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1. NAME OF THE MEDICINAL PRODUCTS

- MIDAZOLAM NORMON 5 mg/5 ml Solution for Injection GSP
- MIDAZOLAM NORMON 15 mg/3 ml Solution for injection GSP
- MIDAZOLAM NORMON 50 mg/10 ml Solution for Injection GSP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: midazolam (Spanish Nonproprietary Name) as hydrochloride.
Ampoules of 15 mg/3 ml, 5 mg/5 ml and 50 mg/10 ml for IV, IM and rectal administration.

List of excipients in 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MIDAZOLAM NORMON is a short-acting sleep inducer that is indicated:

For adults:

- CONSCIOUS SEDATION before and during diagnostic or therapeutic procedures with or without local anaesthesia.
- ANAESTHESIA
  - Premedication prior to induction of anaesthesia.
  - Induction of anaesthesia.
  - As a sedative component in combined anaesthesia.
- SEDATION IN INTENSIVE CARE UNITS

For children:

- CONSCIOUS SEDATION before and during diagnostic or therapeutic procedures with or without local anaesthesia.
- ANAESTHESIA
  - Premedication prior to induction of anaesthesia.
- SEDATION IN INTENSIVE CARE UNITS

4.2. Posology and method of administration

USUAL DOSAGE

Midazolam is a potent sedative that requires dose titration and slow administration. It is strongly recommended to tailor the dose to smoothly achieve the desired degree of sedation according to clinical needs, physical condition, age and concomitant drugs. For adults over 60 years of age, debilitated or chronically ill patients and paediatric patients, the dosage should be determined with caution, taking into account the risk factors associated with each patient. The usual doses are shown in the table below. Further details are provided in the text following the table.

Indication	**Adults < 60 years**	**Adults ≥ 60 years / debilitated or with chronic diseases**	**Children**
Conscious sedation	*IV* Initial dose: 2-2.5 mg. Adjustment dose: 1 mg Total dose: 3.5-7.5 mg.	*IV* Initial dose: 0.5-1 mg Adjustment dose: 0.5-1 mg Total dose: < 3.5 mg	*IV for patients aged 6 months-5 years* Initial dose: 0.05-0.1 mg/kg Total dose: < 6 mg *IV for patients aged 6-12 years* Initial dose: 0.025-0.05 mg/kg Total dose: < 10 mg *rectal > 6 months* 0.3-0.5 mg/kg *IM 1-15 years* 0.05-0.15mg/kg
Premedication for anaesthesia	*IM* 0.07-0.1 mg/kg	*IM* 0.025-0.05 mg/kg	*rectal > 6 months* 0.3-0.5 mg/kg *IM 1-15 years* 0.08-0.2 mg/kg
Induction of anaesthesia	*IV* 0.15-0.2 mg/kg (0.3-0.35 without premedication)	*IV* 0.1-0.2 mg/kg (0.15-0.3 without premedication)	
Sedative component in combined anaesthesia	*IV* intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h	*IV* doses lower than those recommended for adults < 60 years of age	
Sedation in the ICU	*IV* Initial dose: 0.03-0.3 mg/kg in 1-2.5 mg increments Maintenance dose: 0.03-0.2 mg/kg/h		*IV for newborns < 32 weeks gestational age* 0.03 mg/kg/h *IV for newborns > 32 weeks and children up to 6 months of age* 0.06 mg/kg/h *IV for patients > 6 months of age* Initial dose: 0.05-0.2 mg/kg Maintenance dose: 0.06-0.12 mg/kg/h

POSOLOGY FOR CONSCIOUS SEDATION

For conscious sedation prior to diagnostic or surgical intervention, IV midazolam shall be administered. The dose should be individualised and tailored and should not be administered as a rapid injection in a single burst. The onset of sedation may vary individually depending on the physical

condition of the patient and the detailed circumstances of the dosage (e.g. speed of administration, number of doses). If necessary, subsequent doses can be administered according to individual needs. The medicine starts to work approximately 2 minutes after injection. Maximum effect is obtained within 5 to 10 minutes.

Adults:

IV injection of midazolam should be administered slowly at a rate of approximately 1 mg in 30 seconds. For adults under 60 years of age, the starting dose is 2 to 2.5 mg, administered 5 to 10 minutes before the start of the procedure. Additional doses of 1 mg may be administered as needed. Average total doses have been found to vary between 3.5 and 7.5 mg. A total dose of more than 5 mg is not usually necessary. Adults over 60 years of age and debilitated or chronically ill patients should start with a dose of 0.5-1 mg. Additional doses of 0.5 to 1 mg may be administered as needed. A total dose of more than 3.5 mg is not usually necessary.

