

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Hypnovel[®] 7.5mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: midazolam as the maleate

Tablets containing midazolam maleate equivalent to 7.5 mg of midazolam.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Midazolam 7.5mg tablets are white, oval, cylindrical, biconvex. Imprint above is ROCHE 7.5 and below is a single break bar. Dimensions of the tablets are length 11.6mm, width 6.1mm, thickness 3.6mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

- Short-term treatment of insomnia.

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

- Sedation in premedication before surgical or diagnostic procedures.

4.2 Dose and method of administration

In order to minimise the risk of dependence, benzodiazepines should only be prescribed after careful consideration of the indication and should be taken for the shortest possible duration. Generally the duration of treatment varies from a few days to a maximum of 2 weeks. Treatment with Hypnovel should not be terminated abruptly. The tapering-off process should be tailored to the individual. The necessity of continuing treatment should be closely monitored.

In certain cases extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.

Dose

The standard dosage range: 7.5-15 mg.

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Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded because of the increased risk of CNS adverse effects possibly including clinically relevant respiratory and cardiovascular depression.

Premedication

Adults

In premedication, 15mg of Hypnovel should be given 30-60 minutes before the procedure.

Special populations

Elderly and/or debilitated patients

In elderly and/or debilitated patients the recommended dose is 7.5 mg.

In elderly patients, Hypnovel showed a larger sedative effect; therefore they may be at increased risk of cardio-respiratory depression as well. Thus, Hypnovel should be used very carefully in elderly patients, and if needed, a lower dose should be considered.

Renal impairment

There is a greater likelihood of adverse drug reactions in patients with severe kidney disease. 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. The lowest dose should be considered, not exceeding 7.5 mg (see section 5.2, *Pharmacokinetics in Special Populations*).

Hepatic impairment

Patients with severe hepatic impairment should not be treated with Hypnovel tablets (see section 4.3). In patients with mild to moderate hepatic impairment, the lowest dose possible should be considered, not exceeding 7.5 mg (see section 5.2, *Pharmacokinetics in Special Populations*).

Paediatric Populations

Hypnovel tablets should not be given to children 12 years of age and under, because the available tablet strength does not allow for appropriate dosing in this patient population (see section 4.3).

Method of administration

Owing to the rapid onset of action, Hypnovel tablets should be taken immediately before going to sleep, and swallowed whole with fluid. Hypnovel can be taken at any time of the day, provided the patient is subsequently assured of at least 7-8 hours undisturbed sleep.

4.3 Contraindications

Hypnovel must not be used in patients with

- severe respiratory insufficiency;

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- severe hepatic impairment (benzodiazepines are not indicated to treat patients with severe hepatic impairment as they may cause encephalopathy),
- sleep apnoea syndrome;
- known hypersensitivity to benzodiazepines or to any component of the product;
- myasthenia gravis;

Hypnovel tablets should not be given to children, 12 years of age and under, because the available strength of tablets does not allow for appropriate dosing in this patient population

Hypnovel tablets should not be given to patients receiving concomitant therapy with very strong CYP3A inducers or inhibitors (ketoconazole, itraconazole, voriconazole, HIV protease inhibitors including ritonavir boosted formulations and the HCV protease inhibitors boceprevir and telaprevir (see section 4.5).

4.4 Special warnings and precautions for use

General

Information should be given to patients about warnings and precautions pertaining to Hypnovel.

Tolerance

Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines may develop after repeated use for a few weeks.

Duration of treatment

The duration of treatment with benzodiazepine hypnotics should be as short as possible (see section 4.2), and should not exceed 2 weeks. The tapering-off process should be tailored to the individual. Extension beyond this period should not take place without re-evaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued. There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Rebound insomnia

When discontinuing Hypnovel therapy, insomnia may reoccur, possibly with a higher severity than before starting treatment (“rebound insomnia”). Rebound insomnia, a transient syndrome, may be accompanied by other reactions including mood changes, anxiety and restlessness. The risk of rebound phenomena is greater after abrupt discontinuation of treatment. Therefore it is recommended that the dosage of Hypnovel is decreased gradually (see section 4.4 *Medicine Abuse and Dependence*).

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Amnesia

Hypnovel may cause anterograde amnesia which occurs most frequently within the first few hours after ingesting the product. In order to reduce the risk, patients should ensure that they are able to have an uninterrupted sleep of 7-8 hours.

