The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

SUMMARY INFORMATION ON REFERRAL OPINION FOLLOWING ARBITRATION

PURSUANT TO ARTICLE 30 OF COUNCIL DIRECTIVE 2001/83/EC FOR

Hypnovel and associated names

International NonProprietary Name (INN): midazolam

BACKGROUND INFORMATION

Hypnovel is a short-acting sedative and hypnotic imidazobenzodiazepine indicated in EU Member States for conscious sedation, anesthesia (premedication, induction, maintenance, and ataralgesia), and for sedation in the intensive care unit (ICU).

From the registrations in Member States, different Summaries of Product Characteristics have been issued, based on national, divergent decisions. On 31 October 2000, France presented to the EMEA a referral under Article 30 of Directive 2001/83/EC[1].

The referral procedure started on 29 March 2001 in order to harmonise the Summaries of Product Characteristics (SPC) within the Member States and Norway and Iceland. The CPMP having considered the Rapporteur and the Co-Rapporteur assessment reports, scientific discussion within the Committee and comments from the Marketing Authorisation Holders, was of the opinion that the benefit/risk ratio of midazolam is considered to be favourable for the agreed indications. The CPMP issued a positive opinion, on 21 February 2002, recommending the harmonisation of the SPC for Hypnovel and associated names. The grounds for referral are appended to this report.

An overall summary of the scientific evaluation is provided together with the amended summary of product characteristics.

A Decision was issued by the European Commission on 26 June 2002.

[1] Corresponding to Article 11 of Directive 75/319/EEC, for referrals presented before 18 December 2001

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SCIENTIFIC CONCLUSIONS

Overall Summary of the Scientific Evaluation of Hypnovel and Associated names

- Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (sections 6.1, 6.3, 6.4 and 6.5).

- Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Indications Section.

- Long term sedation in intensive care unit
- Premedication before induction of anaesthesia
- Paediatric indications

all of which were approved in some, but not all, EU Member States.

Also, divergences existed relating to the paediatric indication, where differences existed either in the indications approved or in the age groups described, for example;

- Premedication before diagnostic or therapeutic procedures with or without local anaesthesia and long term sedation in intensive care unit
- Induction of anaesthesia
- Maintenance of anaesthesia
- Premedication before anaesthesia
- Ataralgesia (in association with ketamine)

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Hypnovel, no major issues were identified apart from the indication "ataralgesia" (midazolam combined with Ketamine) which was approved in five EU Member States but which has not been included in the harmonised SPC. Midazolam in current medical practice has sometimes been given intravenously at a low dose when combined with ketamine for anaesthesia primarily in order to minimise the adverse effects of ketamine (nightmares). Two recent double blind, placebo-controlled randomised trials comparing ketamine solely versus the combination IV midazolam + ketamine 0.05 mg/kg midazolam IV in one study or midazolam IV 0.1 mg/kg in the other study did not show any effect of midazolam on recovery agitation or nightmares and hallucinations after ataralgesia. The IM combination of Ketamine and Midazolam has never been studied in a placebo-controlled randomised trial, but the data from the two randomised trials cited published in 2000 appear to undermine the rationale for this indication. It has therefore been removed from the SPC.

The following was considered to be the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications

HYPNOVEL is a short-acting sleep-inducing drug that is indicated:

In adults

CONSCIOUS SEDATION before and during diagnostic or therapeutic procedures with or without local anaesthesia.
ANAESTHESIA
- Premedication before induction of anaesthesia.
- Induction of anaesthesia
- As an induction agent or as a sedative component in combined anaesthesia.

SEDATION IN INTENSIVE CARE UNITS

In children
CONSCIOUS SEDATION before and during diagnostic or therapeutic procedures with or without local anaesthesia.
ANAESTHESIA
- Premedication before induction of anaesthesia.