Children:

IV administration: the dose of midazolam should be adjusted slowly until the desired clinical effect is achieved. The initial dose of midazolam should be administered over 2-3 minutes. An additional 2-5 minutes should be waited to verify the exact sedative effect before starting the procedure or repeating the dose. If more sedation is needed, continue to adjust the dosage in small increments until the appropriate degree of sedation is achieved. Infants and children under 5 years of age may require significantly higher doses (mg/kg) than older children and adolescents.

- Paediatric patients under 6 months: Children under 6 months are particularly vulnerable to airway obstruction and hypoventilation. For this reason, it is not recommended for conscious sedation in children under 6 months of age.

- Paediatric patients 6 months to 5 years of age: starting dose 0.05 to 0.1 mg/kg. A total dose of up to 0.6 mg/kg may be necessary to achieve the desired sedation, but the total dose should not exceed 6 mg. Higher doses may be associated with prolonged sedation and risk of hypoventilation.

- Paediatric patients aged 6 to 12 years: starting dose 0.025 to 0.05 mg/kg. A total dose of up to 0.4 mg/kg not exceeding 10 mg may be required. Higher doses may be associated with prolonged sedation and risk of hypoventilation.

- Patients aged 12 to 16 years: the dose should be the same as for adults.

Rectal administration: the total dose of midazolam usually varies between 0.3 and 0.5 mg/kg. Rectal administration of the ampoule solution is done by means of a plastic applicator attached to the end of the syringe. If the volume to be administered is too small, water can be added up to a total volume of 10 ml. The total dose should be administered in one go, repeated rectal administration should be avoided.

Use is not recommended for children under 6 months of age, as there are hardly any data available for this population.

IM administration: doses used vary between 0.05 and 0.15 mg/kg. A total dose of more than 10.0 mg is not usually necessary. This route should only be used in exceptional cases. Rectal administration is preferable, as IM injection is painful.

For children weighing less than 15 kg, midazolam solutions with concentrations greater than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

POSOLOGY FOR ANAESTHESIA

PREMEDICATION

Premedication with midazolam administered shortly before a procedure results in sedation (induction of sleep or lethargy and decreased fear) and preoperative memory loss. Midazolam can also be administered in combination with anticholinergics. For this indication, midazolam should be administered IM, deep into a large muscle mass 20 to 60 minutes before induction of anaesthesia. Rectal administration is preferred in children (see below). Careful observation of the patient after administration of premedication is mandatory because of inter-individual variability in sensitivity and the possibility of overdose symptoms.

Adults:

For preoperative sedation and to reduce recall of preoperative events, the recommended dose for adults of ASA physical status I and II and under 60 years of age is 0.07 to 0.1 mg/kg administered IM. The dose should be reduced and individualised when midazolam is to be administered to adults who are over 60 years of age, debilitated or chronically ill. An IM dose of 0.025 to 0.05 mg/kg is recommended. The usual dose is 2 to 3 mg.

Children:

Rectal administration: The total dose of midazolam, usually 0.3 to 0.5 mg/kg, should be administered 15 to 30 minutes before induction of anaesthesia. Rectal administration of the ampoule solution shall be performed by means of a plastic applicator attached to the end of the syringe. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

IM administration: as IM injection is painful, this route should only be used in exceptional cases. Rectal administration is preferred. However, a dose of 0.08-0.2 mg/kg of midazolam administered IM has been shown to be effective and safe. Children aged 1-15 years require doses proportionally higher than adults in relation to body weight.

Use is not recommended for children under 6 months of age, as there are hardly any data available for this population.

For children weighing less than 15 kg, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

INDUCTION

Adults:

When midazolam is used for induction of anaesthesia before other anaesthetics have been administered, the individual response is variable. The dose should be adapted to the desired effect according to the age and clinical condition of the patient. When midazolam is used before or in combination with other IV or inhalational drugs for induction of anaesthesia, the initial dose of each drug should be significantly reduced. The desired level of anaesthesia is achieved by gradual adjustment. The IV induction dose of midazolam should be administered slowly in increments. Inject

each increment of no more than 5 mg for 20 to 30 seconds, leaving 2 minutes between successive increments.