Residual effects

Provided the oral dose of Hypnovel is not larger than 15 mg/day and the patient is assured of at least 7 to 8 hours undisturbed sleep, no residual effect is observed following oral administration of Hypnovel tablet in standard patients as confirmed by clinical observations using sensitive pharmacological methods.

Depression

Pre-existing depression may be unmasked during therapeutic use and withdrawal of benzodiazepine therapy. Benzodiazepines should not be used alone to treat depression or anxiety associated with depression as suicide may occur in such patients.

Psychiatric and 'paradoxical' reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety and more rarely, delusion, anger, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this be so, use of the medicine should be discontinued.

These effects are more likely to occur in the elderly.

Specific patient groups

In elderly and/or debilitated patients, as well as in patients with respiratory or cardiovascular impairment, the recommended dose is 7.5 mg. These patients may be more sensitive to the clinical side effects of midazolam like cardio-respiratory depression. Thus Hypnovel should be used very carefully in these patient populations and if needed a lower dose should be considered (see section 4.2 *Special Populations*).

Dosage instructions for patients with hepatic and/or renal impairment are described in section 4.2 *Special Populations*

Benzodiazepines are not recommended for the primary treatment of psychotic illness. Benzodiazepines should not be used alone to treat depression or anxiety associated with depression as suicide may occur in such patients.

Concomitant use of alcohol/CNS depressants

The concomitant use of Hypnovel with alcohol or/and 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 cardio-vascular depression (see section 4.5).

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Medical history of alcohol or drug abuse

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

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).

Co-medication with drugs that alter CYP3A activity

Midazolam pharmacokinetics is altered in patients receiving concomitant compounds that inhibit or induce CYP3A. Consequently, the clinical and adverse effects may be increased or decreased respectively (see section 4.5).

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Medicine Abuse and Dependence

Dependence

Use of Hypnovel may lead to the development of physical and psychological dependence. 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

Withdrawal symptoms may consist of headaches, diarrhoea, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or convulsions.

Since the risk of withdrawal phenomena/rebound phenomena is higher after abrupt discontinuation of treatment it is recommended that the dosage be decreased gradually (see sections 4.2 and 4.4).

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4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic Drug-Drug Interaction (DDI) (See Contraindications and General Warnings and Precautions)

Midazolam is almost exclusively metabolised by cytochrome P450 3A (CYP3A4 and CYP3A5), Inhibitors and inducers of CYP3A have the potential to 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 oral midazolam may be enhanced and prolonged and a lower dose of midazolam may be required. Conversely the effect of midazolam may be diminished and be short lived when co-administered with a CYP3A inducer and a higher dose of midazolam may be required.

In case of CYP3A induction and irreversible inhibition (so-called mechanism based inhibition), the effect on the pharmacokinetics of midazolam may persist for several days up to several weeks after administration of the CYP3A modulator. Examples of mechanism-based CYP3A inhibitors include antibacterial drugs (e.g., clarithromycin, erythromycin, isoniazid), anti-retrovirals (e.g. HIV protease inhibitors such as ritonavir, including ritonavir-boosted protease inhibitors; delavirdine, calcium channel blockers (e.g., verapamil, diltiazem), tyrosine kinase inhibitors (e.g., imatinib, lapatinib, idelalisib) or the oestrogen receptor modulator raloxifene.

Ethinylestradiol/norgestrel combined with norgestol or gestodene did not modify exposure to midazolam to a clinically significant degree.

Drugs that inhibit CYP3A

Classification of CYP3A inhibitors

CYP3A inhibitors can be classified according to the strength of their inhibitory effect and to the importance of the clinical modifications when they are administered concomitantly with oral midazolam:

Very strong inhibitors: Midazolam AUC increased > 10-fold. The following medicines fall into this category: e.g., ketoconazole, itraconazole, voriconazole, HIV protease inhibitors including ritonavir boosted protease inhibitors.

The combination of midazolam administered orally with very strong CYP3A inhibitors is contraindicated (see section 4.3).

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Strong inhibitors: Midazolam AUC increased by 5 to 10 fold. The following drugs fall into this category: e.g., high dose clarithromycin, tyrosine kinase inhibitors (such as idelalisib and the HCV protease inhibitors boceprevir and telaprevir).

Concomitant administration of oral midazolam and boceprevir and telaprevir is contraindicated (see section 4.3).

Moderate inhibitors: Midazolam AUC increased by 2 to 5-fold and C_{max} increased by 2 to 3-fold. The following medicines fall into this category: e.g., fluconazole, telithromycin, erythromycin, diltiazem, verapamil, nefazodone, NK1 receptor antagonists (aprepitant, netupitant, casopitant tabimoreline, posaconazole).

Patients receiving midazolam with strong or moderate CYP3A inhibitors require careful evaluation because the side effects of midazolam may be potentiated (see section 4.4 *Co-medication with drugs that alter CYP3A activity*).

Weak inhibitors: Midazolam AUC increased by 1.25 to < 2-fold or C_{max} increased by 1.25 to < 2-fold. The following medicines and herbals fall into this category: e.g., fentanyl, roxithromycin, cimetidine, ranitidine, fluvoxamine, bicalutamide, propiverine, everolimus, cyclosporine, simeprevir, grapefruit juice, echinacea purpurea, berberine as also contained in goldenseal.

The concomitant administration of midazolam with weak CYP3A inhibitors does not usually lead to a relevant change in the clinical effect of midazolam.

Medicines that induce CYP3A

Patients receiving a combination of midazolam with CYP3A inducers may require a higher midazolam dose in particular if midazolam is co-administered with strong CYP3A inducers. Strong CYP3A inducers ($\geq 80\%$ decrease in AUC) include: e.g., rifampin, carbamazepine, phenytoin, enzalutamide and mitotane with its long lasting CYP3A4-inducing effect while moderate CYP3A inducers (50-80% decrease in AUC) include St John's Wort and weak inducers (20-50% decrease in AUC) include efavirenz, clobazam, ticagrelor, vemurafenib, quercetin and Panax ginseng.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative / hypnotic agents including alcohol, is likely to result in increased sedative/hypnotic effects. Examples include opiates/opioids (when they are used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, antihistamines and centrally acting antihypertensive drugs. Midazolam decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

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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.

Enhanced side effects such as sedation and cardio-respiratory depression may also occur when midazolam is co-administered with any centrally acting depressants including alcohol. Alcohol should be avoided in patients receiving midazolam (see section 4.4 Concomitant use of alcohol/CNS depressants).

Drugs increasing alertness/memory like the AchE inhibitor physostigmine reversed the hypnotic effects of midazolam. Similarly, 250mg of caffeine partly reversed the sedative effect of midazolam.

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 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.

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

If the product is prescribed to a woman of childbearing potential, she should contact her physician regarding discontinuation of the product if she intends to become or suspects that she is pregnant.

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 took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

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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).

Breast-feeding

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 to use machines. Prior to receiving Hypnovel, 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. If sleep duration is insufficient or alcohol is consumed, the likelihood of impaired alertness may be increased (see Interactions with other Medicinal Products and other Forms of Interaction).

4.8 Undesirable effects

Post Marketing

Immune System Disorders: Hypersensitivity reactions and angioedema may occur in susceptible individuals.

Psychiatric Disorders: Confusional state, disorientation, emotional and mood disturbances. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. Changes in libido have been reported occasionally.

Depression: pre-existing depression may be unmasked during benzodiazepine use.

Paradoxical reactions such as restlessness, agitation, hyperactivity, nervousness, anxiety, irritability, aggressiveness, anger, nightmares, abnormal dreams, hallucinations, inappropriate behaviour and other adverse behavioural effects are known to occur. Should this be the case, the use of the drug should be discontinued. These effects are more likely to occur in the elderly.

Dependence: Use (even at therapeutic doses) may lead to the development of physical dependence. Abrupt discontinuation of the therapy may result in withdrawal or rebound phenomena including rebound insomnia, mood changes, anxiety and restlessness (see General Warnings and Precautions). Psychological drug dependence may occur. Abuse has been reported in poly-drug abusers.

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Nervous System Disorders: Drowsiness during the day, headache, dizziness, decreased alertness, ataxia. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. When used as premedication, this product may contribute to postoperative sedation. Anterograde amnesia may occur with therapeutic doses, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see General Warnings and Precautions).

Eye Disorders: Diplopia. This phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration.

Gastrointestinal Disorders: Gastrointestinal disturbances have been reported occasionally.

Skin and Subcutaneous Tissue Disorders: Skin reactions have been reported occasionally.

Musculoskeletal and Connective Tissue Disorders: Muscle weakness. This phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration.

General Disorders and Administration Site Conditions: Fatigue. This phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration.

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.

Respiratory Disorders: Respiratory depression was reported.

Cardiac Disorders: Cardiac failure including cardiac arrest was reported.

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

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Hypnovel is seldom life-threatening, if the drug is taken alone, but may lead to areflexia, apnea, hypotonia, hypotension, cardiorespiratory depression and rare cases of 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.