SEDATION IN INTENSIVE CARE UNITS

Section 4.2. Posology and method of administration

Divergent decisions existed relating to the posology and method of administration, especially in children and particularly rectal administration in children.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Hypnovel, the most suitable harmonised Section 4.2 Posology text was approved (See Annex). In children, rectal administration is the recommended route, since it is considered less painful than I.M. administration. Otherwise, the choice of text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

- Safety issues

Section 4.3. Contraindications
The following contraindications were listed in the SPCs of some, but not all, EU Member States, or were considered as a contraindication in some SPCs but were placed in alternative sections in other SPCs;

- Myasthenia gravis
- Sleep apnea
- Alcohol association or intoxication
- Acute respiratory depression
- Pregnancy and lactation
- Severe liver failure or hepatic insufficiency

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Hypnovel, the most suitable harmonised Section 4.3 Contraindications text was approved (See Annex). The choice of text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

Section 4.4. Special warnings and special precautions for use

Important warnings and precautions for use were covered in the SPC of all countries, however the extent of the information provided varied across Member States, in particular with reference to:

- Use in children, elderly and high-risk patients (renal, hepatic or respiratory insufficiency, heart failure).
- The increased risk with increased doses using the i.v. route and the rate of infusion.

- The possibility of residual sedation after discontinuing the infusion for prolonged sedation in intensive care unit.
- The rebound effect after the discontinuation of the treatment.
- Caution in patients with a history of alcohol and drug abuse.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Hypnovel, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (See Annex). The text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

- Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

Benefit/Risk considerations
Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Hypnovel is favourable for use relating to anaesthesia and sedation.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion and under the conditions set out in Annex IV of the Opinion. The major divergences identified at the start of the referral have been resolved.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was annexed to the Commission Decision concerning this referral for arbitration; the text was valid at that time.

It is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

Hypnovel and associated names

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: midazolam as hydrochloride.
Ampoules 5mg/1ml; 15mg/3ml; 50mg/10ml; 10mg/2ml; 10mg/5ml; 5mg/5ml; and 2mg/2ml for i.v., i.m. and rectal administration

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. Clinical particulars

4.1 Therapeutic indications

Hypnovel (and associated names) is a short-acting sleep-inducing drug that is indicated:

In adults

- CONSCIOUS SEDATION before and during diagnostic or therapeutic procedures with or without local anaesthesia

- ANAESTHESIA
  - Premedication before induction of anaesthesia
  - Induction of anaesthesia:
  - As a sedative component in combined anaesthesia.

- SEDATION IN INTENSIVE CARE UNITS

In children

- CONSCIOUS SEDATION before and during diagnostic or therapeutic procedures with or without local anaesthesia

- ANAESTHESIA
  - Premedication before induction of anaesthesia

- SEDATION IN INTENSIVE CARE UNITS

4.2 Posology and method of administration

STANDARD DOSAGE

Midazolam is a potent sedative agent that requires titration and slow administration. Titration is strongly recommended to safely obtain the desired level of sedation according to the clinical need, physical status, age and concomitant medication. In adults over 60 years, debilitated or chronically ill patients and paediatric patients, dose should be determined with caution and risk factors related to each patient should be taken into account. Standard dosages are provided in the table below. Additional details are provided in the text following the table.

Indication	Adults <60 y	Adults ≥60 y / debilitated or chronically ill	Children
Conscious sedation	***i.v.*** Initial dose: 2-2.5 mg Titration doses: 1 mg Total dose: 3.5-7.5 mg	***i.v*** Initial dose: 0.5-1 mg Titration doses: 0.5-1 mg Total dose: <3.5 mg	***i.v. in patients 6 months-5 years*** Initial dose: 0.05-0.1 mg/kg Total dose: <6 mg ***i.v. in patients 6-12 years*** Initial dose: 0.025-0.05 mg/kg Total dose: <10 mg ***rectal >6 months*** 0.3-0.5 mg/kg ***i.m. 1-15 years*** 0.05-0.15mg/kg
Anaesthesia premedication	***i.m.*** 0.07-0.1 mg/kg	***i.m.*** 0.025-0.05 mg/kg	***rectal >6 months*** 0.3-0.5 mg/kg ***i.m. 1-15 years*** 0.08-0.2 mg/kg
Anaesthesia induction	***i.v.*** 0.15-0.2 mg/kg (0.3-0.35 without premedication)	***i.v.*** 0.1-0.2 mg/kg (0.15-0.3 without premedication)	
Sedative component in combined anaesthesia	***i.v.*** intermittent doses of 0.03-0.1 mg/kg or continuous infusion of 0.03-0.1 mg/kg/h	***i.v.*** lower doses than recommended for adults <60 years	
Sedation in ICU	***i.v.*** Loading dose: 0.03-0.3 mg/kg in increments of 1-2.5 mg Maintenance dose: 0.03-0.2 mg/kg/h		***i.v. in neonates <32 weeks gestational age*** 0.03 mg/kg/h ***i.v in neonates >32 weeks and children up to 6 months*** 0.06 mg/kg/h ***i.v. in patients >6 months of age*** Loading dose: 0.05-0.3 mg/Kg Maintenance dose: 0.06-0.12 mg/Kg/h

