

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

Hypnovel<sup>®</sup> 5mg/5mL and 15mg/3mL solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: midazolam as hydrochloride

Ampoules 5mg/5 mL and 15mg/3 mL solution for intravenous (IV), intramuscular (IM), intranasal, oral and rectal administration.

For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Solution for injection

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Hypnovel is indicated for

#### Adults

- Premedication before induction of anaesthesia.
- Conscious sedation before diagnostic or surgical interventions carried out under local anaesthesia.
- Long-term sedation in intensive care units.
- Induction and maintenance of anaesthesia. As an induction agent in inhalation anaesthesia or a sleep-inducing component in combined anaesthesia.

#### Children

- Premedication before induction of anaesthesia.
- Conscious sedation before diagnostic or surgical interventions carried out under local anaesthesia.
- Ataralgia in combination with ketamine.

### 4.2 Dose and method of administration

In the case of elderly patients with organic cerebral changes or impaired cardiac and respiratory function, the dosage should be determined with caution. Special factors relating to each patient should be taken into consideration.

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Initial and subsequent intravenous injections must be given slowly (see Section 4.2, *induction of anaesthesia* and *conscious sedation* for specific recommendations) The medicine takes effect about two minutes after the injection is started.

### **Premedication before an operation**

#### ***Adults – Premedication before an operation***

##### *Intramuscular administration*

In patients suffering from pain before an intervention.

Administration alone or in combination with anticholinergics and possibly analgesics. These doses should be administered about 30 minutes before induction of anaesthesia.

0.07-0.10 mg per kg bodyweight i.m. according to age and general condition of the patient. Usual dosage about 5mg.

*Elderly and debilitated patients:* 0.025 - 0.05 mg/kg bodyweight i.m.

#### ***Paediatric populations –premedication before an operation***

##### *Intramuscular administration*

Proportionately higher doses are required than in adults in relation to bodyweight (0.15-0.20 mg per kg bodyweight i.m.). Administration alone or in combination with anticholinergics and possibly analgesics. These doses should be administered about 30 minutes before induction of anaesthesia.

##### *Rectal administration*

Rectal administration of the ampoule solution by means of a plastic applicator fixed on the end of a syringe, 0.35-0.45 mg/kg bodyweight 20-30 minutes before induction of general anaesthesia. If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

##### *Intranasal administration*

0.2mg/kg, 10-15 minutes prior to anaesthesia.

##### *Oral administration*

0.5mg / kg, 15-30 minutes prior to anaesthesia.

### **Conscious Sedation**

For conscious sedation in diagnostic or surgical interventions carried out under local anaesthesia.

#### ***Adults – Conscious sedation***

##### *Intravenous conscious sedation*

The initial dose should not exceed 2.5mg i.v. 5-10 minutes before the beginning of the operation given at approximately 1mg in 30 seconds. Further doses of 1mg may be given as

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necessary. A total dose greater than 5mg is not usually necessary to reach the desired endpoint. In cases of severe illness, particularly if the patient is in poor general condition or of advanced age, the initial dose must be reduced to 1-1.5mg. Total doses greater than 3.5mg are not usually necessary.

### ***Paediatric populations – conscious sedation***

#### *Intranasal conscious sedation*

0.2mg / kg, 10-15 minutes before the intervention.

#### *Oral conscious sedation*

0.2 - 0.5mg / kg, 15-30 minutes before the intervention.

### **Sedation in Intensive Care Units**

For sedation in the intensive care unit (ICU), the dosage should be individualised and Hypnovel titrated to the desired state of sedation according to the clinical need, physical status, age, concomitant medication.

### ***Adults – sedation in the ICU***

#### *Intravenous sedation*

*Loading dose:* 0.03 - 0.3 mg/kg.

*Maintenance dose:* 0.03 - 0.2 mg/kg/hr. The dosage should be reduced or the loading dose should even be omitted in hypovolemic, vasoconstricted and hypothermic patients.