- For adults under 60 years of age, an IV dose of 0.15-0.2 mg/kg is usually sufficient. For non-premedicated adults under 60 years of age, the dose may be higher (0.3 to 0.35 mg/kg IV). If a full induction is necessary, increments of approximately 25% of the patient's initial dose can be applied. Instead, induction may be supplemented with inhaled anaesthetics. In resistant cases, a total dose of up to 0.6 mg/kg can be used for induction, but such high doses may prolong recovery.

- For adults over 60 years of age, debilitated or chronically ill patients, the dose is 0.1 to 0.2 mg/kg administered IV. Non-premedicated adults over 60 years of age usually require more midazolam for induction; a starting dose of 0.15-0.3 mg/kg is recommended. Non-premedicated patients with severe general illness or other debilitating processes usually require less midazolam for induction. Typically, an initial dose of 0.15 to 0.25 mg/kg.

SEDATIVE COMPONENT IN COMBINED ANAESTHESIA

Adults:

Midazolam can be administered as a sedative component in combined anaesthesia by small intermittent IV doses (0.03-0.1 mg/kg) or continuous IV infusion (0.03-0.1 mg/kg/h), usually in combination with analgesics. Dosage and intervals between doses vary according to the individual patient's reaction.

For adults over 60 years of age and debilitated or chronically ill patients, lower maintenance doses are necessary.

SEDATION IN INTENSIVE CARE UNITS

The desired degree of sedation is achieved by gradual titration of midazolam, followed by continuous infusion or intermittent embolisation, according to clinical needs, physical condition, age and concomitant drugs (see 4.5 Drug interactions and other forms of interaction).

Adults:

Initial IV dose. 0.03 to 0.3 mg/kg should be administered slowly in increments. Each 1 to 2.5 mg increment should be injected for 20 to 30 seconds, allowing 2 minutes between successive increments. For patients with hypovolaemia, vasoconstriction and hypothermia, the initial dose should be reduced or omitted. When midazolam is administered with strong analgesics, the latter should be applied first, so that the sedative effects of midazolam can be adapted smoothly to the margin of sedation caused by the analgesic.

IV maintenance dose. Doses can vary between 0.03 and 0.2 mg/kg/h. For patients with hypovolaemia, vasoconstriction or hypothermia, the maintenance dose should be reduced. The degree of sedation should be assessed regularly. With prolonged sedation, tolerance may develop, implying the need to increase the dose.

Children older than 6 months:

For intubated and ventilated paediatric patients, an initial dose of 0.05-0.2 mg/kg IV should be

administered slowly over at least 2-3 minutes to establish the desired clinical effect. Midazolam should not be administered as a rapid intravenous dose. The initial dose should be followed by a continuous IV infusion of 0.06 to 0.12 mg/kg/h (1 to 2 μg/kg/min). If necessary, the infusion rate can be increased or decreased (usually by 25% of the initial or subsequent infusion rate), or supplemental IV doses of midazolam can be administered to increase or maintain the desired effect.

When starting midazolam infusion in patients with haemodynamic impairment, the usual starting dose should be adjusted in small increments and the patient should be monitored for haemodynamic instability, e.g. hypotension. These patients are also vulnerable to the respiratory depressant effects of midazolam and require careful monitoring of respiratory rate and oxygen saturation.

Newborns and children up to 6 months of age:

Midazolam should be administered as a continuous IV infusion, starting at 0.03 mg/kg/h (0.5 μg/kg/min) for neonates with gestational age < 32 weeks or 0.06 mg/kg/h (1 μg/kg/min) for neonates with gestational age > 32 weeks and infants up to 6 months.

Intravenous shock doses are not recommended for premature infants, newborns and children up to 6 months. Perfusion may be performed more rapidly during the first few hours to establish therapeutic plasma concentrations. The perfusion rate needs to be carefully and frequently checked, especially after the first 24 hours, in order to administer the lowest possible effective dose and to reduce the potential for drug accumulation.

Respiratory rate and oxygen saturation need to be closely monitored.

For premature infants, newborns and children weighing less than 15 kg, midazolam solutions with concentrations higher than 1 mg/ml are not recommended. Higher concentrations should be diluted to 1 mg/ml.

4.3. Contraindications

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

Use of this medicinal product for conscious sedation of patients with severe respiratory failure or acute respiratory depression.