CONSCIOUS SEDATION DOSAGE

For conscious sedation prior to diagnostic or surgical intervention, midazolam is administered i.v. The dose must be individualised and titrated, and should not be administered by rapid or single bolus injection. The onset of sedation may vary individually depending on the physical status of the patient and the detailed circumstances of dosing (e.g. speed of administration, amount of dose). If necessary, subsequent doses may be administered according to the individual need. The onset of action is about 2 minutes after the injection. Maximum effect is obtained in about 5 to 10 minutes.

Adults
The i.v. injection of midazolam should be given slowly at a rate of approximately 1 mg in 30 seconds. In adults below the age of 60 the initial dose is 2 to 2.5 mg given 5 to10 minutes before the beginning of the procedure. Further doses of 1 mg may be given as necessary. Mean total doses have been found to range from 3.5 to 7.5 mg. A total dose greater than 5 mg is usually not necessary. In adults over 60 years of age, debilitated or chronically ill patients, start by administering a dose of 0.5 to 1 mg. Further doses of 0.5 to 1 mg may be given as necessary. A total dose greater than 3.5 mg is usually not necessary.

Children
I.V. administration: midazolam should be titrated slowly to the desired clinical effect. The initial dose of midazolam should be administered over 2 to 3 minutes. One must wait an additional 2 to 5 minutes to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue to titrate with small increments until the appropriate level of sedation is achieved. Infants and young children less than 5 years of age may require substantially higher doses (mg/kg) than older children and adolescents.

- Paediatric patients less than 6 months of age: paediatric patients less than 6 month of age are particularly vulnerable to airway obstruction and hypoventilation. For this reason, the use in conscious sedation in children less than 6 months of age is not recommended.
- Paediatric patients 6 months to 5 years of age: initial dose 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint, but the total dose should not exceed 6 mg. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
- Paediatric patients 6 to 12 years of age: initial dose 0.025 to 0.05 mg/kg. A total dose of up to 0.4 mg/kg to a maximum of 10 mg may be necessary. Prolonged sedation and risk of hypoventilation may be associated with the higher doses.
- Paediatric patients 12 to 16 years of age: should be dosed as adults.

Rectal administration: the total dose of midazolam usually ranges from 0.3 to 0.5 mg/kg. Rectal administration of the ampoule solution is performed by means of a plastic applicator fixed on 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. Total dose should be administered at once and repeated rectal administration avoided.
The use in children less than 6 months of age is not recommended, as available data in this population are limited.

I.M.administration: the doses used range between 0.05 and 0.15 mg/kg. A total dose greater than 10.0 mg is usually not necessary. This route should only be used in exceptional cases. Rectal administration should be preferred as i.m. injection is painful.

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

ANAESTHESIA DOSAGE

PREMEDICATION

Premedication with midazolam given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory. Midazolam can also be administered in combination with anticholinergics. For this indication midazolam should be administered i.m., deep into a large muscle mass 20 to 60 minutes before induction of anaesthesia), or preferably via the rectal route in children (see below). Adequate observation of the patient after administration of premedication is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

Adults
For preoperative sedation and to impair memory of preoperative events, the recommended dose for adults of ASA Physical Status I & II and below 60 years is 0.07 to 0.1 mg/kg administered i.m. The dose must be reduced and individualised when midazolam is administered to adults over 60 years of age, debilitated, or chronically ill patients. A dose of 0.025 to 0.05 mg/kg administered i.m. is recommended. The usual dose is 2 to 3 mg.

