

## **Product Summary**

### **1. Trade Name of the Medicinal Product**

Midazolam Injection 1mg in 1ml

### **2. Qualitative and Quantitative Composition**

Each 1 ml solution contains 1mg midazolam presented in 2ml and 5ml ampoules.

Each 2 ml ampoule contains 2mg midazolam.

Each 5 ml ampoule contains 5mg midazolam.

### **3. Pharmaceutical Form**

Sterile solution for injection.

Clear colourless or slightly yellow sterile solution.

## **Clinical Particulars**

### **4.1. Therapeutic Indications**

As intravenous sedative cover before and during minor medical, dental and surgical procedures such as gastroscopy, endoscopy, cystoscopy, bronchoscopy and cardiac catheterisation.

As an alternative intravenous agent for the induction of anaesthesia in high risk and elderly patients, especially where cardiovascular stability is of particular importance. Induction is more reliable when heavy opiate premedication has been administered or when midazolam is given with a narcotic analgesic such as fentanyl.

### **4.2. Posology and Method of Administration**

Intravenous sedation: One or more intravenous administrations over a single operating session.

*Adults:* An assessment should be made of the degree of sedation necessary for the planned procedure.

The dose should be titrated against the response of the patient. The desired titration end point will depend upon the procedure. Full sedation will be

evident by drowsiness, slurred speech but response to commands will be maintained.

As a guide, it is recommended that 2ml of Midazolam 1mg/1ml solution (equivalent to 2mg midazolam) be administered intravenously over 30 seconds. If after 2 minutes, sedation is not adequate, incremental doses of 0.5ml to 1ml of midazolam 1mg/1ml solution (0.5 to 1mg midazolam) should be given.

Usual dose range 2.5mg - 7.5mg total dose (equivalent to around 0.07mg/kg body weight).

Dosages greater than 5.0mg are not usually necessary.

*Elderly* : THE ELDERLY ARE MORE SENSITIVE TO THE EFFECTS OF BENZODIAZEPINES IN THESE PATIENTS DOSES GREATER THAN 3.5MG ARE NOT USUALLY NECESSARY AND LOW DOSES AS LITTLE AS 1MG - 2MG (1.0 -2ML) MAY BE ADEQUATE. THE INITIAL DOSE SHOULD NOT EXCEED 1 -1.5MG (1 - 1.5ML).

*Children* : Midazolam Injection has not been evaluated for use as an intravenous sedative in children.

*Mode of Administration* : For the administration of Midazolam Injection, the patient should be placed in a supine position and remain there throughout the procedure. Resuscitation facilities should always be available and a second person fully trained in the use of such equipment should always be present. It is recommended that patients should remain under medical supervision until at least 1 hour has elapsed from the time of injection. They should always be accompanied home by a responsible adult.

Patients who have received Midazolam Injection alone for IV sedation prior to minor procedures should be warned not to drive or operate machinery for 12 hours. Where midazolam is used concurrently with other central nervous system depressants (e.g. potent analgesics) recovery may be prolonged. Patients should therefore be assessed carefully before being allowed to go home or resume normal activities.

#### *Combination therapy*

*Intravenous bolus sedation*: where analgesia is provided by a narcotic analgesic the latter should be administered first, the dose of midazolam should be carefully titrated and low doses 1 - 2mg (1.0- 2.0ml) may be adequate. In the elderly, smaller doses as little as 0.5 - 1mg (0.5 - 1.0ml) may be adequate.

*Sedation by continuous infusion in intensive care* : Where analgesia is provided by narcotic analgesics, the rate of infusion of midazolam injection should be titrated carefully to the sedative needs of the patient.

*Intravenous induction of anaesthesia* : One or more bolus intravenous injections over a single anaesthetic session.

*Adults* : The dose should be titrated against the individual response of the patient. Midazolam Injection should be given by slow intravenous injection

until there is a loss of eyelid reflex, response to commands and voluntary movements.

In anticipating the required dose of midazolam, both the premedication already given and the age of the patient are important. Young, fit unpremedicated patients may require at least 0.3mg/kg body-weight, whereas patients premedicated with an opiate usually require only 0.2mg/kg body-weight.