4.4. Special warnings and precautions for use

Midazolam should be used only when age and size appropriate resuscitation equipment is available, as IV administration of midazolam may depress myocardial contractility and cause apnoea. Serious cardiorespiratory adverse events have occurred rarely. These have consisted of respiratory depression, apnoea, respiratory arrest and cardiac arrest. These life-threatening incidents are more likely to occur when the injection is given too quickly or a high dose is used. Children under 6 months of age are particularly vulnerable to airway obstruction and hypoventilation, so dose titration in small increments until clinical effect is achieved is essential, as well as close monitoring of respiratory rate and oxygen saturation.

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

Particular caution should be exercised when midazolam is administered to high-risk patients:

- adults over 60 years of age
- chronically ill or debilitated patients, e.g.
    - patients with chronic respiratory failure
    - patients with chronic renal insufficiency, impaired liver function or impaired cardiac function
    - paediatric patients, especially those with cardiovascular instability.

These high-risk patients require lower doses (see 4.2. Posology and method of administration), and should be continuously monitored for early signs of impaired vital functions.

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

As with any substance with myorelaxant and CNS depressant properties, particular caution should be exercised when administering midazolam to patients with myasthenia gravis.

Tolerance:

Some decrease in efficacy has been reported when midazolam is used for prolonged sedation in intensive care units (ICU).

Dependency:

When midazolam is used for prolonged sedation in the ICU, it should be borne in mind that it may produce physical dependence. The risk of dependence increases with dose and duration of treatment.

Withdrawal symptoms:

Physical dependence may occur during prolonged treatment with midazolam in the ICU. Abrupt discontinuation of treatment will therefore be accompanied by withdrawal symptoms. The following symptoms may occur: headache, myalgia, anxiety, tension, restlessness, confusion, irritability, rebound insomnia, mood disturbances, hallucinations and convulsions. As the risk of withdrawal symptoms is higher after abrupt discontinuation of treatment, a gradual tapering of doses is recommended.

Amnesia:

Midazolam causes anterograde amnesia (this effect is often highly desirable in situations such as before and during surgery and diagnostic procedures), the duration of which is directly related to the dose administered. Prolonged amnesia may pose problems for outpatients who are expected to be discharged after surgery. After receiving parenteral midazolam, patients may leave the hospital or clinic only if accompanied by another person.

Paradoxical reactions:

Paradoxical reactions such as agitation, involuntary movements (tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, anger reaction, aggressiveness, paroxysmal excitement and threats and insults have been described with midazolam. These reactions can occur with high doses or when the injection is administered quickly. Such reactions are characterised by a higher incidence in children and elderly people.

Delayed elimination of midazolam:

The elimination of midazolam may be altered in patients receiving compounds that inhibit or induce CYP3A4 (see 4.5 Drug interactions and other interactions).

Elimination of midazolam may also be delayed in patients with hepatic impairment or low cardiac output and in neonates (see 5.2 Pharmacokinetics in special populations).

Premature infants and newborns:

Given the increased risk of apnoea, extreme caution is advised when sedating newborns and premature infants. Respiratory rate and oxygen saturation should be closely monitored. Rapid injection should be avoided in the neonatal population. Newborns are characterised by reduced or immature organ function and are also vulnerable to profound 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

Metabolism of midazolam is almost exclusively mediated by cytochrome P450 isoenzyme 3A4 (CYP450). Inhibitors (see 4.4. Special warnings and precautions for use) and CYP3A4 inducers, but also other active substances (see below), may interact with midazolam.

As midazolam has a significant first-pass effect, parenterally administered midazolam would theoretically be subject to fewer metabolic interactions and important clinical consequences would be limited.

- **Itraconazole, fluconazole and ketoconazole:**

Concomitant oral administration of midazolam and some azole antifungals (itraconazole, fluconazole and ketoconazole) significantly increased midazolam plasma concentrations and prolonged its elimination half-life, leading to significant alteration of psychosedative tests. Elimination half-lives increased by approximately 3 to 8 hours.

When a single dose of midazolam was administered as a bolus for short-term sedation, itraconazole did not potentiate or prolong the effect of midazolam to a clinically important degree, so no dose reduction is necessary. However, the administration of high doses or long-term infusions of

midazolam to patients treated with itraconazole, fluconazole or ketoconazole, e.g. during intensive care treatment, may result in long-lasting hypnotic effects, delayed recovery and respiratory depression, requiring dose adjustments.

- **Verapamil and diltiazem:**

No *in vivo* interaction studies have been conducted with intravenous midazolam and verapamil or diltiazem.