### **Induction and Maintenance of Anaesthesia**

#### ***Adults – Induction and Maintenance of Anaesthesia***

##### *Intravenous injection*

*Induction:* the dose is 10-15 mg i.v. in combination with analgesics given slowly at approximately 2.5mg in 10 seconds. A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

*Maintenance:* for maintenance of the desired level of unconsciousness, further small doses should be injected i.v. The dose and the intervals between doses vary according to the individual patient's reaction. Alternatively, Hypnovel can be administered by continuous infusion.

##### *Intravenous continuous infusion*

For intravenous anaesthesia combined with ketamine, 0.03 - 0.1 mg/kg/hr; narcotics, 0.03 - 0.3 mg/kg/hr. High-risk surgical patients, elderly and debilitated patients require lower dosages.

### ***Paediatric populations – Induction and Maintenance of Anaesthesia***

#### *Intramuscular administration*

A combination of the sleep-inducing and amnesia-inducing Hypnovel with ketamine (ataralgesia) is recommended. Hypnovel i.m. (0.15-0.20 mg per kg bodyweight) in

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combination with 50-100 mg ketamine i.m. (4-8 mg per kg bodyweight). A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

### *Rectal administration*

See Premedication before an Operation.

### **Special populations**

#### *Elderly patients*

Elderly patients, <sup>3</sup> 60 years, require lower dosages and should be continuously monitored for early signs of alterations of vital functions (see specific dosing recommendations within section 4.2 and section 4.4).

#### *Renal impairment*

In patients with severe renal impairment Hypnovel may be accompanied by more pronounced and prolonged sedation possibly including clinically relevant respiratory and cardiovascular depression. Hypnovel should therefore be dosed carefully in this patient population and titrated for the desired effect (see section 4.4).

#### *Hepatic impairment*

The clinical effects in patients with hepatic impairment may be stronger and prolonged. The dose of midazolam may have to be reduced and vital signs should be monitored (see sections 4.4 and 5.2 *Pharmacokinetics in special populations*).

#### *Paediatric patients*

*see specific dosing recommendations within section 4.2 and section 4.4.*

### **Method of administration**

When Hypnovel is given with potent analgesics, the latter should be administered first so that the sedative effects of Hypnovel can be safely titrated on top of any sedation caused by the analgesic.

When administered orally, the bitter taste of Hypnovel injection may be masked by small quantities of apple juice, sweetened fruit syrup or powdered soft drink.

Hypnovel must not be mixed with other medicines except those mentioned in section 6.6.

### **4.3 Contraindications**

Hypnovel is contraindicated in patients with known hypersensitivity to benzodiazepines or to any component of the product.

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

Hypnovel ampoules should be used only when age- and size-appropriate resuscitation facilities are available, as i.v. administration of Hypnovel may depress myocardial contractility and cause apnoea. Severe cardiorespiratory adverse events have occurred on rare

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occasions. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest. Such life-threatening incidents are more likely to occur in adults over 60 years of age, those with pre-existing respiratory insufficiency or impaired cardiac function and paediatric patients with cardiovascular instability, particularly when the injection is given too rapidly or when a high dosage is administered.

Beonzodiazepines are not recommended for the primary treatment of psychotic illness.

### ***Premedication***

When Hypnovel is used for premedication, adequate observation of the patient after administration is mandatory as interindividual sensitivity varies and symptoms of overdose may occur.

### ***High-Risk Patients***

Special caution should be exercised when administering Hypnovel parenterally to patients representing a higher risk group:

- adults over 60 years of age
- debilitated or chronically ill patients
- patients with impaired respiratory function
- patients with impaired kidney function
- impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment).
- impaired cardiac function
- paediatric patients with cardiovascular instability

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

### ***Tolerance***

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

### ***Dependence***

When Hypnovel is used in long-term sedation in ICU, it should be borne in mind that physical dependence on Hypnovel may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse.

### ***Withdrawal Symptoms***

During prolonged treatment with Hypnovel ampoules in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following withdrawal symptoms may occur: headaches, diarrhoea, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability, sleep disturbances, mood

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changes, hallucinations and convulsions. In severe cases, the following symptoms may occur: depersonalization, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact.

Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended that the dose is decreased gradually.

### ***Concomitant use of Alcohol/CNS Depressants***

The concomitant use of Hypnovel with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Hypnovel possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression.

### ***Risks from Concomitant Use with Opioids***

Concomitant use of benzodiazepines, including Hypnovel, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe Hypnovel concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Hypnovel is used with opioids (see section 4.5).

### ***Medical History of Alcohol or Drug Abuse***

Hypnovel should be avoided in patients with a medical history of alcohol or drug abuse.

### ***Amnesia***

Hypnovel causes anterograde amnesia at therapeutic doses (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the risk and duration of which is directly related to the administered dose. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention.

### ***Discharging Criteria***

After receiving Hypnovel parenterally, patients should be discharged from hospital or consulting room only when recommended by the treating physician and if accompanied by an attendant. It is recommended that the patient is accompanied when returning home after discharge.

### ***"Paradoxical" Reactions***

Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, delusion,

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anger, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement and assault, have been reported to occur with Hypnovel. These reactions may occur with higher doses and/or when the injection is given rapidly. The rare incidence of susceptibility to such reactions has been reported among children and at higher i.v. doses in the elderly. Should such symptoms suggestive of a paradoxical reaction occur, discontinuation of the drug should be considered.

### ***Altered Elimination of midazolam***

Elimination of midazolam may be altered in patients receiving compounds that inhibit or induce certain hepatic enzymes (particularly cytochrome P450 3A4) and the dose of midazolam may need to be adjusted accordingly (see section 4.5).

When midazolam is given intravenously for a prolonged period and in combination with saquinavir, an initial dose reduction of midazolam of 50% is recommended (see Interactions).

It is advisable to lower doses of intravenous midazolam when co-administered with erythromycin (see Interactions).

Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam. Care should be taken to adjust the midazolam dose in patients with epilepsy on treatment with sodium valproate (see Interactions).

Elimination of midazolam may also be delayed, in patients with liver dysfunction, low cardiac output and in neonates (see Pharmacokinetics in special populations).

### ***Sleep Apnoea***

Hypnovel ampoules should be used with extreme caution in patients with sleep apnoea syndrome and patients should be regularly monitored.

### ***Pre-term Infants and Neonates***

Due to an increased risk of apnoea, extreme caution is advised when sedating pre-term and former pre-term patients whose trachea is not intubated.

Rapid injection should be avoided in the neonatal population.

The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of Hypnovel. Therefore, careful monitoring of respiratory rate and oxygen saturation is required.

### ***Paediatric Patients***

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 (see Pre-term Infants and Neonates above).

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

### ***Other***

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

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

#### ***Effects of other medicines on midazolam***

The metabolism of midazolam is predominantly mediated by cytochrome P450 3A4 (CYP3A4, CYP3A5) isozymes. Approximately 25 % of the total cytochrome P450 system in the adult liver is from the CYP3A4 subfamily. Inhibitors (see Precautions) and inducers of CYP3A may increase and decrease the plasma concentrations and subsequently, the pharmacodynamic effects of midazolam. No other mechanism than modulation of CYP3A activity has been proven as a source for a clinically relevant pharmacokinetic drug-drug interaction with midazolam. Midazolam is not known to change the pharmacokinetics of other drugs.

When co-administered with a CYP3A inhibitor, the clinical effects of midazolam may be stronger and also longer lasting and a lower dose may be required. Conversely the effect of midazolam may be weaker and of a shorter duration when co-administered with a CYP3A inducer and a higher dose may be required.

#### ***Interactions Studies conducted with Hypnovel Ampoules***

##### **CYP3A4 inhibitors**

##### ***Azole antifungals***

*Ketoconazole and voriconazole* increased the plasma concentration of intravenous midazolam by 5-fold and by 3-4 fold respectively, while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with these strong CYP3A inhibitors it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dosage adjustment should be considered, especially if more than a single iv dose of midazolam is administered.

*Fluconazole and itraconazole* both increased the plasma concentrations of intravenous midazolam by

2 – 3-folds associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.

*Posaconazole* increased the plasma concentrations of intravenous midazolam by about 2-fold.



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### ***Macrolide antibiotics***

#### ***Erythromycin***

Co-administration of Hypnovel and erythromycin prolonged the elimination half-life of midazolam from 3.5 to 6.2 hours. Although only relatively minor pharmacodynamic changes were observed, it is advised to adjust doses of intravenous midazolam, especially if high doses are being administered (see Precautions).

*Clarithromycin* increased midazolam's plasma concentrations by up to 2.5-fold associated with an increase in terminal half-life by 1.5 – 2-fold

#### ***Intravenous anaesthetics***

Disposition of intravenous midazolam was also changed by intravenous propofol (AUC and half-life increased by 1.6-fold).

#### ***Cimetidine and ranitidine***

Cimetidine increased the steady-state plasma concentration of midazolam by 26%, whereas ranitidine had no effect.

Co-administration of midazolam and cimetidine or ranitidine had no clinically significant effect on the pharmacokinetics and pharmacodynamics of midazolam. These data indicate that intravenous midazolam can be used in usual doses with cimetidine and ranitidine and dosage adjustment is not required.

#### ***Cyclosporin***

There is no pharmacokinetic and pharmacodynamic interaction between cyclosporin and midazolam. Therefore, the dosage of midazolam needs no adjustment when given concomitantly with cyclosporin.

#### ***Nitrendipine***

Nitrendipine did not affect the pharmacokinetics and pharmacodynamics of midazolam. Both medicines can be given concomitantly and no dosage adjustment of midazolam is required.

#### ***Protease Inhibitors***

*Saquinavir and other HIV protease inhibitors:* Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life. If parenteral midazolam is co-administered with HIV protease inhibitors, treatment setting should follow the description in the section above for ketoconazole within azole antifungals (see Precautions).

*HCV protease inhibitors: Boceprevir and telaprevir* reduce midazolam clearance. This effect resulted in a 3.4-fold increase of midazolam AUC after i.v. administration and prolonged its elimination half-life 4-fold.

#### ***Oral contraceptives***

The pharmacokinetics of intramuscular midazolam was not affected by the use of oral contraceptives. Both medicines can be given concomitantly and no dosage adjustment of midazolam is required.

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### Other interactions

#### *Sodium valproate*

Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam and, therefore, care should be taken to adjust the midazolam dosage in patients with epilepsy (see Precautions).

#### *Lidocaine*

Midazolam had no effect on the plasma protein binding of lidocaine in patients undergoing anti-arrhythmic therapy or regional anaesthesia with lidocaine.

#### *Halothane*

The i.v. administration of Hypnovel decreases the minimum alveolar concentration (MAC) of halothane required for general anaesthesia.

#### *Fentanyl*

Intravenous fentanyl is a weak inhibitor of midazolam's elimination: AUC and half-life of i.v. midazolam were increased by 1.5-fold in presence of fentanyl.

#### *Alcohol*

Alcohol may enhance the sedative effect of midazolam.

#### *Opioids*

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. The potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

### Drugs that induce CYP3A

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

*Ticagrelor* is a weak CYP3A inducer [246] but has only small effects on intravenously administered midazolam (-12%) and 4-hydroxy-midazolam (-23%) exposures.

#### *Paediatric population*

Interaction studies have only been performed in adults.