**ELDERLY:** THE ELDERLY ARE MORE SENSITIVE TO THE EFFECTS OF BENZODIAZEPINES. INDUCTION MAY BE ADEQUATE WITH 0.1MG/KG BODY-WEIGHT IN PREMEDICATED PATIENTS AND 0.2MG/KG BODY-WEIGHT IN UNPREMEDICATED PATIENTS.

*Children over 7 years:* Midazolam Injection has been shown to be an effective agent for induction of anaesthesia in children over 7 years of age, at a dose of 0.15 mg/kg body-weight.

### **4.3 Contraindications**

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

Use of this drug for conscious sedation in patients with severe respiratory failure, acute respiratory depression or unstable myasthenia gravis.

### **4.4 Special warnings and precautions for use**

Midazolam should be used only when age- and size- appropriate resuscitation facilities are available, as i.v. administration of midazolam may depress myocardial contractility and cause apnoea. Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur when the injection is given too rapidly or when a high dosage is administered. Paediatric patients less than 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to clinical effect and careful respiratory rate and oxygen saturation monitoring are essential.

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

Special caution should be exercised when administering midazolam to high-risk patients:

- adults over 60 years of age
- chronically ill or debilitated patients, e.g.
- patients with chronic respiratory insufficiency
- patients with chronic renal failure, impaired hepatic function or with impaired cardiac function

– paediatric patients specially those with cardiovascular instability.

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

Benzodiazepines should be used with caution in patients with a history of alcohol or drug abuse.

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

#### *Tolerance*

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

#### *Dependence*

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

#### *Withdrawal symptoms*

During prolonged treatment with midazolam in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, muscle pain, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended to decrease doses gradually.

#### *Amnesia*

Midazolam causes anterograde amnesia (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention. After receiving midazolam parenterally, patients should be discharged from hospital or consulting room only if accompanied by an attendant.

#### *Paradoxical reactions*

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported to occur with midazolam. These reactions may occur with high doses and/or when the injection is given rapidly. The highest incidence to such reactions has been reported among children and the elderly.

#### *Delayed elimination of midazolam*

Midazolam elimination may be altered in patients receiving compounds that inhibit or induce CYP3A4 (see *Interaction with other medicaments and other forms of interaction*).

Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates.

*Preterm infants and neonates*

Due to an increased risk of apnoea, extreme caution is advised when sedating pre-term and former pre-term patients. Careful monitoring of respiratory rate and oxygen saturation is required.

Rapid injection should be avoided in the neonatal population.

Neonates have reduced and/or immature organ function and are also vulnerable to profound and/or prolonged respiratory effects of midazolam.

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

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The metabolism of midazolam is almost exclusively mediated by the isoenzyme CYP3A4 of the cytochrome P450 (CYP450). CYP3A4 inhibitors (see *Special warnings and precautions for use*) and inducers, but also other active substances (see below), may lead to drug-drug interactions with midazolam.

Since midazolam undergoes significant first pass effect, parenteral midazolam would theoretically be less affected by metabolic interactions and clinical relevant consequences should be limited.

- Itraconazole, fluconazole and ketoconazole

Co-administration of oral midazolam and some azole antifungals (itraconazole, fluconazole, ketokonazole) increased markedly midazolam plasma levels and prolonged its elimination half-life, leading to major impairment of psychosedative tests. Elimination half-lives were increased from 3 to 8 hours approximately.

When a single bolus dose of midazolam was given for short-term sedation, the effect of midazolam was not enhanced or prolonged to a clinically significant degree by itraconazole, and dosage reduction is therefore not required. However, administration of high doses or long-term infusions of midazolam to patients receiving itraconazole, fluconazole or ketoconazole, e.g. during intensive care treatment, may result in long-lasting hypnotic effects, possible delayed recovery, and possible respiratory depression, thus requiring dose adjustments.

- Verapamil and diltiazem

No *in vivo* interaction studies are available with intravenous midazolam and verapamil or diltiazem.

However, as expected, oral midazolam pharmacokinetics varied in a clinically significant way when combined to these calcium channel blockers, notably with almost a doubling of half-life value and peak plasma level, resulting in a strongly reduced performance in co-ordination and cognitive function tests while producing profound sedation. When oral midazolam is used, dosage adjustment is usually recommended. Although no clinically significant interaction is expected with midazolam used for short-term sedation, caution should be exercised if intravenous midazolam is concomitantly given with verapamil or diltiazem.