However, as expected, the pharmacokinetics of oral midazolam changed in a clinically important way when combined with these calcium antagonists; in particular, the half-life and peak plasma concentration almost doubled, resulting in a marked decrease in performance on tests of coordination and cognitive function and profound sedation. When midazolam is administered orally, dose adjustment is usually recommended. Although clinically significant interactions are not expected when midazolam is used for short-term sedation, caution should be exercised when simultaneously administering intravenous midazolam with verapamil or diltiazem.

- **Macrolide antibiotics: erythromycin and clarithromycin:**

Concurrent administration of oral midazolam and erythromycin or clarithromycin significantly increased the AUC of midazolam, almost fourfold, and increased the elimination half-life of midazolam more than twofold, depending on the study. Significant alterations in psychomotor tests were observed and it is recommended to adapt the doses of midazolam, if administered orally, due to significant delay in recovery.

When a single dose of midazolam was administered in a bolus for short-term sedation, erythromycin did not potentiate or prolong the effect of midazolam to a clinically important extent, although there was a significant decrease in plasma clearance. Caution is advised when midazolam is administered concomitantly intravenously with erythromycin or clarithromycin. No clinically important interactions of midazolam with other macrolide antibiotics have been demonstrated.

- **Cimetidine and ranitidine:**

Concomitant administration of cimetidine (at doses equal to or higher than 800 mg/day) and intravenous midazolam slightly increased the plasma concentration of midazolam, at steady state, which could delay recovery, while concomitant administration of ranitidine had no effect. Cimetidine and ranitidine did not affect the pharmacokinetics of oral midazolam. These data indicate that midazolam can be administered intravenously with usual doses of cimetidine (i.e. 400 mg/day) and ranitidine without adjusting the dosage.

- **Saquinavir:**

Concomitant administration of a single intravenous dose of 0.05 mg/kg midazolam after 3 or 5 days of saquinavir administration (1,200 mg three times daily) to 12 healthy volunteers decreased midazolam elimination by 56% and increased the elimination half-life from 4.1 to 9.5 hours. Saquinavir only intensified the subjective effects of midazolam (visual analogue scales with the item “overall drug effect”).

Thus, a single bolus dose of intravenous midazolam can be administered in combination with saquinavir. However, during a prolonged infusion of midazolam, it is recommended to decrease the total dose so as not to delay recovery (see 4.4. Special warnings and precautions for use).

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

No in vivo interaction studies have been conducted with intravenous midazolam and other protease inhibitors. Considering that saquinavir is characterised by the weakest CYP3A4 inhibitory potency among all protease inhibitors, the dose of 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 the effects of midazolam.

Pharmacological groups of CNS depressants include opioids (when used as analgesics, cough suppressants or substitution treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, phenobarbital, sedative antidepressants, antihistamines and centrally acting antihypertensives.

Additional sedation should be considered when midazolam is combined with other sedatives.

In addition, a further increase of respiratory depression in case of concomitant treatment with opioids, phenobarbital or benzodiazepines should be especially monitored.

Alcohol can significantly enhance the sedative effect of midazolam. Alcohol consumption should be avoided when midazolam is administered.

Other interactions:

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

4.6. Pregnancy and breastfeeding

There are insufficient data on midazolam to establish its safety during pregnancy. Animal studies have not indicated a teratogenic effect, but foetal toxicity has been observed as with other benzodiazepines. No data on exposure during the first two trimesters of pregnancy are available.

Administration of high doses of midazolam in the last trimester of pregnancy, or during labour or as an anaesthesia induction drug for caesarean section has been reported to produce adverse maternal and foetal effects (risk of aspiration in the mother, foetal heart rate irregularities, hypotonia, poor suckling, hypothermia and respiratory depression in the newborn).

In addition, children born to mothers treated with benzodiazepines during late pregnancy may experience physical dependence and have some risk of withdrawal symptoms in the postnatal period.

Therefore, midazolam should not be used during pregnancy unless absolutely necessary. It is preferable not to use it for caesarean section.

The risk to the newborn must be considered when administering midazolam for any surgical intervention near the end of pregnancy.

Midazolam is excreted in small amounts in breast milk. Nursing mothers are advised not to breast-feed for 24 hours after administration of midazolam.

