MODULE 1.3.1.1 – Package Insert

Product proprietary name:	***Accord Midazolam 5mg/5ml; 15mg/3 ml; 50mg/10 ml***
Dosage form and strength:	***5mg/5ml; 15mg/3 ml; 50mg/10 ml Midazolam Injection***
Applicant/PHCR:	***Accord Healthcare (Pty) Ltd***

SCHEDULING STATUS:

S5

PROPRIETARY NAME AND DOSAGE FORM:

Accord Midazolam 5 mg/5 ml solution for injection

Accord Midazolam 15 mg/3 ml solution for injection

Accord Midazolam 50 mg/10 ml solution for injection

COMPOSITION:

Accord Midazolam 5 mg/5 ml: contains 5 mg midazolam as the hydrochloride, per ampoule.

Accord Midazolam 15 mg/3 ml: contains 15 mg midazolam as the hydrochloride, per ampoule.

Accord Midazolam 50 mg/10 ml: contains 50 mg midazolam as the hydrochloride, per ampoule.

PHARMACOLOGICAL CLASSIFICATION:

A.2.2. Sedatives, hypnotics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Midazolam possesses hypnotic, anxiolytic, muscle relaxant, anticonvulsant and sedative properties.

Pharmacokinetic properties:

Midazolam is rapidly and completely absorbed from the muscle tissue after IM injection. Maximum plasma concentrations are reached within 30 minutes. Bioavailability after IM injection is over 90 %.

Distribution:

When midazolam is injected intravenously, the course of the plasma concentration shows a short distribution phase of 5-15 minutes, followed by an elimination phase. The volume of distribution calculated under steady-state conditions is 0,7-1,2 l/kg body weight. Studies show a protein binding of 96-98 %.

Metabolism:

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Initials:

Midazolam is completely metabolised and the primary metabolite is alpha-hydroxy-midazolam. The fraction extracted by the liver is 40-50 %. Many medicaments have been found to inhibit the production of this metabolite *in vitro***.**

For some of these medicines, this has been confirmed *in vivo* (refer to "Interactions").

Immediately after its formation, this active metabolite conjugates with glucuronic acid (inactivation) and is then eliminated by the kidneys more than midazolam.

Elimination:

The elimination half-life is between 1,5 and 2,5 hours. Plasma clearance is in the region of 300-400 ml per minute. When midazolam is given by IV infusion, its elimination kinetics does not differ from those, following bolus injection. After 48 hours infusion elimination may be prolonged. About 50 to 70 % of midazolam is eliminated by the kidneys in the form of a conjugate of the alpha-hydroxy metabolite.

Pharmacokinetics in special situations:

The elimination half-life may be prolonged by up to 3 times in adults over 60 years of age. The elimination half-life may be prolonged by up to six times in some patients requiring intensive care when given midazolam by IV infusion for long-term sedation. In these patients, infusion at an unchanged rate results in higher plasma levels at steady-state. Consequently, the infusion rate should be adjusted according to the patient's clinical response. The elimination half-life may be prolonged in patients with congestive heart failure, with chronic renal failure and with hepatic dysfunction. The elimination half-life is between 1 and 1,5 hours, in children (3-10 years). In neonates the elimination half-life is prolonged with a mean of 6 hours (3-12 hours) due to liver immaturity.

INDICATIONS:

Basal sedation before diagnostic or surgical interventions carried out under local anaesthesia. Pre-medication 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

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Initials:

purpose of recovery and stabilisation. Long-term sedation in intensive care units (IV administration as bolus injection or continuous infusion). Midazolam is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

CONTRA-INDICATIONS:

- Myasthenia gravis.
- Hypersensitivity to benzodiazepines.
- Safety in pregnancy and lactation have not been established. Accord Midazolam is shown to cross the placenta and to enter foetal circulation. Accord Midazolam passes into breast milk and should not be administered to breastfeeding mothers.
- Severe respiratory insufficiency.
- Sleep apnoea syndrome.
- Severe hepatic insufficiency.