- Macrolide Antibiotics: Erythromycin and clarithromycin

Co-administration of oral midazolam and erythromycin or clarithromycin significantly increased the AUC of midazolam about four fold and more than doubled the elimination half-life of midazolam, depending on the study. Marked changes in psychomotor tests were observed and it is advised to adjust doses of midazolam, if given orally, due to significantly delayed recovery.

When a single bolus dose of midazolam was given for short-term sedation, the effect of midazolam was not enhanced or prolonged to a clinically significant degree by erythromycin, although a significant decrease in plasma clearance was recorded. Caution should be exercised if intravenous midazolam is concomitantly given with erythromycin or clarithromycin. No clinical significant interaction has been shown with midazolam and other macrolide antibiotics.

- Cimetidine and ranitidine

Co-administration of cimetidine (at doses equal or higher than 800mg/day) and intravenous midazolam slightly increased the steady-state plasma concentration of midazolam, which could possibly lead to a delayed recovery, whereas co-administration of ranitidine had no effect. Cimetidine and ranitidine did not affect oral midazolam pharmacokinetics. These data indicate that intravenous midazolam can be administered at usual doses of cimetidine (i.e. 400mg/day) and ranitidine without dosage adjustment.

- Saquinavir

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

Therefore, a single bolus dose of intravenous midazolam can be given in combination with saquinavir. Nevertheless, during a prolonged midazolam infusion, a total dose reduction is recommended to avoid delayed recovery (see *Special warnings and precautions for use*).

- Other protease inhibitors: ritonavir, indinavir, nelfinavir and amprenavir

No *in vivo* interaction studies are available with intravenous midazolam and other protease inhibitors. Considering that saquinavir has the weakest CYP3A4 inhibitory potency among all protease inhibitors, midazolam should be systematically reduced during prolonged infusion when administered in combination with protease inhibitors other than saquinavir.

- CNS depressants

Other sedative drugs may potentiate midazolam effects.

The pharmacological classes of CNS depressants include opiates (when they are used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, phenobarbital, sedative antidepressants, antihistaminics and centrally acting antihypertensive drugs.

Additional sedation should be taken into account when midazolam is combined with other sedative drugs.

Moreover, additional increase of respiratory depression should be particularly monitored in case of concomitant treatment with opiates, phenobarbital or benzodiazepines.

Alcohol may markedly enhance the sedative effect of midazolam. Alcohol intake should be strongly avoided in case of midazolam administration.

- Other interactions

The i.v. administration of midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics required for general anaesthesia.

#### **4.6. Pregnancy and Lactation**

Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity 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 agent 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).

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 post-natal period.

Consequently, midazolam should not be used during pregnancy unless clearly necessary. It is preferable to avoid using it for caesarean.

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

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

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

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive or use machines. Patients who have received Midazolam Injection alone for I.V. sedation prior to minor procedures should be warned not to drive or operate machinery for 12 hours. Where midazolam is used concurrently with other central nervous system depressants (e.g. potent analgesics) recovery may be prolonged. Patients should therefore be assessed carefully before being allowed to go home or resume normal activities.

#### **4.8 Undesirable effects**

The following undesirable effects have been reported (very rarely) to occur when midazolam is injected:

***Skin and appendages disorders:*** skin rash, urticarial reaction, pruritus.

***Central and peripheral nervous system and psychiatric disorders:*** drowsiness and prolonged sedation, reduced alertness, confusion, euphoria, hallucinations, fatigue, headache, dizziness, ataxia, post-operative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

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

Convulsions have been reported more frequently in premature infants and neonates.

Use of midazolam - even in therapeutic doses - may lead to the development of physical dependence after prolonged i.v. administration, abrupt discontinuation may be accompanied by withdrawal symptoms including withdrawal convulsions.

***Gastrointestinal system disorders:*** nausea, vomiting, hiccough, constipation, dry mouth.

**Cardiorespiratory disorders:** severe cardiorespiratory adverse events: respiratory depression, apnoea, respiratory arrest and/or cardiac arrest, hypotension, heart rate changes, vasodilating effects, dyspnoea, laryngospasm. 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 *Special warnings and precautions for use*).

**Body-as-a-whole - general disorders:** generalised hypersensitivity reactions: skin reactions, cardiovascular reactions, bronchospasm, anaphylactic shock.

**Application site disorders:** erythema and pain on injection site, thrombophlebitis, thrombosis.

## 4.9 Overdose

### *Symptoms*

The symptoms of overdose are mainly an intensification of the pharmacological effects; drowsiness, mental confusion, lethargy and muscle relaxation or paradoxical excitation. More serious symptoms would be areflexia, hypotension, cardiorespiratory depression, apnoea and coma.

### *Treatment*

In most cases monitoring of vital functions is only required. In the management of overdose special attention should be paid to the respiratory and cardiovascular functions in intensive care unit. The benzodiazepine antagonist flumazenil is indicated in case of severe intoxication accompanied with coma or respiratory depression. Caution should be observed in the use of flumazenil in case of mixed drug overdosage and in patients with epilepsy already treated with benzodiazepines. Flumazenil should not be used in patients treated with tricyclic antidepressant drugs, epileptogenic drugs, or patients with ECG abnormalities (QRS or QT prolongation).

## Pharmacological Properties

### 5.1. Pharmacodynamic Properties

Midazolam is a potent imidazobenzodiazepine, forming water-soluble salts which are stable and well tolerated by injection. Midazolam possesses the typical pharmacological properties of the benzodiazepines, namely hypnotic,

anxiolytic, muscle-relaxant and anticonvulsant activity. In clinical use, the induction of sleep is the main action.

## **5.2. Pharmacokinetic Properties**

At sedative and anaesthetic doses, given intravenously, the action is rapid in onset and of short duration; anterograde amnesia frequently accompanies the period of peak sedation.

The mean elimination half-life of midazolam is about 2 hours, in the normal surgical patient, but may be prolonged in patients in intensive care.

The 'second peak' effect, which is known to occur following intravenous diazepam, has not been observed with midazolam.

The metabolites of midazolam do not contribute significantly to the clinical effects of the drug.

## **5.3. Preclinical Safety Data**

Midazolam did not show any evidence of mutagenic activity in *Salmonella typhimurium*, human lymphocytes or in the micronucleus test in mice. In cultured hamster cells, midazolam produced dose-dependent reductions in the number of diploid cells and increases in hypodiploidy and hyperdiploidy.

No evidence of carcinogenic potential was seen in rats or mice given midazolam maleate orally in doses up to 9 mg/kg/day (25 times a human dose of 0.35 mg/kg) for up to 2 years. When midazolam maleate was administered with diet in rats and mice for 2 years at dosages of 1, 9 and 80 mg/kg/day, an increased incidence of hepatic tumors was noted in female mice in the highest dose group.

Reproduction toxicology and teratological studies have shown that midazolam is neither embryotoxic nor teratogenic and exerts no influence on the fertility and post-natal development of animals.

## **Pharmaceutical Particulars**

### **6.1 List of Excipients**

Sodium chloride, hydrochloric acid, sodium hydroxide, water for injections.

### **6.2 Incompatibilities**

Midazolam Injection when mixed with 500ml infusion fluids containing dextrose 4% with sodium chloride 0.18%, dextrose 5% or sodium chloride 0.9% is chemically and physically stable for up to 24 hours at 25°C and up to 72 hours at 2 to 8°C. However, for pharmaceutical microbiological reasons, the product should be used immediately after dilution. When aseptically prepared, the diluted solution may be kept for not more than 24 hours if stored under refrigeration at a temperature between 2 - 8°C.

Admixture with Hartmann's solution is not recommended, as the potency of midazolam decreases.

### **6.3 Shelf life**

3 years.

### **6.4 Special Precautions for Storage**

Keep container in outer carton in order to protect from light.  
Do not store above 25°C.

### **6.5 Nature and contents of container**

Clear glass ampoules, glass type I, Ph. Eur.  
Pack sizes: 5 x 2ml ampoules; 10 x 2ml ampoules; 5 x 5ml ampoules; 10 x 5ml ampoules.

### **6.6 Instructions for use/handling**

If only part used, discard the remaining solution.

## **Administrative Data**

### **7. Marketing Authorisation Holder**

Antigen International Ltd  
Roscrea  
Co. Tipperary  
Ireland

**8. Marketing Authorisation Number**

PL 02848/0207

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

24/11/2006

**10 DATE OF REVISION OF THE TEXT**

24/11/2006