock
Psychiatric Disorders	
frequency not known	Confusional state, euphoric mood, hallucinations Agitation*, hostility*, rage reaction*, aggressiveness*, excitement* Physical drug dependence and withdrawal symptom Abuse
Nervous system disorders	
frequency not known	Involuntary movements (including tonic/clonic movements and muscle tremor) *, hyperactivity* Sedation (prolonged and postoperative), alertness decreased, somnolence, headache, dizziness, ataxia, anterograde amnesia**, the duration of which is directly related to the administered dose. Convulsions have been reported in premature infants and neonates. Drug withdrawal convulsions
Cardiac disorders	
frequency not known	Cardiac arrest, bradycardia
Vascular disorders	
frequency not known	Hypotension, vasodilation, thrombophlebitis, thrombosis
Respiratory Disorders	
frequency not known	Respiratory depression, apnea, respiratory arrest, dyspnea, laryngospasm, hiccups
Gastrointestinal Disorders	
frequency not known	Nausea, vomiting, constipation, dry mouth
Skin and Subcutaneous Tissue Disorders	
frequency not known	Rash, urticaria, pruritus
General Disorders and Administration Site Conditions	
frequency not known	Fatigue, injection site erythema, injection site pain
Injury, Poisoning and Procedural Complications	
frequency not known	Falls, fractures***
Social Circumstances	
frequency not known	Assault*

*Such paradoxical drug reactions have been reported, particularly among children and the elderly.

**Anterograde amnesia may still be present at the end of the procedure and in few cases prolonged amnesia has been reported..

***There have been reports of falls and fractures in benzodiazepine users. The risk of falls and fractures is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Dependence: Use of Midazolam - even in therapeutic doses - may lead to the development of physical dependence. After prolonged i.v. administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions. Cases of abuse have been reported.

Severe cardiorespiratory adverse events have occurred. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via pv@eda.mohealth.gov.eg

4.9 Overdose

Symptoms

Like other benzodiazepines, Midazolam commonly causes drowsiness, ataxia, dysarthria and nystagmus. Overdose of Midazolam is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnea, hypotension, cardiorespiratory depression and in rare cases to coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. Patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If taken orally further absorption should be prevented using an appropriate method e.g. treatment within 1–2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine antagonist.

This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Hypnotics and sedatives: benzodiazepine derivatives,

Midathetic has hypnotic and sedative effects characterized by rapid onset and short duration. It also has anxiolytic, anticonvulsant and muscle relaxant effects. **Midathetic®** causes impaired psychomotor function after single and / or repeated doses, but causes minimal hemodynamic changes. The central actions of benzodiazepines are mediated by an increase in GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines, the affinity of the GABA receptor for the neurotransmitter is enhanced by positive allosteric modulation resulting in increased action of released GABA on the postsynaptic transmembrane flow of the chlorine ions. Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water.

The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of Midazolam to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

Associated with rapid metabolic transformation, this explains the rapid onset and short duration of effects. Due to its low toxicity, Midazolam has a wide therapeutic range.

After i.m. or i.v. administration anterograde amnesia of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound).

5.2 Pharmacokinetic properties

Absorption after i.m. injection

Absorption of **Midathetic®** from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after i.m. injection is over 90%.

Distribution

When **Midathetic®** is injected i.v., the plasma concentration-time curve shows one or two distinct phases of distribution. The volume of distribution at steady state is 0.7 - 1.2 l/kg.

96 - 98% of Midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of Midazolam into the cerebrospinal fluid. In humans, Midazolam has been shown to cross the placenta slowly and to enter fetal circulation. Small quantities of Midazolam are found in human milk. Midazolam is not a substrate for drug carriers.

Biotransformation

Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30 - 60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxy Midazolam. Plasma concentrations of alpha hydroxy Midazolam are 12% of those of the parent compound. Alphahydroxy Midazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous Midazolam.

Elimination

In healthy volunteers, the elimination half-life of Midazolam is between 1.5 – 2.5 hours. The elimination half-life of the metabolite is less than 1 hour; therefore, after administration of Midazolam, the concentration of the parent compound and that of the main metabolite decrease in parallel. Plasma clearance is in the range of 300 - 500ml/min. Midazolam is excreted mainly by renal route (60 - 80% of the injected dose) and recovered as glucuroconjugated alpha-hydroxy Midazolam. Less than 1% of the dose is recovered in urine as unchanged drug. The elimination half-life of alphahydroxy-Midazolam is shorter than 1 hour.

When Midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection. Repeated administration of Midazolam does not induce the enzymes of drug metabolism.

Pharmacokinetics in special populations

Elderly

In adults over 60 years of age, the elimination half-life may be prolonged up to four times.

Children

The elimination half-life after i.v. administration is shorter in children 3 - 10 years old (1 - 1.5 hours) as compared with that in adults. The difference is consistent with an increased metabolic clearance in children.

Neonates

In neonates, the elimination half-life is on average 6 - 12 hours, probably due to liver immaturity and the clearance is reduced. Neonates with hepatic and renal insufficiency associated with asphyxia present a risk of unusually high serum concentrations of Midazolam due to significantly reduced and variable clearance.

Obese

The mean half-life is greater in obese than in non-obese patients (5.9 vs 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

Patients with hepatic impairment

The elimination half-life in cirrhotic patients may be longer and the clearance smaller as compared to those in healthy volunteer.

Patients with renal impairment

The pharmacokinetics of unbound Midazolam are unaffected in patients with severe renal impairment. The major pharmacologically inactive metabolite of Midazolam, the glucuronide conjugated 1'-hydroxy Midazolam, which is excreted by the kidneys, accumulates in patients with severe renal impairment. This accumulation produces prolonged sedation. Midazolam should be administered with caution and titrated until the desired effect is achieved.

Critically ill patients

The elimination half-life of Midazolam is prolonged up to six times in the critically ill.

Patients with cardiac insufficiency

The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects.

6 PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

This medicinal product must not be diluted with other solutions for parenteral use than those mentioned in section 6.5. Instructions for use/handling.

Compatibility must be checked before administration, if intended to be mixed with other drugs.

Midazolam precipitates in solutions containing bicarbonate. Theoretically, the midazolam injection solution is likely to be unstable in solutions of neutral or alkaline pH. If midazolam is mixed with albumin, amoxicillin sodium, ampicillin sodium, bumetanide, dexamethasone sodium phosphate, dimenhydrinate, floxacillin sodium, furosemide, hydrocortisone sodium succinate, pentobarbital sodium, perphenazine, prochlorperazine edisylate, ranitidine or thiopental sodium or trimethoprim-sulfamethoxazole, a white precipitate forms immediately. A haze is formed immediately followed by a white precipitate with nafcillin sodium. With ceftazidime a haze is formed. With methotrexate sodium a yellow precipitate forms. With clonidine hydrochloride an orange discoloration forms. With omeprazole sodium a brown discoloration forms, followed by a brown precipitate. With foscarnet sodium a gas is produced. Further midazolam should not be mixed with aciclovir, albumin, alteplase, acetazolam disodium, diazepam, enoximone, flecainide acetate, fluorouracil, imipenem, mezlocillin sodium, phenobarbital sodium, phenytoin sodium, potassium canrenoate, sulbactam sodium, theophylline, trometamol, urokinase.

6.2 Shelf life

3 years

6.3 Special precautions for storage

Stored at temperature not exceeding 30°C & protect from light and to be used immediately after dilution.

6.4 How Supplied

For **Midathetic®** 3 ml:

Carton Box contains 3 amber glass ampoules (Type I), each of 3 ml with insert leaflet

For **Midathetic®** 1 ml:

Carton Box contains 1 or 10 amber glass ampoules (Type I) , each of 1 ml with insert leaflet

6.5 Special precautions for disposal

Compatible with the following solutions for infusion

– 0.9% Nacl
– 5% Dextrose
– 10% Dextrose
– Ringer solution

The solution for injection should be examined visually before administration. Only solutions without visible particles should be used.

Keep all medicaments out of reach of children

Product of:
AMOUN PHARMACEUTICAL CO. S.A.E.
El-Obour City, Al Qalyubia, Egypt.

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