4.7. Effects on the ability to drive vehicles and operate machinery

Sedation, amnesia, decreased attention and impaired muscle function may adversely affect the ability to drive or use machines. Before receiving midazolam, the patient should be advised not to drive or operate machinery until fully recovered. The doctor will decide when such activities can be resumed. It is recommended that the patient be accompanied when returning home after discharge.

4.8. Undesirable effects

The following adverse reactions have been reported (very rarely) when injecting midazolam:

Skin and adnexal disorders: rash, urticarial reaction, pruritus.

Central and peripheral nervous system and psychiatric disorders: prolonged somnolence and sedation, decreased alertness, confusion, euphoria, hallucinations, fatigue, headache, dizziness, ataxia, post-surgical sedation and anterograde amnesia, the duration of which is directly related to the dose administered. Anterograde amnesia may persist at the end of the procedure and prolonged amnesia has been described in isolated cases.

Paradoxical reactions, such as agitation, involuntary movements (tonic/clonic movements and muscle tremor), hyperactivity, hostility, anger reaction, aggressiveness, paroxysmal excitement and threats and insults have been described, particularly in children and elderly people.

Seizures have been reported more frequently in premature infants and newborns.

The use of midazolam - even in therapeutic doses - may promote the development of physical dependence after prolonged IV administration; abrupt discontinuation of the drug may be accompanied by withdrawal symptoms such as seizures.

Digestive system disorders: nausea, vomiting, hiccups, constipation and dry mouth.

Cardiorespiratory disorders: serious cardiorespiratory adverse events: respiratory depression, apnoea, respiratory arrest or cardiac arrest, hypotension, altered heart rate, vasodilatory effects, dyspnoea and laryngospasm.

Life-threatening incidents are more likely to occur in adults over 60 years of age and in patients with previous respiratory failure or impaired cardiac function, particularly when the injection is given too quickly or when a high dose is administered (see 4.4. Special warnings and precautions for use).

General disorders: generalised hypersensitivity reactions: skin reactions, cardiovascular reactions, bronchospasm, anaphylactic shock.

Application site disorders: erythema and pain at the injection site, thrombophlebitis and thrombosis.

4.9. Overdose

Symptoms:

Symptoms of overdose mainly represent an intensification of pharmacological effects: drowsiness, mental confusion, lethargy and muscle relaxation or paradoxical excitement. The most severe symptoms would consist of areflexia, hypotension, cardiorespiratory depression, apnoea and coma.

Treatment:

In most cases, it is sufficient to monitor vital functions. In the treatment of overdose, special attention should be paid to respiratory and cardiovascular functions in the intensive care unit. Flumazenil, a benzodiazepine antagonist, is indicated in case of severe poisoning accompanied by coma or respiratory depression. Caution should be exercised when using flumazenil in case of mixed drug overdose and for patients with epilepsy already treated with benzodiazepines. Flumazenil should not be used in patients treated with tricyclic antidepressants, or epileptogenic drugs, or in patients with ECG abnormalities (QRS or QT prolongation).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group. Hypnotics and sedatives: benzodiazepine derivatives, ATC code: N05CD08.

Midazolam is a derivative of the immidazobenzodiazepine group. The free base is a lipophilic substance that is not very soluble in water.

The basic nitrogen at position 2 of the imidazobenzodiazepine ring structure allows the active substance of midazolam to form water-soluble salts with acids. They produce a stable and well-tolerated solution for injection.

The pharmacological action of midazolam is characterised by a short duration due to rapid metabolic transformation. Midazolam exerts a pronounced sedative and sleeping effect. It also has an anxiolytic, anticonvulsant and muscle relaxant effect.

After IM or IV administration, brief anterograde amnesia occurs (the patient has no memory of events that occurred during the peak activity of the compound).

5.2. Pharmacokinetic properties

Absorption after IM injection:

The absorption of midazolam into muscle tissue is rapid and complete. Peak plasma concentrations are reached within 30 minutes. Absolute bioavailability after IM injection is greater than 90%.

Absorption after rectal administration:

After rectal administration, midazolam is rapidly absorbed. Peak plasma concentration is reached in approximately 30 minutes. Absolute bioavailability is 50%.

Distribution:

When midazolam is injected IV, the plasma concentration-time curve is characterised by one or two distinct distribution phases. The volume of distribution at steady state is 0.7-1.2 l/kg. 96-98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In

humans, midazolam has been shown to cross the placenta slowly and enter the foetal circulation. Small amounts of midazolam have been found in human milk.