Children
Rectal administration: The total dose of midazolam, usually ranging from 0.3 to 0.5 mg/kg should be administered 15 to 30 minutes before induction of anaesthesia. Rectal administration of the ampoule solution is performed by means of a plastic applicator fixed on 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.

I.M. administration: As i.m. injection is painful, this route should only be used in exceptional cases. Rectal administration should be preferred. However, a dose range from 0.08 to 0.2 mg/kg of midazolam administered i.m. has been shown to be effective and safe. In children between ages 1 and 15 years, proportionally higher doses are required than in adults in relation to body-weight.

The use in children less than 6 months of age is not recommended as available data are limited.

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

INDUCTION

Adults
If midazolam is used for induction of anaesthesia before other anaesthetic agents have been administered, the individual response is variable. The dose should be titrated to the desired effect according to the patient's age and clinical status. When midazolam is used before or in combination with other i.v. or inhalation agents for induction of anaesthesia, the initial dose of each agent should be significantly reduced. The desired level of anaesthesia is reached by stepwise titration. The i.v. induction dose of midazolam should be given slowly in increments. Each increment of not more than 5 mg should be injected over 20 to 30 seconds allowing 2 minutes between successive increments.

- In adults below the age of 60 years, an i.v. dose of 0.15 to 0.2 mg/kg will usually suffice. In non-premedicated adults below the age of 60 the dose may be higher (0.3 to 0.35 mg/kg i.v.). If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used. Induction may instead be completed with inhalational anaesthetics. In resistant cases, a total dose of up to 0.6 mg/kg may be used for induction, but such larger doses may prolong recovery.
- In adults over 60 years of age, debilitated or chronically ill patients, the dose is 0.1 to 0.2 mg/kg administered i.v. Non-premedicated adults over 60 years of age usually require more midazolam for induction; an initial dose of 0.15 to 0.3 mg/kg is recommended. Non-premedicated patients with severe systemic disease or other debilitation usually require less midazolam for induction. An initial dose of 0.15 to 0.25 mg/kg will usually suffice.

SEDATIVE COMPONENT IN COMBINED ANAESTHESIA

Adults
Midazolam can be given as a sedative component in combined anaesthesia by either further intermittent small i.v. doses (range between 0.03 and 0.1 mg/kg) or continuous infusion of i.v. midazolam (range between 0.03 and 0.1 mg/kg/h) typically in combination with analgesics. The dose and the intervals between doses vary according to the patient's individual reaction.
In adults over 60 years of age, debilitated or chronically ill patients, lower maintenance doses will be required.

SEDATION IN INTENSIVE CARE UNITS

The desired level of sedation is reached by stepwise titration of midazolam followed by either continuous infusion or intermittent bolus, according to the clinical need, physical status, age and concomitant medication (see 4.5 Interactions).

Adults
I.V. loading dose: 0.03 to 0.3 mg/kg 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. In hypovolemic, vasoconstricted, or hypothermic patients the loading dose should be reduced or omitted. When midazolam is given with potent analgesics, the latter should be administered first so that the sedative effects of midazolam can be safely titrated on top of any sedation caused by the analgesic.

I.V. maintenance dose: doses can range from 0.03 to 0.2 mg/kg/h. In hypovolemic, vasoconstricted, or hypothermic patients the maintenance dose should be reduced. The level of sedation should be assessed regularly. With long-term sedation, tolerance may develop and the dose may have to be increased.

Children over 6 months of age
In intubated and ventilated paediatric patients, a loading dose of 0.05 to 0.2 mg/kg i.v. should be administered slowly over at least 2 to 3 minutes to establish the desired clinical effect. Midazolam should not be administered as a rapid intravenous dose. The loading dose is followed by a continuous i.v. infusion at 0.06 to 0.12 mg/kg/h (1 to 2 µg/kg/min). The rate of infusion can be increased or decreased (generally by 25% of the initial or subsequent infusion rate) as required, or supplemental i.v. doses of midazolam can be administered to increase or maintain the desired effect.

When initiating an infusion with midazolam in haemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient 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.