## 4.6 Fertility, pregnancy and lactation

### Pregnancy

#### *Risk summary statement:*

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. however insufficient data are available

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on midazolam to assess its safety during pregnancy. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

The administration of midazolam in the last trimester of pregnancy or at high doses during labour has been reported to produce irregularities in the foetal heart rate, hypotonia, poor sucking and hypothermia and moderate respiratory depression in the neonate. Moreover, infants born to 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.

An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested.

### *Preclinical data*

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

### **Lactation**

Since midazolam passes into breast milk, Hypnovel should not be administered to breast-feeding mothers.

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

Sedation, amnesia, impaired concentration and impaired muscular function adversely affect the ability to drive or use machines. Prior to receiving Hypnovel, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. If sleep duration is insufficient or alcohol is consumed, the likelihood of impaired alertness may be increased (see section 4.5).

### **4.8 Undesirable effects**

The following adverse effects have been reported to occur post-marketing when Hypnovel is injected:

#### **Central and peripheral nervous system and psychiatric disorders**

Drowsiness and prolonged sedation, reduced alertness, confusion, disorientation, emotional and mood disturbances, , 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.

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Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, nervousness, hostility, anger, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

Convulsions have been reported in premature infants and neonates.

Changes in libido have been reported occasionally.

### **Dependence**

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

Abuse has been reported in poly-drug abusers.

### **Gastrointestinal system disorders**

Nausea, vomiting, constipation, dry mouth.

### **Cardiorespiratory disorders**

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 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 Precautions).

The following other cardiorespiratory adverse events have been reported: hypotension, slight increase in heart rate, bradycardia, vasodilating effects, dyspnoea and hiccough. In isolated cases laryngospasm has occurred following injection of Hypnovel.

### **Skin and appendages disorders**

Skin rash, urticarial reaction, pruritus.

### **Immune System Disorders**

Generalised hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), angioedema, anaphylactic shock.

### **Local reactions**

Erythema and pain on injection site, thrombophlebitis, thrombosis.

### **Injury, poisoning and procedural complications**

There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

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## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

## 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. As with other benzodiazepines, overdosage should not present a threat to life unless combined with other CNS depressants including alcohol. More serious symptoms would be areflexia, hypotension, cardiorespiratory depression, apnoea and, rarely, coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease. Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

### *Treatment*

In most cases only observation of vital functions is required and initiate supportive measures as indicated by the patient's clinical state. In the management of overdose special attention should be paid to the respiratory and cardiovascular functions in intensive care.

If taken orally further absorption should be prevented using an appropriate method (e.g. treatment within 1-2 hours with activated charcoal). If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe, consider the use of the benzodiazepine antagonist Anexate® (active ingredient: flumazenil). This should only be administered under closely monitored conditions. It has a short half-life (about an hour); therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800764766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnovel is a sleep-inducing agent belonging to the benzodiazepines class of medicines.

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ATC code: N05CD08.

Midazolam, the active ingredient of Hypnovel, 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 Hypnovel to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

The pharmacological action of midazolam is characterized by rapid onset and, because of rapid metabolic transformation, short duration. Because of its low toxicity, midazolam has a wide therapeutic range.

Hypnovel has a very rapid 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 recall events that occurred during the peak of activity of the compound).

## 5.2 Pharmacokinetic properties

### Absorption

#### *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%.

#### *Absorption after intranasal administration*

Midazolam is absorbed quickly. Mean peak plasma concentrations are reached within 10.2 to 12.6 minutes. The bioavailability is between 55 and 57%.

#### *Absorption after oral administration*

Oral midazolam is absorbed rapidly from the gastrointestinal tract and undergoes extensive first-pass hepatic metabolism. Peak plasma concentrations are reached within 1 hour. Bioavailability is between 40 and 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

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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 foetal circulation. Small quantities of midazolam are found in human milk.

### **Biotransformation**

Midazolam is almost entirely eliminated by biotransformation. Midazolam is hydroxylated by the cytochrome P450 3A4 isozyme.  $\alpha$ -hydroxymidazolam is the major urinary and plasma metabolite. Plasma concentrations of  $\alpha$ -hydroxymidazolam are 12% of those of the parent compound. The fraction of the dose extracted by the liver has been estimated to be 30-60%.  $\alpha$ -hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10%) to the effects of intravenous midazolam. There is no evidence of a genetic polymorphism in the oxidative metabolism of midazolam (see Interactions).

### **Elimination**

In healthy volunteers, the elimination half-life is between 1.5 - 2.5 hours. Plasma clearance is in the range of 300-500 ml/min. 60-80% of the dose is excreted in urine as glucuroconjugated  $\alpha$ -hydroxymidazolam. Less than 1% of the dose is recovered in urine as unchanged drug. The elimination half-life of the metabolite 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. However, the elimination half-life ( $t_{1/2}$ ) after i.v. and rectal administration is shorter in children 3-10 years 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 Precautions).

#### *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 Precautions).

#### *Patients with renal impairment*

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

#### *Critically ill patients*

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The elimination half-life of midazolam is prolonged 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 Precautions).

### **5.3 Preclinical safety data**

#### *Animal toxicology and/or pharmacology*

Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Sodium chloride (9 mg/ml sodium chloride in the 5mg/5ml Hypnovel ampoule, 5mg/ml sodium chloride in the 15mg/3ml Hypnovel ampoule), hydrochloric acid, sodium hydroxide, water for injection.

### **6.2 Incompatibilities**

Do not dilute Hypnovel ampoule solutions with macrodex 6% in dextrose (see Special Dosage Instructions).

Do not mix Hypnovel ampoule solutions in alkaline injections. Midazolam precipitates in sodium bicarbonate.



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Hypnovel must not be mixed with other medicines except those mentioned in section 6.6.

### 6.3 Shelf life

Hypnovel<sup>®</sup> 5mg/5mL and Hypnovel 15mg/3mL solution for injection: 5 years

### 6.4 Special precautions for storage

Store below 30°C (approved to 35°C).

Keep the ampoules in the outer carton in order to protect from light.

Ampoules are for use in one patient only.

Hypnovel ampoules should not be frozen because they can burst. Furthermore, precipitation can occur which dissolves on shaking at room temperature.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

### 6.5 Nature and contents of container

Glass ampoules containing Hypnovel 5mg/5ml in packs of 10.

Glass ampoules containing Hypnovel 15mg/3ml in packs of 5.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

*Compatibility with infusion solutions:* the Hypnovel ampoule solution can be diluted with sodium chloride 0.9%, dextrose 5% and 10%, levulose 5%, Ringer's solution and Hartmann's solution in a mixing ratio 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 three days at 5°C).

## 7. MEDICINE SCHEDULE

Controlled Drug (C5).

## 8. SPONSOR

Roche Products (New Zealand) Limited  
PO Box 109113 Newmarket  
Auckland 1149  
NEW ZEALAND  
Medical enquiries: 0800 656 464

## NEW ZEALAND DATA SHEET

### 9. DATE OF FIRST APPROVAL

Hypnovel 5mg/mL: 25 May 1989  
Hypnovel 15mg/mL 04 April 1983

### 10. DATE OF REVISION OF THE TEXT

20 July 2017

#### Summary of Changes Table

Section Changed	Summary of new information
Throughout Data Sheet	Conversion to March 2017 Data Sheet Template Format including new section titles and re ordering of existing information..
	Additional warnings regarding hepatic encephalopathy, withdrawal symptoms, concomitant use with alcohol and opioids, paradoxical reactions and sleep apnoea
4.5	Additional information on drug interactions including concomitant use of benzodiazepines and opioids
4.6	Additional information regarding risks during pregnancy
4.7	Additional situations where alertness may be impaired
4.8	Additional adverse reactions
5.3	Addition of animal toxicology and pharmacology data relating to use in pregnancy