Metabolism:

Midazolam is almost completely eliminated by biotransformation. The fraction of the dose removed by the liver has been estimated to be 30-60%. Midazolam is hydroxylated by cytochrome P450 isoenzyme 3A4 and the major urinary and plasma metabolite is alpha-hydroxymidazolam. Plasma concentrations of alpha-hydroxyimidazolam are 12% of those of the parent compound. Alpha-hydroxyimidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam.

Elimination:

In healthy volunteers, the elimination half-life of midazolam is 1.5 to 2.5 hours. Plasma clearance is 300-500 ml/min. Midazolam is primarily eliminated by the renal route (60-80% of the injected dose) and recovered as alpha-hydroxyimidazolam glucuroconjugate. Less than 1% of the dose is recovered in the urine as unchanged drug. The elimination half-life of alpha-hydroxyimidazolam is less than 1 hour. When midazolam is administered as an IV infusion, its elimination kinetics do not differ from those of bolus injection.

Pharmacokinetics for special populations:

Elderly people:

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

Children:

The rate of rectal absorption in children is similar to that of adults, but the bioavailability is lower (5-18%). The elimination half-life after IV and rectal administration is shorter for children aged 3-10 years (1-1.5 hours) than for adults. The difference is consistent with increased metabolic clearance in children.

Newborns:

In newborns, the elimination half-life averages 6-12 hours, probably due to the immaturity of the liver, and clearance is decreased (see 4.4. Special warnings and precautions for use).

Obese:

The half-life is longer in obese patients than in non-obese patients (5.9 vs. 2.3 hours). This is due to an approximately 50% increase in the volume of distribution corrected for total body weight. Elimination is not significantly different among the obese compared to the non-obese.

Patients with liver failure:

The elimination half-life of cirrhotic patients may be longer and clearance may be lower compared to healthy volunteers (see 4.4. Special warnings and precautions for use).

Patients with kidney failure:

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

Critically ill patients:

The elimination half-life of midazolam is prolonged up to 6-fold in critically ill patients.

Patients with heart failure:

The elimination half-life is longer in patients with congestive heart failure than in healthy people (see 4.4. Special warnings and precautions for use).

5.3. Preclinical safety data

There are no preclinical data of interest to the clinician other than those already included in other sections of the PCS.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride, hydrochloric acid (pH adjuster) and water for injection.

6.2. Incompatibilities

Ampoules should not be diluted with MIDAZOLAM NORMON with Macrodex 6% solution in glucose.

MIDAZOLAM NORMON ampoule solution should not be mixed with injections of alkaline compounds.

6.3. Shelf life

2 years

6.4. Special precautions for storage

Ampoules of MIDAZOLAM NORMON Solution for Injection must not be frozen because they may burst. In addition, a precipitate may form which dissolves when the contents are shaken at room temperature.

6.5. Nature and contents of the container

3 ml glass ampoules containing 5 mg/ml of the active substance.
5 ml glass ampoules containing 1 mg/ml of the active substance.
10 ml glass ampoules containing 5 mg/ml of the active substance.

6.6. Instructions for use/handling

Compatibility with infusion solutions: Midazolam ampoule solutions can be diluted with 0.9% sodium chloride, 5% and 10% glucose, 5% laevulose, Ringer’s and Hartmann’s solution to a mixture of 15 mg midazolam per 100 - 1,000 ml infusion solution. These solutions remain physically and

chemically stable for 24 hours at room temperature (or 3 days in the refrigerator at 2-8°C). No adsorption of midazolam was detected in solutions containing 15 mg in 250 ml 0.9% sodium chloride, stored for 24 hours at room temperature in PVC infusion bags and infused over 6 hours through a PVC infusion set.

More concentrated midazolam infusion solutions may cause midazolam precipitation, especially if the pH of the sample exceeds 4.5 - 5.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

MIDAZOLAM NORMON 5 mg/5 ml Solution for injection, Registration No: 63.936
MIDAZOLAM NORMON 15 mg/3 ml Solution for injection, Registration No: 63.935
MIDAZOLAM NORMON 50 mg/10 ml Solution for injection, Registration No: 65.796

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

MIDAZOLAM NORMON 5 mg/5 ml Solution for injection: 25-05-01
MIDAZOLAM NORMON 15 mg/3 ml Solution for injection: 25-05-01
MIDAZOLAM NORMON 50 mg/10 ml Solution for injection: 24-11-03

10. DATE OF REVISION OF THE TEXT

October 2003