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1.3.1.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1 NAME OF THE MEDICINE

ADCO MIDAZOLAM INJECTION 5 mg/5 ml Injection

ADCO MIDAZOLAM INJECTION 15 mg/3 ml Injection

ADCO MIDAZOLAM INJECTION 50 mg/10 ml Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ADCO MIDAZOLAM INJECTION 5 mg/5 ml: Each ampoule contains midazolam 5 mg per 5 mL

ADCO MIDAZOLAM INJECTION 15 mg/3 ml: Each ampoule contains midazolam 15 mg per 3 mL

ADCO MIDAZOLAM INJECTION 50 mg/10 ml: Each ampoule contains midazolam 50 mg per 10 mL

Excipient(s) with known effect:

ADCO MIDAZOLAM INJECTION 5 mg/5 ml: Each ampoule contains 17,71 mg sodium

ADCO MIDAZOLAM INJECTION 15 mg/3 ml: Each ampoule contains 10,63 mg sodium

ADCO MIDAZOLAM INJECTION 50 mg/10 ml: Each ampoule contains 35,42 mg sodium

Sugar free

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

ADCO MIDAZOLAM INJECTION 5 mg/5 ml: A clear, colourless solution packaged in a 5 mL, glass ampoule or a 5 mL, plastic ampoule.

ADCO MIDAZOLAM INJECTION 15 mg/3 ml: A clear, colourless solution packaged in a 3 mL, glass ampoule or a 5 mL, plastic ampoule, containing 3 mL of solution.

ADCO MIDAZOLAM INJECTION 50 mg/10 ml: A clear, colourless solution packaged in a 10 mL, glass ampoule or a 10 mL, plastic ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Intramuscular administration:

- Pre-operative sedation
- Induction of anaesthesia in children.

Intravenous administration:

- Pre-operative sedation and conscious sedation before diagnostic or surgical interventions carried out under local anaesthesia
- Premedication before induction of anaesthesia
- Induction of anaesthesia. As an induction agent in inhalation anaesthesia or a sleep-inducing component in combined anaesthesia, including total intravenous anaesthesia (IV injection, IV infusion)
- Maintenance of anaesthesia where subsequent ICU administration with ventilation is envisaged for the purpose of recovery and stabilisation
- Long-term sedation in intensive care units (IV administration as bolus injection or continuous infusion).

4.2 Posology and method of administration

Posology

ADCO MIDAZOLAM INJECTION is a potent sedative agent, which requires slow administration and individualisation of dosage. The dose should be individualised and titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication.

Intramuscular administration:

Pre-operative sedation:

Adults: 0,07 to 0,10 mg/kg, in accordance with age and general physical condition of the patient. The usual dose is about 5 mg.

Children: 0,15 to 0,20 mg/kg.

These dosages should be administered 30 minutes before the induction of anaesthesia.

Induction of anaesthesia in children:

0,15 to 0,20 mg/kg body weight, combined with 8 mg of ketamine per kg body weight given intramuscularly.

Intravenous administration:

Pre-operative sedation and conscious sedation:

The starting dose is 2,5 mg, 5 to 10 minutes before the procedure. When needed, additional doses of 1 mg can be administered. Dosages greater than 5 mg are not usually required. The injection should be administered slowly, about 1 mg in 30 seconds.

For elderly or debilitated patients, the initial dosage should be decreased to 1 to 1,5 mg. Total doses of more than 3,5 mg are usually not necessary.

Sedation in intensive care units (ICU):

For sedation in ICU, the dosage should be individualised and ADCO MIDAZOLAM INJECTION titrated to the desired state of sedation according to the clinical need, physical status, age, concomitant medication. Induce sedation by a loading dose of 0,03 to 0,3 mg/kg, administered over a 5-minute period. The maintenance dose is between 0,03 to 0,2 mg/kg/hour. The loading dose should be reduced or omitted in hypovolaemic, vasoconstricted or hypothermic patients.

Induction and maintenance of anaesthesia:

In premedicated adults below the age of 60, the dose can range from 0,15 to 0,2 mg/kg, combined with an analgesic drug. The dosage must be administered slowly, about 2,5 mg in 10 seconds. Additional small doses may be necessary for maintenance; these doses must be individualised.

For intravenous anaesthesia, combined with opioids, the dose of midazolam is 0,03 to 0,3 mg/kg/ hour. The injections can be replaced with continuous infusions. The dose should be decreased in surgical patients with increased risk, elderly and debilitated patients.

Method of administration

Intravenous (injection or infusion) or intramuscular injection.

4.3 Contraindications

- Use in patients with known hypersensitivity to midazolam or any medicine from the benzodiazepine group or to any of the ingredients listed in section 6.1
- Myasthenia gravis
- Severe respiratory insufficiency
- Sleep apnoea syndrome
- Severe hepatic insufficiency. ADCO MIDAZOLAM INJECTION is not indicated to treat patients with severe hepatic impairment as it may cause encephalopathy (see section 4.4)
- Pregnancy and lactation (see Section 4.6).

4.4 Special warnings and precautions for use

ADCO MIDAZOLAM INJECTION should be used only when resuscitation facilities are available, as IV administration of ADCO MIDAZOLAM INJECTION may depress myocardial contractility and cause apnoea.

The use of ADCO MIDAZOLAM INJECTION has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. Cerebral hypoxia or paradoxical reactions should be contemplated.

Severe cardiorespiratory adverse events may occur. These include respiratory depression, apnoea 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 in paediatric patients with cardiovascular instability, particularly when the injection is given too rapidly or when a high dosage is administered.

ADCO MIDAZOLAM INJECTION is not recommended for the primary treatment of psychotic illness.
Conscious sedation should be provided by a medical practitioner experienced in the use of this technique.

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

Use in premedication:

When ADCO MIDAZOLAM INJECTION is used for premedication, adequate observation of the patient after administration is mandatory as inter-individual sensitivity varies and symptoms of overdose may occur.

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

- elderly (adults over 60 years)
- debilitated or chronically ill patients
- patients with chronic renal failure or impaired kidney function

- patients with impaired hepatic function (ADCO MIDAZOLAM INJECTION is contraindicated in patients with severe hepatic impairment as it may precipitate or exacerbate encephalopathy)
- patients with obstructive pulmonary disease
- patients with congestive heart failure or impaired cardiac function
- paediatric patients with cardiovascular instability

These higher-risk patients require lower and individualised dosages and should be continuously monitored for early signs of alterations of vital functions.

Patients with chronic renal failure, impaired hepatic function and congestive heart failure may eliminate ADCO MIDAZOLAM INJECTION more slowly.

After parenteral administration of ADCO MIDAZOLAM INJECTION, patients should not be discharged from hospital for at least four hours. They must then be accompanied by a responsible person. Prior to receiving ADCO MIDAZOLAM INJECTION, they should be warned not to drive a vehicle or operate machinery for at least twelve hours thereafter (see section 4.7).

The possibility of severe undesirable effects is particularly high with very high dosages or very rapid intravenous administration. Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These reactions can be caused by inadequate or too high dosages or incorrect administration of ADCO MIDAZOLAM INJECTION. After prolonged intravenous administration, abrupt discontinuation may lead to withdrawal symptoms; therefore, a gradual reduction of the dosage is recommended.

Special care must be taken when ADCO MIDAZOLAM INJECTION is used during labour and delivery, as high single doses may produce respiratory depression, irregularities in the foetal heart rate and hypotonia, poor sucking and hypothermia in the neonate.

Usage in 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 without trachea intubation. Careful monitoring of respiratory rate and oxygen saturation is required.

Rapid injection should be avoided in neonates as they are vulnerable to profound and/or prolonged respiratory effects of ADCO MIDAZOLAM INJECTION.

ADCO MIDAZOLAM INJECTION administered rapidly as an intravenous injection (less than 2 minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration.

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

Tolerance

Loss of efficacy has been reported when ADCO MIDAZOLAM INJECTION has been used as prolonged sedation in intensive care units (ICU).

Dependence

When ADCO MIDAZOLAM INJECTION is used in long-term sedation physical dependence on ADCO MIDAZOLAM INJECTION may develop, which is related to the dose and duration of treatment (see section 4.8).

Withdrawal symptom

Abrupt termination of the treatment after prolonged administration will be accompanied by withdrawal symptoms. The following symptoms may occur; headaches, diarrhoea, muscle pain, extreme anxiety, tension, sleep disturbances, 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 be gradually decreased (see section 4.8).

Amnesia

ADCO MIDAZOLAM INJECTION causes anterograde amnesia which may occur at therapeutic doses, with the risk increasing at higher dosages. Prolonged amnesia can present problems in outpatients who are scheduled for discharge following intervention (see section 4.8).

Psychiatric and "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, may occur with the use of ADCO MIDAZOLAM INJECTION. The highest incidence of susceptibility to such reactions has been reported among children and the elderly. Should such symptoms suggestive of paradoxical reaction occur, the response to ADCO MIDAZOLAM INJECTION should be evaluated before proceeding (see section 4.8).

Altered elimination

ADCO MIDAZOLAM INJECTION elimination may also be altered in patients receiving compounds that inhibit or induce CYP3A4, and the dose of ADCO MIDAZOLAM INJECTION may need to be adjusted accordingly (see section 4.5). ADCO MIDAZOLAM INJECTION elimination may be delayed in patients receiving compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4) (see section 4.5).

The concomitant use of ADCO MIDAZOLAM INJECTION with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of ADCO MIDAZOLAM INJECTION possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5).

When midazolam is given as an intravenous infusion in combination with saquinavir, an initial dose reduction of midazolam of 50 % is recommended (see section 4.5).

It is advisable to lower doses of intravenous midazolam when co-administered with erythromycin (see section 4.5).

ADCO MIDAZOLAM INJECTION elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates (see section 5.2).

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

Routine intravenous ADCO MIDAZOLAM INJECTION induction is not recommended in children under 7 years of age.

ADCO MIDAZOLAM INJECTION contains sodium:

ADCO MIDAZOLAM INJECTION 5 mg/5 ml

This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially ‘sodium-free’.

ADCO MIDAZOLAM INJECTION 15 mg/3 ml

This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially ‘sodium-free’.

ADCO MIDAZOLAM INJECTION 50 mg/10 ml

This medicine contains 35,42 mg sodium per ampoule, equivalent to 1,77 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicines and other forms of interaction

Because ADCO MIDAZOLAM INJECTION is almost exclusively metabolised by cytochrome P450 3A (CYP3A), modulators of CYP3A have the potential to alter the plasma concentrations and subsequently the clinical effects of ADCO MIDAZOLAM INJECTION.

ADCO MIDAZOLAM INJECTION is not known to change the pharmacokinetics of other medicines.

It is recommended to carefully monitor the clinical effects and vital signs during the use of ADCO MIDAZOLAM INJECTION considering the clinical effects of ADCO MIDAZOLAM INJECTION might be stronger and also last longer after administration of a CYP3A inhibiting medicine. Depending on the magnitude of the CYP3A inhibiting effect the dose of ADCO MIDAZOLAM INJECTION may be largely reduced. Conversely administration of a CYP3A inducing medicine may lead to a higher dose of ADCO MIDAZOLAM INJECTION required to achieve the desired effect.

The method of administration of ADCO MIDAZOLAM INJECTION use also determines the magnitude of change in its pharmacokinetics due to CYP3A modulation.

After intramuscular administration the medicine directly enters the systemic circulation, so it is expected that the effects of CYP3A modulation will be similar to those for intravenous ADCO MIDAZOLAM INJECTION.