WARNINGS AND SPECIAL PRECAUTIONS:

Accord Midazolam ampoules should be used only when resuscitation facilities are available, as IV administration of Accord Midazolam may depress myocardial contractility and cause apnoea.

Patients should not be discharged from hospital for at least four hours following the parenteral administration of Accord Midazolam. They must then be accompanied by a responsible person. Before receiving Accord Midazolam patients must be warned not to operate machinery or drive a vehicle for at least twelve hours thereafter.

When Accord Midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of Accord Midazolam can be safely titrated on top of any sedation caused by the analgesic. Special caution should be exercised when Accord Midazolam is administered parenterally to patients representing a higher risk group: elderly (adults over 60 years), debilitated or chronically ill

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patients, patients with obstructive pulmonary disease, with chronic renal failure, impaired hepatic function or with congestive heart failure.

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

Special care must be taken when benzodiazepines are 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.

Routine intravenous Accord Midazolam induction is not recommended in children under 7 years of age. Paradoxical reactions such as hyperactivity, agitation and combativeness occurred. Involuntary movements (including tonic/clonic convulsions and muscle tremor) have also been observed. Should such reactions occur, the response to each dose of Accord Midazolam should be evaluated before proceeding.

After prolonged IV administration of Accord Midazolam abrupt discontinuation of the product may be accompanied by withdrawal symptoms.

Therefore, a gradual reduction of Accord Midazolam is recommended.

DEPENDENCE:

There is a potential for abuse and the development of physical and psychic dependence, especially with prolonged use and high doses. The risk of dependence is also greater in patients with a history of alcohol or medicine abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension restlessness, confusion and irritability.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

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REBOUND EFFECTS:

A transient syndrome whereby the symptoms that led to treatment with Accord Midazolam recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

INTERACTIONS:

Enhancement of the central depressive effect may occur when midazolam is used concomitantly with:

- Antipsychotics
- Hypnotics
- Anxiolytics
- Antidepressants
- Narcotic analgesics
- Antiepileptic drugs
- Anaesthetics
- Sedative antihistamines

This potentiation of effect can in certain cases be of therapeutic advantage. Special attention must be paid to the possibility of potentiation in patients at particular risk.

The mutual potentiation of alcohol and Accord Midazolam can produce unforeseeable reactions (alcoholic beverages should not be consumed for at least 12 hours following parenteral administration of midazolam). There is a potentially relevant interaction between Accord Midazolam and compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 3A). Data clearly indicates that these compounds influence the pharmacokinetics of Accord Midazolam and may lead to increased and prolonged sedation. At present this reaction is known to occur with ranitidine, cimetidine, erythromycin,

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diltiazem, verapamil, itraconazole, ketoconazole and saquinavir but not with ciclosporin and nitrendipine.

Prescriptions of midazolam in patients receiving the above compound or other compounds which inhibit CYP450 3A, should thus be monitored carefully for the first few hours after administration of Accord Midazolam. Studies involving healthy individuals suggest that a clinically important pharmacokinetic interaction between parenteral midazolam and ranitidine is unlikely to occur in clinical practice. One study in vitro has shown the hydroxylation of midazolam to be inherited by a number of other substances (e.g. amiodarone, neuroleptics); accordingly, interaction with a whole range of medicaments is theoretically possible. However, the clinical relevance of these findings is unknown.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established. Accord Midazolam has been shown to cross the placenta and enter the foetal circulation. Accord Midazolam passes into breast milk and should not be administered to breastfeeding mothers.

DOSAGE AND DIRECTIONS FOR USE:

Accord Midazolam is a potent sedative agent, requiring slow administration and individualised dosing. The dose should be individualised and titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication. In the case of elderly (adults over 60 years) with organic cerebral changes or impaired cardiac and respiratory function, debilitated or chronically ill patients, the dosage should be determined with caution, the special factors relating to each patient being taken into consideration.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

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1.Basal sedation:

Intravenous basal sedation:

Intravenous injections must be given slowly (approximately 1 mg in 30 seconds for sedation). Accord Midazolam takes effect in about two minutes after the injection is given.