Neonates and children up to 6 months of age
Midazolam should be given as a continuous i.v. infusion, starting at 0.03 mg/kg/h (0.5 µg/kg/min) in neonates with a gestational age <32 weeks or 0.06 mg/kg/h (1 µg/kg/min) in neonates with a gestational age >32 weeks and children up to 6 months.

Intravenous loading doses is not recommended in premature infants, neonates and children up to 6 months, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for drug accumulation.

Careful monitoring of respiratory rate and oxygen saturation is required.

In premature infants, neonates and children less than 15 kg of body weight, midazolam solutions with concentrations higher than 1mg/ml are not recommended. Higher concentrations should be diluted to 1mg/ml.

4.3 Contraindications

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

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

4.4 Special warnings and special 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 apnea. Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnea, 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 interindividual 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 4.2 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 4.5 Interactions).

Midazolam elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates (see 5.2 Pharmacokinetics in special populations).

Preterm infants and neonates

Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm 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 4.4 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 were 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 800 mg/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. 400 mg/day) and ranitidine without dosage adjustment.

- Saquinavir
  Co-administration of a single intravenous dose of 0.05 mg/kg midazolam after 3 or 5 days of saquinavir dosing (1200 mg 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 4.4 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 fetal 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 postnatal 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. Prior to receiving midazolam, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician 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 (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, postoperative 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, apnea, respiratory arrest and/or cardiac arrest, hypotension, heart rate changes, vasodilating effects, dyspnea, 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 4.4 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, apnea 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).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 system enables the active ingredient of midazolam to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.
The pharmacological action of midazolam is characterised by short duration because of rapid metabolic transformation. Midazolam has a sedative and sleep-inducing effect of pronounced intensity. It also exerts an anxiolytic, an anticonvulsant and a muscle-relaxant effect.
After i.m. or i.v. administration anterograde amnesia of short duration occurs (the patient does not remember events that occurred during the maximal activity of the compound).

5.2 Pharmacokinetic properties

Absorption after i.m. injection
Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability after i.m. injection is over 90%.

Absorption after rectal administration
After rectal administration midazolam is absorbed quickly. Maximum plasma concentration is reached in about 30 minutes. The absolute bioavailability is about 50%.

Distribution
When midazolam is injected i.v., the plasma concentration-time curve shows one or two distinct phases of distribution. 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 to enter fetal circulation. Small quantities of midazolam are found in human milk.

Metabolism
Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30-60%. Midazolam is hydroxylated by the cytochrome P4503A4 isozyme and the major urinary and plasma metabolite is alpha-hydroxymidazolam. Plasma concentrations of alpha-hydroxymidazolam are 12% of those of the parent compound. Alpha-hydroxymidazolam 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 between 1.5 - 2.5 hours. Plasma clearance is in the range of 300-500 ml/min. Midazolam is excreted mainly by renal route (60-80% of

the injected dose) and recovered as glucuroconjugated alpha-hydroxymidazolam. Less than 1% of the dose is recovered in urine as unchanged drug. The elimination half-life of alpha-hydroxy-midazolam is shorter than 1 hour. When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection.

Pharmacokinetics in special populations

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

Children
The rate of rectal absorption in children is similar to that in adults but the bioavailability is lower (5-18%).The elimination half-life after i.v. and rectal administration is shorter in children 3-10 years old (1-1.5) as compared with that in adults. The difference is consistent with an increased metabolic clearance in children.

Neonates
In neonates the elimination half-life is on average 6-12 hours, probably due to liver immaturity and the clearance is reduced (see 4.4 Special warnings and precautions for use).

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

Patients with hepatic impairment
The elimination half-life in cirrhotic patients may be longer and the clearance smaller as compared to those in healthy volunteers (see 4.4 Special warnings and precautions for use).

Patients with renal impairment
The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

Critically ill patients
The elimination half-life of midazolam is prolonged up to six times in the critically ill.

Patients with cardiac insufficiency
The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects (see 4.4 Special warnings and precautions for use).

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

6.3 Shelf life

6.4 Special precautions for storage

6.5 Nature and contents of container

See Annex II.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling <and disposal>

7. MARKETING AUTHORISATION HOLDER

See Annex II

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT