**FINAL PROFESSIONAL INFORMATION**

**SCHEDULING STATUS**

S5

**1. NAME OF THE MEDICINE**

**Midazolam 1 mg/ml Accord**

Solution for injection or infusion

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

*Excipients:*

Contains 3,53 mg sodium (as sodium chloride) per ml of solution for injection or infusion.

For the full list of excipients, see section 6.1.

Sugar free.

**3. PHARMACEUTICAL FORM**

Solution for injection or infusion.

Clear, colourless to pale yellow solution in a clear glass pre-filled syringe, with a pH in the range of 2,9 – 3,7 and 270 mOsm/kg to 330 mOsm/kg osmolality.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic 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 medicine 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.

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

**4.2 Posology and method of administration**

**Posology**

**Midazolam 1 mg/ml Accord** is a potent sedative medicine, 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.

***Basal sedation***

*Intravenous basal sedation:*

Intravenous injections must be given slowly (approximately 1 mg in 30 seconds for sedation). **Midazolam 1 mg/ml Accord** 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.

***Pre-medication before an operation***

*Intramuscular administration:*

Pre-medication with **Midazolam 1 mg/ml Accord** given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension), and pre-operative impairment of memory.

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***Special populations***

*Adults below the age of 60 years:*

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 years: 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:*

0,025 – 0,05 mg/kg body weight IM. The usual dose is 2 to 3 mg.

***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 stepwise titration. The intravenous induction dose of **Midazolam 1 mg/ml Accord** 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 to 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.

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***Sedation in intensive care units (ICU)***

*Intravenous sedation in ICU:*

The desired level of sedation is reached by stepwise titration of **Midazolam 1 mg/ml Accord**, followed by either continuous infusion, or intermittent bolus.

For sedation in ICU, the dosage should be individualised and **Midazolam 1 mg/ml Accord** 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 intravenous loading dose can range from 0,03 to 0,3 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 if permitted by the patient's condition.

**Method of administration**

Midazolam 1 mg/ml Accord is indicated for parenteral use only.

**4.3 Contraindications**

- Hypersensitivity to midazolam, benzodiazepines or to any of the excipients of Midazolam 1 mg/ml Accord listed in section 6.1.
- Conscious sedation in patients with severe respiratory insufficiency or acute respiratory depression.
- Safety in pregnancy has not been established. Midazolam has been shown to cross the placenta and to enter foetal circulation.
- Midazolam passes into breast milk and should not be administered to breast feeding mothers.

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| **4.4 Special warnings and precautions for use** |
|---|
| **Midazolam 1 mg/ml Accord** should be administered only by experienced healthcare professionals 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, apnoea, 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 (see section 4.8). |
| |
| Special caution is required for the indication of conscious sedation in patients with impaired respiratory function. |
| |
| When **Midazolam 1 mg/ml Accord** 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 1 mg/ml Accord** to high-risk patients:<br>- adults over 60 years of age<br>- chronically ill or debilitated patients.<br>- patients with chronic respiratory insufficiency<br>- patients with chronic renal failure, impaired hepatic function or with impaired cardiac function<br>- paediatric patients especially those with cardiovascular instability. |
| |
| 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. |

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These high-risk patients require lower dosages (see section 4.2) and should be continuously monitored for early signs of alterations of vital functions.

Due to CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering **Midazolam 1 mg/ml Accord** to a patient with myasthenia gravis.

**Tolerance**

Some loss of efficacy has been reported when **Midazolam 1 mg/ml Accord** was used as long-term sedation in intensive care units (ICU).

**Dependence**

When **Midazolam 1 mg/ml Accord** 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 medicine abuse (see section 4.8).

**Withdrawal symptoms**

During prolonged treatment with **Midazolam 1 mg/ml Accord** 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.

**Altered elimination of midazolam**

Midazolam elimination may be altered in patients receiving compounds that inhibit or induce CYP3A4 and the dose of **Midazolam 1 mg/ml Accord** may need to be adjusted accordingly (see section 4.5).

Midazolam elimination may also be delayed in patients with liver dysfunction and low cardiac output (see section 5.2).

**Paediatric patients**

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

**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 1 mg/ml Accord** possibly including severe sedation or clinically relevant respiratory depression (see section 4.5).

**Risk from concomitant use of opioids**

Concomitant use of **Midazolam 1 mg/ml Accord** 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 medicines such as **Midazolam 1 mg/ml Accord** with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe **Midazolam 1 mg/ml Accord** concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

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 (see section 4.5).

**Medical history of alcohol or medicine abuse**

**Midazolam 1 mg/ml Accord** should be avoided in patients with a medical history of alcohol or drug abuse.

**Discharging criteria**

After parenteral administration of Midazolam 1 mg/ml Accord, patients should not be discharged from hospital or consulting rooms for at least four hours or only when recommended by the treating doctor and if accompanied by an attendant. It is recommended that the patient is accompanied by a responsible person when returning home after discharge.

**Information about excipients**

**Midazolam 1 mg/ml Accord** contains less than 1 mmol sodium (23 mg) per dose i.e. essentially 'sodium free'.

**4.5 Interaction with other medicines and other forms of interaction**

**Pharmacokinetic Interactions**

Midazolam is metabolised 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.

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| Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to IV midazolam, in particular 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 IV 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 IM administration the effects of CYP3A4 modulation should not substantially differ from those seen with IV 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. 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 medicine interactions 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 medicines. |
| |

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| **Medicines that inhibit CYP3A** |
| ***Azole antifungals***<br>• 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 IV dose of midazolam is administered. The same recommendation may apply also for other azole antifungals (see further), since increased sedative effects of IV 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. |
| **Midazolam 1 mg/ml Accord** is not indicated for oral administration. |
| |
| ***Macrolide antibiotics***<br>• 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* |

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- Roxithromycin: While no information on roxithromycin with IV 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-booster 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 co administered with HIV protease inhibitors, treatment setting should follow the description in the above section for azole antifungals, ketoconazole.

*Additional information from oral midazolam*

- 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 increased the plasma concentrations of intravenous midazolam by about 25 % and the terminal half-life was prolonged by 43 %.

*Additional information from oral midazolam*

- Verapamil / diltiazem increased the plasma concentrations of oral midazolam by 3- and 4-fold, respectively. The terminal- half-life of midazolam was increased by 41 % and 49 %, respectively.

***Various mecidines/herbs***

- Atorvastatin showed a 1,4-fold increase in plasma concentrations of IV midazolam compared to control group.

*Additional information from oral midazolam*

- Nefazodone increased the plasma concentrations of oral midazolam by 4,6-fold with an increase of its terminal half-life by 1,6-fold.

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- 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.

**Medicines that induce CYP3A**

- Rifampicin decreased the plasma concentrations of intravenous midazolam by about 60 % after 7 days of rifampicin 600 mg once daily. The terminal half-life decreased by about 50 – 60 %.

*Additional information from oral midazolam*

- Rifampicin decreased the plasma concentrations of oral midazolam by 96 % in healthy subjects and its psychomotor effects where almost totally lost.
- Carbamazepine/phenytoin: Repeated dosages of carbamazepine 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 %.
- Efavirenz: The 5-fold increase in the ratio of the CYP3A4 generated metabolite α-hydroxy-midazolam to midazolam confirms its CYP3A4-inducing effect.

***Herbs and food***

- St John's Wort decreased plasma concentrations of midazolam by about 20 – 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.

**Pharmacodynamic medicine interactions**

The co-administration of midazolam with other sedative/hypnotic medicines and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiates 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 medicines.

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***Opioids***

The concomitant use of sedative medicines such as benzodiazepines or related medicines such as **Midazolam 1 mg/ml Accord** 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 (see section 4.4).

Alcohol may markedly enhance the sedative effect of **Midazolam 1 mg/ml Accord**. Alcohol intake should be strongly avoided in case of **Midazolam 1 mg/ml Accord** administration (see section 4.4).

**Midazolam 1 mg/ml Accord** decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

**4.6 Fertility, pregnancy and lactation**

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 labour or when used as an induction medicine of anaesthesia for caesarean section has been reported to produce maternal or foetal adverse effects (inhalation risk in mother, irregularities in the foetal heart rate, hypotonia, poor sucking, hypothermia and respiratory depression in the neonate). (see section 4.4)

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.

The risk for neonates should be considered in case of administration of midazolam for any surgery near the term.

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Midazolam passes in low quantities into breast milk. Nursing mothers should be advised to discontinue breastfeeding for 24 hours following administration of midazolam. (see section 4.3)

**4.7 Effects on ability to drive and use machines**

**Midazolam 1 mg/ml Accord** has a major influence on the 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 midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The prescribing doctor should decide when these activities may be resumed. It is recommended that the patient is accompanied when returning home after discharge.

**4.8 Undesirable effects**

The following undesirable effects have been reported to occur when **Midazolam 1 mg/ml Accord** is injected:

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|---|---|
| ***Immune System Disorders*** | |
| Frequency not known | Hypersensitivity, angioedema, anaphylactic shock |
| ***Psychiatric Disorders*** | |
| Less frequent | Depressed mood, affective disorder, confusional state, disorientation |
| Frequency not known | Euphoric mood, hallucinations, agitation*, hostility*, rage*, aggressiveness*, excitement*, physical drug dependence and withdrawal syndrome, abuse |
| ***Nervous System Disorders*** | |
| Frequent | Drowsiness |
| Less frequent | Ataxia |
| Frequency not known | Involuntary movements (including tonic/clonic movements and muscle tremor)*, hyperactivity*. |

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| | Sedation (prolonged and postoperative), alertness decreased, somnolence, headache, dizziness, anterograde amnesia**, the duration of which is directly related to the administered dose.<br>Convulsions have been reported in premature infants and neonates.<br>Medicine withdrawal convulsions. |
| ***Cardiac Disorders*** | |
| Frequency not known | Cardiac arrest, bradycardia |
| ***Vascular Disorders*** | |
| Frequency not known | Hypotension, vasodilation, thrombophlebitis, thrombosis |
| ***Respiratory, thoracic and mediastinal Disorders*** | |
| Frequency not known | Respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm, hiccups |
| ***Gastrointestinal Disorders*** | |
| Frequency not known | Nausea, vomiting, constipation, dry mouth |
| ***Skin and Subcutaneous Tissue Disorders*** | |
| Frequency not known | Rash, urticaria, pruritis |
| ***General Disorders and Administration Site Conditions*** | |
| Less frequent | Lethargy |
| 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* |

* Paradoxical medicine reactions have been reported, particularly among children and the elderly (see section 4.4)

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

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amnesia has been reported (see section 4.4).

*** 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 IV administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions (see section 4.4). 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 (see section 4.4).

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of **Midazolam 1 mg/ml Accord** is important. It allows continued monitoring of the benefit/risk balance of **Midazolam 1 mg/ml Accord**. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

**4.9 Overdose**

***Symptoms***

**Midazolam 1 mg/ml Accord** commonly causes drowsiness, ataxia, dysarthria and nystagmus. Overdose of **Midazolam 1 mg/ml Accord** may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and coma. If coma occurs, it 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, such as **Midazolam 1 mg/ml Accord**, 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 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 medicines that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this medicines.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Category and class:** A 2.2 Sedatives, hypnotics

**Pharmacotherapeutic group:** Hypnotics and sedatives (benzodiazepine derivatives)

**ATC code:** N05CD08

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 enables the active ingredient in

midazolam to form water-soluble salts with acids. These produce a stable and well tolerated solution for injection or infusion.

The pharmacological effect of midazolam is characterised by short duration because of a rapid metabolic transformation over a short time. Midazolam has a potent sedative and sleep-inducing effect. Furthermore, it has the effect of relieving anxiety and convulsions and of relaxing muscles.

After intramuscular or intravenous administration, anterograde amnesia of short duration occurs; (the patient does not remember events occurring at the time of the medicine's maximal activity).

**5.2 Pharmacokinetic properties**

***Absorption***

Midazolam is rapidly and fully absorbed from the muscle tissue. The maximum plasma concentrations are achieved within 30 minutes. The absolute bioavailability after intramuscular injection is over 90 %.

***Distribution***

After intravenous injection of midazolam, one or two clear distribution phases are clear from the plasma concentration time curve. The steady-state distribution volume is 0,7–1,2 L/kg.
96 – 98 % of midazolam binds to plasma proteins. Most of the plasma protein binding is attributable to albumin. Midazolam passes slowly and in small quantities into the cerebrospinal fluid. It has been shown in humans that midazolam crosses the placenta and enters the foetal circulation slowly. Small quantities of midazolam have been found in human breast milk.

***Metabolism***

Midazolam is almost completely metabolised through biotransformation. It has been estimated that 30 – 60 % of the dose is eliminated through the liver. Midazolam is hydroxylated by cytochrome P-450 3A4-isoenzyme, and the main metabolite in the urine and plasma is alpha-hydroxy-midazolam. The plasma concentrations of alpha-hydroxy-midazolam are 12 % of the parent compound. Alpha-hydroxy-midazolam is pharmacologically active but contributes only to a small degree (approx. 10 %) to the effects of midazolam applied intravenously.

***Elimination***

In healthy test subjects, the elimination half-life of midazolam is 1,5 – 2,5 hours. Plasma clearance is 300

– 500 ml/min. Midazolam is eliminated primarily through the kidneys (60 – 80 % of the dose injected) and is recovered as glucuronide-conjugated alpha-hydroxy- midazolam. Less than 1% of the dose is recovered as an unmodified substance in the urine. The elimination half-life of alpha-hydroxy-midazolam is under one hour. The elimination kinetics of midazolam are the same for the intravenous infusion as after bolus injection.

**Pharmacokinetics in special populations**

*Elderly patients*

In adults over 60 years of age, the elimination half-life may be prolonged up to 3 times.

*Children*

The rectal absorption rate in children is similar to that in adults, although bioavailability is lower (5 – 18 %). The elimination half-life after intravenous and rectal application is shorter in children aged 3 – 10 years (1 – 1,5 hours) than in adults. The difference corresponds to the elevated metabolic clearance in children. In neonates the elimination half-life is prolonged, with a mean of 6 hours (3 – 12 hours), due to liver immaturity.

*Obese*

In obese patients, the mean half-life is greater than in non-obese persons (5,9 hours compared to 2,3 hours). This is because of an approx. 50 % increase in the distribution volume corrected for body weight. Clearance is similar in obese and in non-obese persons.

*Patients with hepatic insufficiency*

The elimination half-life in patients with cirrhosis can be prolonged, and the clearance, shorter than in healthy test subjects (see section 4.2).

*Patients with renal insufficiency*

The elimination half-life in patients with chronic renal insufficiency is similar to that in healthy test subjects.

*Critically ill patients*

In the case of critically ill patients, the elimination half-life of midazolam is prolonged by up to a factor of six.

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*Patients with cardiac insufficiency*

The elimination half-life in patients with congestive heart failure is longer than that in healthy test subjects (see section 4.4).

**5.3. Preclinical safety data**

There are no further relevant preclinical data for the prescribing doctor beyond the information set out in other sections of this professional information.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Sodium chloride

Concentrated hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water for Injections

**6.2 Incompatibilities**

**Midazolam 1 mg/ml Accord** must not be diluted with 6 % *m/v* dextran (with 0,9 % sodium chloride) in glucose.

**Midazolam 1 mg/ml Accord** must not be mixed with alkaline solutions for injection. Midazolam precipitates in solutions containing hydrogen carbonate.

**Midazolam 1 mg/ml Accord** must not be mixed with other medicines except those mentioned in section 6.6.

**6.3 Shelf life**

2 years.

Store at or below 25 °C.

***Shelf life after dilution***

Chemical and physical in-use stability of the dilutions has been demonstrated for 24 hours at room

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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.

**6.4 Special precautions for storage**

Protect the syringes from light. Do not refrigerate.

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

For storage condition of the diluted medicine see section 6.3.

**6.5 Nature and contents of container**

5 ml clear glass pre-filled syringe with plunger stopper and plunger rod.

Pack sizes: 1 or 10 pre-filled syringes.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other 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 1 mg/ml Accord** is 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

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| 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. |
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| **7. HOLDER OF CERTIFICATE OF REGISTRATION**<br>Accord Healthcare (Pty) Ltd<br>Building 2, Tuscany Office Park,<br>6 Coombe Place<br>Rivonia<br>Gauteng<br>South Africa |
| **8. REGISTRATION NUMBER**<br>55/2.2/0375 |
| |
| **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** |
| 13 September 2022 |
| |
| **10. DATE OF REVISION OF THE TEXT** |
| To be allocated |