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Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

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

If CNS depression is severe consider the use of flumazenil (Anexate[®]), a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil for further information on the correct use of this medicine.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: N05CD08.

Mechanism of Action

Hypnovel has a hypnotic and sedative effect characterised by a rapid onset and short duration of action. It also exerts anxiolytic, anticonvulsant and muscle-relaxant effects. Hypnovel impairs psychomotor function after single and/or multiple doses but causes minimal haemodynamic changes.

The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines, the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.

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5.2 Pharmacokinetic properties

Absorption

Midazolam is absorbed rapidly and completely after oral administration. Due to the substantial first-pass effect, absolute bioavailability of oral midazolam ranges between 30-70%. Midazolam exhibits linear pharmacokinetics following oral doses of 7.5-20 mg.

After a single administration of a Hypnovel 15 mg tablet, maximum plasma concentrations of 70-120 ng/mL are reached within one hour. Food prolongs the time to peak plasma concentration by around one hour, indicating a reduced absorption rate of midazolam. The absorption half-life is 5-20 minutes.

Distribution

The tissue distribution of midazolam is very rapid and in most cases a distribution phase is not apparent or is essentially completed within 1-2 hours after oral administration. 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 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. Midazolam is not a substrate for drug transporters.

Biotransformation

The tissue distribution of midazolam is very rapid and in most cases a distribution phase is not apparent or is essentially completed within 1-2 hours after oral administration. 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 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.

Elimination

In young healthy volunteers, the elimination half-life of midazolam ranges between 1.5 to 2.5 hours. The elimination half-life of 1'-hydroxymidazolam is shorter than 1 hour [36, 37]; therefore after midazolam administration the concentration of the parent compound and the main metabolite decline in parallel. Less than 1% of the dose is recovered in urine as unchanged drug [31]. 60-80% of the dose is glucuronidated and excreted in the urine in the form of 1'-hydroxymidazolam conjugate. Midazolam is a non-accumulating medicine when given once daily. Repeated administrations of midazolam do not induce drug-metabolizing enzymes.

Pharmacokinetics in special populations

Elderly

In elderly male subjects over 60 years of age, the elimination half-life of midazolam was significantly prolonged by a factor of 2.5 as compared with younger male subjects. Total midazolam clearance was significantly reduced in male elderly subjects and the

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bioavailability of the oral tablet was significantly increased. However no significant differences were observed in elderly female compared to younger subjects.

Patients with hepatic impairment

The pharmacokinetics of midazolam were significantly modified in patients with chronic liver disease including advanced liver cirrhosis. In particular, as a consequence of a decreased liver clearance, the elimination half-life was prolonged and the absolute bioavailability of oral midazolam was significantly increased in cirrhotic patients compared to control.

Patients with renal impairment

The pharmacokinetics of unbound midazolam are not altered in patients with severe renal impairment. The major midazolam metabolite, 1'-hydroxymidazolam glucuronide, which is excreted through the kidney, accumulates in patients with severe renal impairment. This accumulation produces a prolonged sedation. Oral midazolam should therefore be administered carefully in patients with renal impairment and titrated to the desired effect (see section 4.2 *Special Populations*).

Obese patients

In obese patients the volume of distribution of midazolam is increased. As a consequence, the mean elimination half-life of midazolam is longer in obese than in non-obese patients (5.9 hours vs 2.3 hours). The oral bioavailability of the midazolam tablet was not different in obese patients compared to non-obese patients.

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

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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

Lactose 92.6mg, microcrystalline cellulose 70.3mg, pregelatinized starch 25mg, magnesium stearate 1.9mg, talc 1.25mg, hypromellose 2.5mg and the colourant titanium dioxide (E171) 1.25mg.

(Hypnovel tablets contain anhydrous lactose. See Warnings and Precautions for a warning relating to lactose monohydrate.)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30°C in the original container.
Protect from heat and light.

6.5 Nature and contents of container

Hypnovel tablets 7.5mg are supplied in blister packs of 100.

6.6 Special precautions for disposal <and other handling>

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

7. MEDICINE SCHEDULE

Controlled Drug (C5)

8. SPONSOR

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

9. DATE OF FIRST APPROVAL

27 November 1986

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..
4.3	Clarification of contraindication in children and in patients with severe hepatic impairment
4.4	Additional warnings regarding hepatic encephalopathy, withdrawal symptoms, concomitant use with alcohol and opioids, paradoxical reactions
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