In line with the pharmacokinetic principles, studies have shown that after IV single dose of ADCO MIDAZOLAM INJECTION, the change in maximal clinical effect due to CYP3A modulation will be minor while the duration of effect may be prolonged. However, after prolonged dosing of ADCO MIDAZOLAM INJECTION, both the magnitude and the duration of effect will be increased in the presence of CYP3A inhibition.

The list below provides examples of clinical pharmacokinetic medicine-medicine interactions with ADCO MIDAZOLAM INJECTION after intravenous administration. Importantly, any medicine shown to possess CYP3A modulating effects, has the potential to change the plasma concentrations of ADCO MIDAZOLAM INJECTION and therefore its effects.

Medicines that inhibit CYP3A

Azole antifungals

- Ketoconazole and voriconazole increased the plasma concentrations of ADCO MIDAZOLAM INJECTION by 5-fold and by 3 - 4-fold respectively while the terminal half-life increased by about 3-fold. If parenteral ADCO MIDAZOLAM INJECTION is co-administered with these strong CYP3A inhibitors, 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 dose of ADCO MIDAZOLAM INJECTION is administered.

- Fluconazole and itraconazole both increased the plasma concentrations of intravenous ADCO MIDAZOLAM INJECTION 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 ADCO MIDAZOLAM INJECTION by about 2-fold.

Macrolide antibiotics

- Erythromycin resulted in an increase in plasma concentrations of ADCO MIDAZOLAM INJECTION by about 1,6 - 2-fold associated with an increase in ADCO MIDAZOLAM INJECTION's terminal half-life by 1,5 - 1,8-fold
- Clarithromycin increased ADCO MIDAZOLAM INJECTION's plasma concentrations by up to 2,5-fold associated with an increase in terminal half-life by 1,5 - 2-fold

Intravenous anaesthetics

- Disposition of ADCO MIDAZOLAM INJECTION was also changed by intravenous propofol (AUC and half-life increased by 1,6-fold).

Protease inhibitors

- Saquinavir and other HIV protease inhibitors: Upon co-administration with ritonavir boosted lopinavir, the plasma concentrations of ADCO MIDAZOLAM INJECTION increased by 5,4-fold, associated with a similar increase in terminal half-life. If parenteral ADCO MIDAZOLAM INJECTION is co-administered with HIV protease inhibitors, treatment setting should follow the description in the section above for ketoconazole within azole antifungals.

- HCV protease inhibitors: Boceprevir and telaprevir reduce ADCO MIDAZOLAM INJECTION clearance. This effect resulted in a 3,4-fold increase of ADCO MIDAZOLAM INJECTION AUC after IV administration and prolonged its elimination half-life 4-fold.

Histamine receptor 2 antagonists

- Cimetidine increased the steady state plasma concentrations of ADCO MIDAZOLAM INJECTION by 26 %.

Calcium-channel blockers

- Diltiazem: A single dose of diltiazem increased the plasma concentrations of ADCO MIDAZOLAM INJECTION by about 25 % and the terminal half-life was prolonged by about 43 %.

Various medicines

- Atorvastatin showed an about 1,4-fold increase in plasma concentrations of ADCO MIDAZOLAM INJECTION compared to control group.
- Intravenous fentanyl is a weak inhibitor of ADCO MIDAZOLAM INJECTION's elimination: AUC and half-life of ADCO MIDAZOLAM INJECTION were increased by 1,5-fold in presence of fentanyl.

Medicines that induce CYP3A

- Rifampicin decreased the plasma concentrations of ADCO MIDAZOLAM INJECTION by about 60 % after 7 days of rifampicin 600 mg once daily. The terminal half-life decreased by about 50 - 60 %.
- Ticagrelor is a weak CYP3A inducer but has only small effects on intravenously administered ADCO MIDAZOLAM INJECTION (-12 %) and 4-hydroxy- midazolam (-23 %) exposures.

Herbs and food

- *Echinacea purpurea* root extract decreased plasma concentrations of ADCO MIDAZOLAM INJECTION by 20 % associated with a decrease in half-life by about 42 %.
- St John's wort decreased plasma concentrations of ADCO MIDAZOLAM INJECTION by about 20 - 40 % associated with a decrease in terminal half-life of about 15 - 17 %.

Acute protein displacement

- Valproic acid: In one publication, protein displacement of ADCO MIDAZOLAM INJECTION by valproic acid was discussed as a potential mechanism of medicine-medicine interaction. The clinical relevance of this study is considered very limited because of methodological concerns. However, due to the high therapeutic plasma concentration of valproic acid, the protein displacement of ADCO MIDAZOLAM INJECTION in the acute dose setting, resulting in more apparent clinical effect of ADCO MIDAZOLAM INJECTION, cannot be excluded.

Pharmacodynamic interactions

Sedatives and hypnotics

The co-administration of ADCO MIDAZOLAM INJECTION with other sedative/hypnotic agents is likely to result in increased sedative/hypnotic effects. Such sedative/hypnotic agents include alcohol, opiates/opioids (when they are used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, antihistamines and centrally acting antihypertensive medicines.

Anaesthetics

ADCO MIDAZOLAM INJECTION decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

It has been shown that spinal anaesthesia can increase the sedative effect of ADCO MIDAZOLAM INJECTION. The ADCO MIDAZOLAM INJECTION dose may therefore be reduced.

When lidocaine (lignocaine) and bupivacaine, were administered intramuscularly, the dose of ADCO MIDAZOLAM INJECTION required for sedation was reduced.

Alcohol

Enhanced side effects such as sedation and cardiorespiratory depression may also occur when ADCO MIDAZOLAM INJECTION is co-administered with any centrally acting depressants including alcohol. The combination of alcohol and ADCO MIDAZOLAM INJECTION should be avoided (see section 4.4).

See section 4.9 for warnings on other central nervous system depressants, including alcohol.

Medicines increasing alertness/memory

Medicines increasing alertness/memory like the AchE inhibitor, physostigmine, reversed the hypnotic effects of ADCO MIDAZOLAM INJECTION. Similarly, 250 mg of caffeine partly reversed the sedative effect of ADCO MIDAZOLAM INJECTION.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. ADCO MIDAZOLAM INJECTION has been shown to cross the placenta and to enter the foetal circulation. Benzodiazepines, including ADCO MIDAZOLAM INJECTION, should be avoided in pregnancy.

An increased risk of congenital malformation associated with the use of ADCO MIDAZOLAM INJECTION during the first trimester of pregnancy may occur.

If, exceptionally, it is considered by a medical practitioner that administration of ADCO MIDAZOLAM INJECTION during the last three months of pregnancy, or during labour, is essential, effects on the neonate such as irregularities in the foetal heart rate, hypothermia, hypotonia, poor sucking and moderate respiratory depression can be expected, due to the pharmacological action of the product. Moreover, infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Breastfeeding

ADCO MIDAZOLAM INJECTION passes into breast milk and should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Prior to receiving ADCO MIDAZOLAM INJECTION, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The medical practitioner should decide when these activities may be resumed.

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Not applicable

b. Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse event
Immune system disorders	Less frequent	Anaphylactoid reactions
Psychiatric disorders	Frequency not known	Confusional state, emotional and mood disturbances Paradoxical reactions: restlessness, agitation, psychomotor hyperactivity, irritability, aggression, delusion, anger, nightmare, hallucination Dependence: drug dependence, withdrawal syndrome, substance abuse
Nervous system	Frequent	Drowsiness, dizziness, oversedation and ataxia

disorders	Less frequent	Depression of mood and affect, disorientation, confusion and lethargy. Anterograde amnesia which may be dose related, headache and hallucinations.
	Frequency not known	Convulsions in premature infants and neonates and prolonged amnesia. Premedication: impact on post-operative sedation
Cardiac disorders	Less frequent	Cardiac arrest
	Frequency not known	A decrease in arterial blood pressure and changes of pulse rate may occur. As a rule, the systolic blood pressure falls by a maximum of 15 %, while the pulse rate simultaneously shows a corresponding rise. Cardiovascular collapse may occur following intravenous administration. Kounis syndrome*
Vascular disorders	Frequency not known	Thrombophlebitis, thrombosis, hypotension, vasodilation.
Respiratory, thoracic and mediastinal disorders	Less frequent	Severe cardio-respiratory adverse events including respiratory depression and respiratory arrest
	Frequency not known	Laryngospasm, dyspnoea. A change of breathing may occur. Apnoea may occur due to a depressant effect on the respiratory centre. Hiccups
Gastrointestinal disorders	Less frequent	Nausea and vomiting
	Frequency not known	Constipation, dry mouth

Skin and subcutaneous tissue disorders	Frequency not known	Skin rash, urticaria, pruritus, erythema on injection site
General disorders and administration site conditions	Frequent	Local effects on veins (pain on injection) can occur.
	Frequency not known	Fatigue
Injury, poisoning and procedural complications	Frequency not known	Fall, fracture

* Particularly after parenteral administration

c. Description of selected adverse reactions

Psychiatric disorders: The use of the medicine should be discontinued if paradoxical reactions occur. These effects are more likely to occur in the elderly (see section 4.4). Abuse has been reported in poly-drug abusers.

Nervous system disorders: These adverse events occur predominantly at the start of therapy and usually disappear with repeated administration. The duration 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. Convulsions have been reported in premature infants and neonates. Drowsiness is more frequent in elderly and debilitated patients and in patients receiving high doses.

Cardiac disorders: Severe cardiorespiratory adverse events have occurred. Such life-threatening incidents are more likely to occur in adults older than 60 years 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 section 4.4).

Respiratory, thoracic and mediastinal disorders: Severe cardiorespiratory adverse events have occurred. Such life-threatening incidents are more likely to occur in adults older than 60 years 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 section 4.4).

Injury, poisoning and procedural complications: The risk of falls and fractures is increased in ADCO MIDAZOLAM INJECTION users taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc-org) found on SAHPRA website.

For reporting of side effects directly to the Holder of the Certificate of Registration, contact +27 11 635 0134 or email Adcock.aereports@adcock.com

4.9 Overdose

Symptoms: these are primarily an intensification of the therapeutic effects (mental confusion, lethargy, sedation, muscle weakness, profound sleep) or paradoxical excitation. In these cases, only observation of vital functions is required. Extreme overdosage may lead to coma, areflexia, cardio-respiratory depression, apnoea, hypotonia and hypotension, requiring appropriate countermeasures (ventilation, cardiovascular support).

Benzodiazepines, including ADCO MIDAZOLAM INJECTION, commonly cause drowsiness, ataxia, dysarthria and nystagmus. 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, including ADCO MIDAZOLAM INJECTION, 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. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

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 affects have worn off. Flumazenil is to be used with extreme caution in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the professional information for flumazenil, for further information on the correct use of this medicine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.2 Sedatives, hypnotics

Pharmacotherapeutic group: Benzodiazepine derivatives

ATC code: N05CD08

Mechanism of action

Midazolam has hypnotic, anxiolytic, sedative, muscle-relaxant and anticonvulsant effects and causes anterograde amnesia. Midazolam impairs psychomotor function after single and/or multiple doses. This is thought to be caused by enhancement of GABA-mediated inhibition in the central nervous system. Midazolam binds to the benzodiazepine receptors in various regions in the brain such as the spinal cord, brain stem, cerebellum, limbic system and cerebral cortex.

5.2 Pharmacokinetic properties

Absorption

Absorption of midazolam from the muscle tissue is rapid and complete.

Maximum plasma concentrations are reached within 30 minutes.

Bioavailability after IM injection is over 90 %.