For basal sedation in diagnostic or surgical interventions carried out under local anaesthesia:

In adults below the age of 60, the initial dose is 2,5 mg (0,04 mg/kg) 5-10 minutes before the beginning of the procedure. Further doses of 1 mg may be given as necessary. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint. In adults over 60 years, debilitated or chronically ill patients, the initial dose must be reduced to 1 to 1,5 mg and given 5-10 minutes before the beginning of the procedure. Further doses of 0,5 to 1,0 mg may be given as necessary. Total doses greater than 3,5 mg are not usually necessary.

2. Pre-medication before an operation:

Intramuscular administration:

Pre-medication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension), and pre-operative impairment of memory.

Adults below the age of 60:

0,07-0,1 mg/kg body weight IM according to the general condition of the patient. Usual dose is about 5 mg.

Children:

(between ages 1 and 15) proportionately higher doses are required than in adults in relation to bodyweight. The dose range from 0,08 to 0,20 mg/kg body weight has been shown to be effective and safe.

These doses should be administered into a large muscle mass about 30 to 60 minutes before induction of anaesthesia.

In adults over 60 years, debilitated and chronically ill patients:

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Initials:

0,025-0,05 mg/kg bodyweight IM. The usual dose is 2 to 3 mg.

3. Induction and maintenance of anaesthesia:

Intravenous injection:

Induction: intravenous injections must be given slowly (approximately 2,5 mg in 10 seconds for induction of anaesthesia). The desired level of anaesthesia is reached by step-wise titration. The intravenous induction dose of midazolam 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 pre-medicated adults below the age of 60 the dose can range from 10-15 mg IV (0,15 to 0,2 mg/kg). A total dose greater than 15 mg is usually not necessary. A sufficiently deep level of sleep is generally achieved after 2-3 minutes. In non pre-medicated adults below the age of 60, the dose may be higher (0,3 to 0,35 mg/kg body weight), but a total dose greater than 20 mg is usually not necessary. In adults over 60 years of age, debilitated and chronically ill patients, lower doses will be required.

Maintenance:

Intravenous continuous infusion:

The maintenance dose usually ranges from 0,03 to 0,1 mg/kg/hr when used in combination with narcotics or ketamine. In high-risk surgical patients, adults over 60 years, debilitated and chronically ill patients, lower maintenance doses will be required.

4**. Sedation in intensive care units (ICU):**

Intravenous sedation in ICU:

The desired level of sedation is reached by step-wise titration of Accord Midazolam followed by either continuous infusion or intermittent bolus. For sedation in ICU, the dosage should be individualised and Accord Midazolam titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication.

The intravenous loading dose 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. The

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intravenous loading dose can range from 0,03 mg/kg, but a total dose greater than 15 mg is usually not necessary.

The loading dose should be reduced or omitted in hypovolaemic, vasoconstricted or hypothermic patients. The maintenance dose ranges from 0,03 to 0,2 mg/kg/hr. In hypovolaemic, vasoconstricted or hypothermic patients the maintenance dose should be reduced, at times to as low as 25 % of the usual dose. The level of sedation should be assessed regularly by the patient's condition.

Compatible with the following solutions for infusion:

- Glucose (5 %) solution
- Sodium chloride (0,9 %) solution
- Fructose 50 mg/ml (5 %) solution
- Ringer's solution
- Ringers Lactate Injection (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.

Chemical and physical in-use stability of the dilutions has been demonstrated for 12 hours at or below 25 °C and 24 hours at 2 to 8 °C.

From a microbiological point of view, the diluted solution should be used immediately.

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

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Initials:

INCOMPATIBILITIES:

Do not dilute Accord Midazolam ampoule solutions with macrodex 6 % in dextrose. Do not mix Accord Midazolam ampoule solutions in alkaline injections.

Accord Midazolam precipitates in sodium bicarbonate.

SIDE-EFFECTS:

The following side effects have been reported:

Psychiatric disorders:

Frequent: Impairment of psychomotor skills.

Frequency unknown: Hallucinations, psychiatric/paradoxical reactions.

Nervous system disorders:

Less frequent: Dizziness, light headedness, feeling faint, numbness, tingling, pain or weakness in hands and feet, uncontrolled or jerky movements, unusual excitement, irritability, restlessness.

Frequency unknown: Over sedation, headaches, anterograde/prolonged amnesia, convulsions in premature infants and neonates.

Cardiac disorders:

Frequent: Decrease in arteriolar blood pressure.

Less frequent: Change in pulse rate or breath rate, emergence delirium.

Frequency unknown: Local effects on the veins, cardiovascular collapse, cardiac arrest/depression and myocardial contractility.

Eye disorders:

Less frequent: Change in vision.

Respiratory, thoracic and mediastinal disorders:

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Initials:

Frequent: Apnoea, respiratory depression/arrest.

Less frequent: Dyspnoea, laryngospasm, hiccups, hyperventilation, wheezing, difficulty in breathing, coughing.

Gastrointestinal disorders:

Less frequent: Nausea, vomiting.

Frequency unknown: Gastro-intestinal disturbances.

Skin and subcutaneous tissue disorders:

Less frequent: Skin reactions, skin rash, hives, itching.

Immune system disorders:

Less frequent: Hypersensitivity including anaphylactoid reactions.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Muscle tremor.

Frequency unknown: Ataxia

General disorders and administration site conditions:

Less frequent: Phlebitis, pain at injection site, redness, lumps and hardness**.**

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The symptoms of Accord Midazolam overdosage 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.

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Initials:

Extreme overdosage may lead to coma, areflexia, cardio-respiratory depression and apnoea, requiring appropriate counter-measures (ventilation, cardiovascular support).

The effects of overdosage can be controlled with the benzodiazepine antagonist flumazenil.

IDENTIFICATION:

Accord Midazolam 5 mg/5 ml solution for injection: Clear, colourless to pale yellow solution, free from foreign particles

Accord Midazolam 15 mg/3 ml solution for injection: Clear, colourless to pale yellow solution, free from foreign particles

Accord Midazolam 50 mg/10 ml solution for injection: Clear, colourless to pale yellow solution, free from foreign particles

PRESENTATION:

Accord Midazolam 5 mg/5 ml solution for injection: Type I, clear, colourless glass ampoule, with a blue ring and white OPC dot (10 ampoules are packed in a unit carton).

Accord Midazolam 15 mg/3 ml solution for injection: Type I, clear, colourless glass ampoule, with a blue ring and white OPC dot (10 ampoules are packed in a unit carton).

Accord Midazolam 50 mg/10 ml solution for injection: Type I, clear, colourless glass ampoule, with a red ring and white OPC dot OR a blue ring and white OPC dot (1 ampoule per carton).

STORAGE INSTRUCTIONS:

Store at or below 25 ˚C. Protect the ampoules from light. Do not refrigerate.

Keep the ampoules in the outer carton until required for use.

Keep out of reach of children.

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Initials:

MODULE 1.3.1.1 – Package Insert

Product proprietary name:	***Accord Midazolam 5mg/5ml; 15mg/3 ml; 50mg/10 ml***
Dosage form and strength:	***5mg/5ml; 15mg/3 ml; 50mg/10 ml Midazolam Injection***
Applicant/PHCR:	***Accord Healthcare (Pty) Ltd***

REGISTRATION NUMBER:

Accord Midazolam 5 mg/5 ml solution for injection: 42/26/0329

Accord Midazolam 15 mg/3 ml solution for injection: 42/26/0327

Accord Midazolam 50 mg/10 ml solution for injection: 42/26/0328

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Accord Healthcare (Pty) Ltd

Tuscany Office Park,

6 Coombe Place,

Rivonia,

Gauteng,

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

14 September 2012

5 February 2015

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Initials: