
DATA SHEET**MIDACCORD**

Midazolam (as hydrochloride)

NAME OF MEDICINE

MIDACCORD 1 mg/mL, solution for injection or infusion, 5 mL

MIDACCORD 5 mg/mL, solution for injection or infusion, 1 mL, 3 mL and 10 mL

QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

Midazolam as hydrochloride

MIDACCORD 1 mg/mL, solution for injection or infusion, 5 mL

Each ml of solution for injection or infusion contains 1 mg of midazolam (as hydrochloride).

Presentations	5 ml
Amount of Midazolam	5 mg

Excipient: sodium chloride 9 mg/mL, Water for Injection q.s., Sodium hydroxide and Hydrochloride acid q.s. (for pH adjustment)

MIDACCORD 5 mg/mL, solution for injection or infusion, 1 mL, 3 mL and 10 mL

Each ml of solution for injection or infusion contains 5 mg of midazolam (as hydrochloride)

Presentations	1 ml	3 ml	10 ml
Amount of Midazolam	5 mg	15 mg	50 mg

Excipient: sodium chloride 5 mg/mL, Water for Injection q.s., Sodium hydroxide and Hydrochloride acid q.s. (for pH adjustment)

PHARMACEUTICAL FORM

Product Description: Midazolam Injection is a sterile, clear, and colourless to pale yellow solution practically free from particles in clear glass ampoule. It does not contain preservatives.**Strength:** 1mg/mL and 5mg/mL

Dosage Form: Solution for Injection or Infusion

Routes of Administration: Intravenous, intramuscular or rectal use

INDICATIONS

Premedication before induction of anaesthesia (i.m. or, especially in children, rectal administration).

Conscious sedation before diagnostic or surgical interventions carried out under local anaesthesia (i.v. administration).

Long-term sedation in intensive care units (i.v. administration as bolus injection or continuous infusion).

Induction and maintenance of anaesthesia. As an induction agent in inhalation anaesthesia or a sleep-inducing component in combined anaesthesia, including total intravenous anaesthesia (i.v. injection, i.v. infusion).

Ataralgia in combination with ketamine in children (i.m. administration).

DOSAGE AND ADMINISTRATION

In the case of elderly patients with organic cerebral changes or impaired cardiac and respiratory function, the dosage should be determined with caution, the special factors relating to each patient being taken into consideration.

Initial and subsequent intravenous injections must be given slowly (approximately 2.5mg in 10 seconds for induction of anaesthesia and 1mg in 30 seconds for conscious sedation). The medicine takes effect about two minutes after the injection is started.

Premedication Before An Operation

Intramuscular administration

In patients suffering from pain before an intervention.

Administration alone or in combination with anticholinergics and possibly analgesics. These doses should be administered about 30 minutes before induction of anaesthesia.

Adults: 0.07-0.10 mg per kg bodyweight i.m. according to age and general condition of the patient. Usual dosage about 5mg.

Children: proportionately higher doses are required than in adults in relation to bodyweight (0.15-0.20 mg per kg bodyweight i.m.).

Elderly and debilitated patients: 0.025 - 0.05 mg/kg bodyweight i.m.

Rectal administration

Children: for preoperative sedation. Rectal administration of the ampoule solution by means of a plastic applicator fixed on the end of a syringe, 0.35-0.45 mg/kg bodyweight 20-30 minutes before induction of general anaesthesia. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

Conscious Sedation

Intravenous conscious sedation

For conscious sedation in diagnostic or surgical interventions carried out under local anaesthesia.

Adults: the initial dose should not exceed 2.5mg i.v. 5-10 minutes before the beginning of the operation. Further doses of 1mg may be given as necessary. A total dose greater than 5mg is not usually necessary to reach the desired endpoint. In cases of severe illness, particularly if the patient is in poor general condition or of advanced age, the initial dose must be reduced to 1-1.5mg. Total doses greater than 3.5mg are not usually necessary.

Sedation in Intensive Care Units

Intravenous sedation

For sedation in ICU, the dosage should be individualised and Midaccord titrated to the desired state of sedation according to the clinical need, physical status, age, concomitant medication.

Adults

Loading dose: 0.03 - 0.3 mg/kg.

Maintenance dose: 0.03 - 0.2 mg/kg/hr. The dosage should be reduced or the loading dose should even be omitted in hypovolemic, vasoconstricted and hypothermic patients.

Induction and Maintenance of Anaesthesia

Intravenous injection

Adults

Induction: the dose is 10-15 mg i.v. in combination with analgesics. A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

Maintenance: for maintenance of the desired level of unconsciousness, further small doses should be injected i.v. The dose and the intervals between doses vary according to the individual patient's reaction. Alternatively, Midaccord can be administered by continuous infusion.

Intravenous continuous infusion

Adults: for intravenous anaesthesia combined with ketamine, 0.03 - 0.1 mg/kg/hr; narcotics, 0.03 - 0.3 mg/kg/hr. High-risk surgical patients, elderly and debilitated patients require lower dosages.

Intramuscular administration

Children: a combination of the sleep-inducing and amnesia-inducing Midaccord with ketamine (ataralgesia) is recommended. Midaccord i.m. (0.15-0.20 mg per kg bodyweight) in combination with 50-100 mg ketamine i.m. (4-8 mg per kg bodyweight). A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

Rectal administration

Children: see Premedication before an Operation.

Special Dosage Instructions

When Midaccord is given with potent analgesics, the latter should be administered first so that the sedative effects of Midaccord can be safely titrated on top of any sedation caused by the analgesic.

CONTRAINDICATIONS

Use of this medicine in patients with known hypersensitivity to benzodiazepines or to any component of the product.

PRECAUTIONS

Midaccord ampoules should be used only when age- and size-appropriate resuscitation facilities are available, as i.v. administration of Midaccord may depress myocardial contractility and cause apnoea. Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur in adults over 60 years of age, those with pre-existing respiratory insufficiency or impaired cardiac function and paediatric patients with cardiovascular instability, particularly when the injection is given too rapidly or when a high dosage is administered.

Special caution should be exercised when administering Midaccord parenterally to patients representing a higher risk group:

- adults over 60 years of age
- debilitated or chronically ill patients
- patients with chronic respiratory insufficiency

- patients with chronic renal failure, impaired hepatic function or with congestive heart failure
- paediatric patients with cardiovascular instability

These higher-risk patients require lower dosages (see Dosage and Administration) and should be continuously monitored for early signs of alterations of vital functions. Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering Midaccord to a patient with myasthenia gravis, owing to pre-existing muscle weakness.

Tolerance

Some loss of efficacy has been reported when Midaccord has been used as long-term sedation in intensive care units (ICU).

Dependence

When Midaccord is used in long-term sedation in ICU, it should be borne in mind that physical dependence on Midaccord may develop. The risk of dependence increases with dose and duration of treatment.

Withdrawal Symptoms

During prolonged treatment with Midaccord ampoules 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 that the dose is decreased gradually.

Amnesia

Midaccord 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 Midaccord 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 Midaccord. The highest incidence of susceptibility to such reactions has been reported among children and the elderly. Should such symptoms suggestive of a paradoxical reaction occur, the response to Midaccord should be evaluated before proceeding.

Elimination of midazolam may be delayed in patients receiving compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) (see Interactions).

When midazolam is given intravenously for a prolonged period and in combination with saquinavir, an initial dose reduction of midazolam of 50% is recommended (see Interactions).

It is advisable to lower doses of intravenous midazolam when co-administered with erythromycin (see Interactions).

Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam. Care should be taken to adjust the midazolam dose in patients with epilepsy on treatment with sodium valproate (see Interactions).

Elimination of midazolam may also be delayed, in patients with liver dysfunction, low cardiac output and in neonates (see Pharmacokinetics in special populations).

Adverse haemodynamic events have been reported in paediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.

Pre-term Infants and Neonates

Due to an increased risk of apnoea, extreme caution is advised when sedating pre-term and former pre-term patients whose trachea is not intubated.

Rapid injection should be avoided in the neonatal population.

The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of Midaccord.

Effects on Ability to Drive or Use Machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or use machines. Prior to receiving Midaccord, the patient should be warned not to drive a vehicle or operate a machine until recovered.

PREGNANCY, NURSING MOTHERS

Insufficient data are available on midazolam to assess its safety during pregnancy. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. The administration of midazolam in the last trimester of pregnancy or at high doses during labour has been reported to produce irregularities in the foetal heart rate, hypotonia, poor sucking and hypothermia and moderate respiratory depression in the neonate. Moreover, infants born to 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.

Since midazolam passes into breast milk, Midaccord should not be administered to breast-feeding mothers.

UNDESIRABLE EFFECTS

The following undesirable effects have been reported to occur when Midaccord is injected:

Central and peripheral nervous system and psychiatric disorders

Drowsiness and prolonged sedation, reduced alertness, confusion, euphoria, hallucinations, fatigue, headache, dizziness, ataxia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

Convulsions have been reported in premature infants and neonates.

Use of Midaccord - 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.

Gastrointestinal system disorders

Nausea, vomiting, hiccough, constipation, dry mouth.

Cardiorespiratory disorders

Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such 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 (see Precautions).

The following other cardiorespiratory adverse events have been reported: hypotension, slight increase in heart rate, vasodilating effects, dyspnoea. In isolated cases laryngospasm has occurred following injection of Midaccord.

Skin and appendages disorders

Skin rash, urticarial reaction, pruritus.

Body-as-a-whole disorders

In isolated cases, generalized hypersensitivity, from skin reactions to anaphylactoid reactions, have been reported.

Local reactions

Erythema and pain on injection site, thrombophlebitis, thrombosis.

INTERACTIONS

The metabolism of midazolam is predominantly mediated by cytochrome P450 3A4 (CYP3A4) isozyme. Approximately 25 % of the total cytochrome P450 system in the adult liver is from the CYP3A4 subfamily. Inhibitors (see Precautions) and inducers of this isozyme may lead to interaction with midazolam.

INTERACTIONS STUDIES CONDUCTED WITH MIDACCORD AMPOULES**CYP3A4 inhibitors*****Itraconazole and fluconazole***

Co-administration of Midaccord and itraconazole or fluconazole prolonged the elimination half-life of midazolam from 2.9 to 7.0 hours (itraconazole) or 2.9 to 4.4 hours (fluconazole).

Bolus doses of midazolam given for short-term sedation did not enhance the effect of midazolam to a clinically significant degree by itraconazole and fluconazole, and dosage reduction is not required. However, administration of high doses of midazolam may require dosage adjustments. Long-term infusions of midazolam to patients receiving

systemic antimycotics, e.g., during intensive care treatment, may result in long-lasting hypnotic effects if the dose is not titrated according to the effect.

Erythromycin

Co-administration of Midaccord and erythromycin prolonged the elimination half-life of midazolam from 3.5 to 6.2 hours. Although only relatively minor pharmacodynamic changes were observed, it is advised to adjust doses of intravenous midazolam, especially if high doses are being administered (see Precautions).

Cimetidine and ranitidine

Cimetidine increased the steady-state plasma concentration of midazolam by 26%, whereas ranitidine had no effect.

Co-administration of midazolam and cimetidine or ranitidine had no clinically significant effect on the pharmacokinetics and pharmacodynamics of midazolam. These data indicate that intravenous midazolam can be used in usual doses with cimetidine and ranitidine and dosage adjustment is not required.

Cyclosporin

Cyclosporin There is no pharmacokinetic and pharmacodynamic interaction between cyclosporin and midazolam. Therefore, the dosage of midazolam needs no adjustment when given concomitantly with cyclosporin.

Nitrendipine

Nitrendipine did not affect the pharmacokinetics and pharmacodynamics of midazolam. Both medicines can be given concomitantly and no dosage adjustment of midazolam is required.

Saquinavir

Co-administration of a single intravenous dose of 0.05 mg/kg midazolam after 3 or 5 days of saquinavir dosing (1200mg t.i.d.) to 12 healthy volunteers decreased the midazolam clearance by 56% and increased the elimination half-life from 4.1 to 9.5 h. Only the subjective effects to midazolam (visual analogue scales with the item “overall drug effect”) were intensified by saquinavir.

Therefore, bolus doses of intravenous midazolam can be given in combination with saquinavir. During a prolonged midazolam infusion, an initial dose reduction of 50 % is recommended (see Precautions).

Oral contraceptives

The pharmacokinetics of intramuscular midazolam was not affected by the use of oral contraceptives. Both medicines can be given concomitantly and no dosage adjustment of midazolam is required.

Other interactions

Sodium valproate

Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam and, therefore, care should be taken to adjust the midazolam dosage in patients with epilepsy (see Precautions).

Lidocaine

Midazolam had no effect on the plasma protein binding of lidocaine in patients undergoing anti-arrhythmic therapy or regional anaesthesia with lidocaine.

Alcohol may enhance the sedative effect of midazolam.

The i.v. administration of Midaccord decreases the minimum alveolar concentration (MAC) of halothane required for general anaesthesia.

OVERDOSAGE

Symptoms

The symptoms of overdose are mainly an intensification of the pharmacological effects; drowsiness, mental confusion, lethargy and muscle relaxation or paradoxical excitation. As with other benzodiazepines, Overdosage should not present a threat to life unless combined with other CNS depressants including alcohol. More serious symptoms would be areflexia, hypotension, cardiorespiratory depression, apnoea and, rarely, coma.

Treatment

In most cases only observation of vital functions is required. In the management of overdose special attention should be paid to the respiratory and cardiovascular functions in intensive care. The effects of overdosage can be controlled with the benzodiazepine antagonist Anexate® (active ingredient: flumazenil). Caution should be observed in the use of flumazenil in cases of mixed drug overdosage and in patients with epilepsy treated with benzodiazepines.

PHARMACOLOGICAL PROPERTIES

Midazolam, the active ingredient of Midaccord, 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 Midaccord to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

The pharmacological action of midazolam is characterized by rapid onset and, because of rapid metabolic transformation, short duration. Because of its low toxicity, midazolam has a wide therapeutic range.

Midaccord has a very rapid sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect.

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

PHARMACOKINETICS

Absorption

Absorption after i.m. injection

Absorption of midazolam 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%.

Absorption after rectal administration

After rectal administration midazolam is absorbed quickly. Maximum plasma concentration is reached in about 30 minutes. The absolute bioavailability is about 50%.

Distribution

When Midazolam 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 foetal circulation. Small quantities of midazolam are found in human milk.

Metabolism

Midazolam is almost entirely eliminated by biotransformation. Less than 1% of the dose is recovered in urine as the unchanged substance. Midazolam is hydroxylated by the cytochrome P450 3A4 isozyme. α -hydroxymidazolam is the major urinary and plasma metabolite. 60-80% of the dose is excreted in urine as glucuroconjugated α -hydroxymidazolam. Plasma concentrations of α -hydroxymidazolam are 12% those of the parent compound. The fraction of the dose extracted by the liver has been estimated to be 30-60%. The elimination half-life of the metabolite is shorter than 1 hour. α -hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam. There is no evidence of a genetic polymorphism in the oxidative metabolism of midazolam (see Interactions).

Elimination

In healthy volunteers, the elimination half-life is between 1.5 - 2.5 hours. Plasma clearance is in the range of 300-500 ml/min. When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection.

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 rate of rectal absorption in children is similar to that in adults. However, the elimination half-life ($t_{1/2}$) after i.v. and rectal administration is shorter in children 3-10 years 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 (see Precautions).

Patients with hepatic impairment

The elimination half-life in cirrhotic patients may be longer and the clearance smaller as compared to those in healthy volunteers (see Precautions).

Patients with renal impairment

The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

Critically ill patients

The elimination half-life of midazolam is prolonged 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 (see Precautions).

PHARMACEUTICAL PARTICULARS

List of excipients

Sodium chloride
Concentrated hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH-adjustment)
Water for Injections

Incompatibilities

Midazolam solution for injection or infusion must not be diluted with 6% w/v dextran (with 0.9% sodium chloride) in glucose.

Midazolam solution for injection or infusion must not be mixed with alkaline solutions for injection. Midazolam precipitates in solutions containing hydrogen carbonate.

Shelf life

2 years

Shelf life after dilution

Chemical and physical in-use stability of the dilutions has been demonstrated for 24 hours at room temperature (15 – 25°C) or for 3 days at +2 to +8 °C.

From the microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are at the responsibility of the user and would normally not be longer than 24 hours at +2 to +8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Store below 25°C. Keep the ampoules in the outer carton in order to protect from light.

Midaccord ampoules should not be frozen because they can burst. Furthermore, precipitation can occur which dissolves on shaking at room temperature.

Nature and Contents of Container

For 1 mg/mL

Midazolam solution for injection or infusion 1 mg/ml is filled in 5 ml Type - I, OPC (One Point Cut), clear, white point and blue band ampoules. 10 ampoules are packed in a carton.

For 5 mg/mL, 1 ml,

Midazolam solution for injection or infusion 5 mg/ml is filled in 1 ml Type – I, OPC (One Point Cut), clear, white point and yellow band ampoule. 10 ampoules are packed in a carton.

For 5 mg/mL, 3 ml,

Midazolam solution for injection or infusion 5 mg/ml is filled in 3 ml Type – I, OPC (One Point Cut), clear, white point and blue band ampoule. 10 ampoules are packed in a carton.

For 5 mg/mL, 10 ml,
Midazolam solution for injection or infusion 5 mg/ml is filled in 10 ml Type – I, OPC (One Point Cut), clear, white point and red band ampoule. 1 ampoule is packed in a carton.

Instructions for use/handling

Compatible with the following solutions for infusion

- Sodium chloride 9 mg/ml (0.9 %) solution
- Glucose 50 mg/ml (5 %) solution
- Glucose 100 mg/ml (10 %) solution
- Fructose 50 mg/ml (5 %) solution
- Ringer's solution
- Hartmann's solution

Midazolam ampoules are intended for single use. Any unused product or waste material should be disposed of in accordance with local requirements.

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

In case of continuous intravenous infusion, midazolam injection solution may be diluted in the range of 0.015 to 0.15 mg per ml with one of the solution mentioned above.

MEDICINES CLASSIFICATION

Controlled Drug (C5)

NAME AND ADDRESS

Distributed in New Zealand by:

Arrow Pharmaceuticals (NZ) Ltd.
PO Box 128244.
Remuera, Auckland
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