Distribution

The course of the plasma concentrations shows a short distribution phase of 5 - 15 minutes, followed by an elimination phase. 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 minimal passage of midazolam into cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta and to enter foetal circulation. Midazolam is found in human milk. Midazolam is not a substrate for medicine transporters.

Metabolism

The hepatic clearance of midazolam is about 50 % of hepatic blood flow. Midazolam is metabolised quickly and completely by the hepatic P450 cytochrome system into two main metabolites (1'-hydroxymidazolam (also named α-hydroxymidazolam) and 4-hydroxymidazolam), which are rapidly glucuronidated and mainly excreted in the urine in the form of 1'-hydroxymidazolam. Less than 1 % of the dose is recovered in the urine as unchanged drug.

Elimination

In healthy young volunteers, the elimination half-life of midazolam ranges between 1,5 - 2,5 hours. Repeated administration of midazolam does not induce drug-metabolising enzymes. The elimination half-life of 1'-hydroxymidazolam is shorter than 1 hour. When midazolam is given by *IV* infusion, its elimination kinetics does not differ from those following bolus injections.

Pharmacokinetics in special populations

Elderly

In adults over 60 years of age, the elimination half-life may be prolonged by 8 - 9 hours.

Patients with hepatic impairment

The elimination half-life in cirrhotic patients may be longer and the clearance smaller, compared to those in healthy volunteers (see section 4.4).

Patients with renal impairment

The pharmacokinetics of midazolam are not altered in patients with severe renal impairment. However, the major midazolam metabolite, 1'-hydroxymidazolam glucuronide, which is excreted through the kidney, accumulates in patients with severe renal impairment. This accumulation produces a prolonged sedation.

Obese patients

In obese patients the volume of distribution of midazolam is increased. As a consequence, the main elimination half-life of midazolam is longer in obese than in non-obese patients (8,4 hours vs 2,7 hours).

Children

The elimination half-life after IV administration is shorter in children 3 - 10 years 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 asphyxia-related hepatic and renal impairment are at risk of generating unexpectedly high serum midazolam concentrations due to a significantly decreased and variable clearance (see section 4.4).

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 section 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injections

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

ADCO MIDAZOLAM INJECTION 5 mg/5 ml: 24 Months

ADCO MIDAZOLAM INJECTION 15 mg/3 ml: 24 Months

ADCO MIDAZOLAM INJECTION 50 mg/10 ml: 24 Months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

ADCO MIDAZOLAM INJECTION 5 mg/5 ml: Clear, closed, easy break, 5 mL, Type 1 glass ampoule, 25 ampoules per carton. Transparent, low-density polyethylene (LDPE), 5 mL, plastic ampoule in strips of 10 plastic ampoules in an outer carton.

ADCO MIDAZOLAM INJECTION 15 mg/3 ml: Clear, closed, easy break, 3 mL, Type 1 glass ampoule, 50 ampoules per carton. Transparent, low-density polyethylene (LDPE), 5 mL, plastic ampoule in strips of 10 plastic ampoules in an outer carton.

ADCO MIDAZOLAM INJECTION 50 mg/10 ml: Clear, closed, easy break, 10 mL, Type 1 glass ampoule, 10 ampoules per carton. Transparent, low-density polyethylene (LDPE), 10 mL, plastic ampoule in strips of 10 plastic ampoules in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

1 Sabax Road

Aeroton

Johannesburg

2013

Tel: +27 11 494 8000

8 REGISTRATION NUMBERS

ADCO MIDAZOLAM INJECTION 5 mg/5 ml: A40/2.2/0753

ADCO MIDAZOLAM INJECTION 15 mg/3 ml: A40/2.2/0754

ADCO MIDAZOLAM INJECTION 50 mg/10 ml: A40/2.2/0755

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

16 November 2007

10 DATE OF REVISION OF THE TEXT

17 June 2025

Namibia: ADCO MIDAZOLAM INJECTION 5 mg/5 ml: NS3 10/2.2/0435

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