

Data Sheet

Hypnovel[®]

Midazolam 7.5mg tablets

Hypnovel Tablet is a sleep-inducing agent belonging to the benzodiazepine class of therapeutic agents.

Description

Active ingredient

Midazolam as the maleate. Tablets containing midazolam maleate equivalent to 7.5 mg of midazolam.

Excipients

Lactose, microcrystalline cellulose, pregelatinized starch, magnesium stearate, methylhydroxypropyl cellulose, talc and the colourant titanium dioxide (E171).

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

Appearance

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.

Pharmacology

Mechanism of Action

Hypnovel is a sleep-inducing agent characterised by a rapid onset and short duration of action. It also exerts anxiolytic, hypnotic, anticonvulsant and muscle-relaxant effects. Hypnovel impairs psychomotor function after single and/or multiple doses but causes minimal haemodynamic changes. As for other benzodiazepines, it is believed that the effects of Hypnovel are mainly mediated via agonistic binding to gamma-aminobutyric acid receptors (GABA_A) in the CNS. The hypothesis is that benzodiazepines do not directly activate GABA_A receptors, but require the endogenous ligand, i.e. GABA, to exert the effects.

Pharmacokinetics

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%. The pharmacokinetics

of midazolam are linear in the 7.5-20mg oral dose range. 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 finished 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.

Metabolism

Midazolam is almost entirely eliminated by biotransformation. Less than 1% of the dose is recovered in urine as the unchanged substance. Midazolam is hydroxylated by cytochrome P450 CYP3A4 isozymes. Both isozymes, CYP3A4 and CYP3A5, are actively involved in the hepatic oxidative metabolism of midazolam. There are two main oxidized metabolites: 1'-hydroxymidazolam (also named α -hydroxymidazolam) and 4-hydroxymidazolam. 1'-hydroxymidazolam is the major urinary and plasma metabolite. 60-80% of the dose is glucuronidated and excreted in the urine in the form of the 1'-hydroxymidazolam conjugate. Plasma concentrations of 1'-hydroxymidazolam may reach 30-50% those of the parent compound. 1'-hydroxymidazolam is pharmacologically active and contributes significantly (about 34%) to the effects of oral midazolam. Previous investigation did not show a clinically relevant genetic polymorphism in the oxidative metabolism of midazolam.

Elimination

In young healthy volunteers, the elimination half-life of midazolam ranges between 1.5 to 2.5 hours. Midazolam is a non-accumulating medicine when given once daily. Repeated administrations of midazolam do not induce drug-metabolizing enzymes.

The elimination half-life of 1'-hydroxymidazolam is shorter than 1 hour.

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 2.5 as compared with younger male subjects. Total midazolam clearance was significantly reduced in male elderly subjects and the 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 midazolam are not altered in patients with chronic renal failure. However the major midazolam metabolite, 1'-hydroxymidazolam glucuronide, which is excreted through the kidney, accumulates in patients with severe chronic renal failure. This accumulation produces a prolonged sedation. Oral midazolam should therefore be administered carefully in patients with renal impairment.

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.

Indications

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.

Dosage and 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 reevaluation of the patient's status. 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.

Standard dosage

Dosage range: 7.5-15 mg.

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.

Special dosage instructions

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.

Patients with hepatic impairment

In patients with impaired liver function, the recommended dose is 7.5 mg. Hypnovel should be used very carefully in patients with hepatic impairment. If necessary a lower dose should be considered (see Pharmacokinetics in special populations).

Patients with renal impairment

In patients with severe renal impairment, accumulation of the major midazolam metabolite, 1'-hydroxymidazolam glucuronide, may occur resulting in more apparent and prolonged sedation possibly including clinically relevant respiratory and cardiovascular depression. Hypnovel should therefore be dosed carefully in this patient population. The recommended dose is 7.5 mg and when needed a lower dose should be considered.

Premedication

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

Contraindications

- Severe respiratory insufficiency;
- Severe hepatic insufficiency;
- Sleep apnea syndrome;
- Children;
- Use in patients with known hypersensitivity to benzodiazepines or to any component of the product;

- Myasthenia gravis;
- Concomitant therapy with ketoconazole, itraconazole, voriconazole, HIV protease inhibitors including ritonavir boosted protease inhibitors formulations (see Interactions with other Medicinal Products and other Forms of Interaction).

Warnings and Precautions

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 Dosage and Administration), 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 Drug Abuse and Dependence).

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 (see Undesirable effects).

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.

Psychiatric and 'paradoxical' reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggression, 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 Special dosage instructions).

Dosage instructions for patients with hepatic and/or renal impairment are described under Special dosage instructions.

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, clinically relevant respiratory and/or cardio-vascular depression (see Interactions with other Medicinal Products and other Forms of Interaction).

Medical history of alcohol or drug abuse

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

Co-medication with drugs that alter CYP3A activity

Midazolam pharmacokinetics are altered in patients receiving concomitant compounds that inhibit or induce CYP3A. Consequently, the clinical and adverse effects may be increased or decreased respectively (see Interactions with other Medicinal Products and other Forms of Interaction).

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, 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 Dosage and Administration, and Warnings and Precautions).

Effect on ability to drive or to use machines

Sedation, amnesia, impaired concentration and impaired muscular function adversely affect the ability to drive or to use machines. If sleep duration is insufficient, the likelihood of impaired alertness may be increased (see Interactions with other Medicinal Products and other Forms of Interaction).

Interactions with other Medicinal Products and other Forms of Interaction

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

Because midazolam is almost exclusively metabolised by cytochrome P450 3A (CYP3A), modulators of CYP3A have the potential to alter the plasma concentrations, and subsequently the clinical effects of midazolam.

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 few weeks after administration of the CYP3A modulator. Examples include: clarithromycin, erythromycin, HIV protease inhibitors, verapamil, diltiazem.

During co-administration with ethinylestradiol/norgestrel (mechanism based inhibitors) used as oral contraceptives, the exposure to midazolam is not significantly modified.

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 and C_{max} increased > 3-fold. The following medicines fall into this category: 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 Contraindications).

Strong inhibitors: midazolam AUC increased by 5 to 10 fold and C_{max} increased > 3-fold and **Moderate inhibitors:** midazolam AUC increased by 2 to 5-fold and C_{max} increased by 2 to 3-fold. The following medicines are identified as moderate inhibitors: fluconazole, clarithromycin, telithromycin, erythromycin, diltiazem, verapamil, nefazodone, aprepitant, tabimoreline.

The combination of midazolam with strong and moderate CYP3A inhibitors requires a careful evaluation of the patient's condition and could make the patient sensitive to the potential clinical side effects of midazolam (see General Warnings and Precautions).

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 are included in this category: posaconazole, roxithromycin, cimetidine, ranitidine, fluvoxamine, bicalutamide, propiverine, grapefruit juice, echinacea purpurea, 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. Well known strong CYP3A inducers include: rifampicin, carbamazepine, and phenytoin while moderate CYP3A inducers include efavirenz and St John's Wort.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative / hypnotic agents is likely to result in increased sedative/hypnotic effects. Such sedative/hypnotic agents include alcohol, 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.

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. The combined influence of alcohol and midazolam should be avoided (see General Warnings and Precautions). (Refer to the Overdosage section for a warning regarding other central nervous system depressants, including alcohol.)

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.

Use in Special Populations

Pregnancy

Insufficient data are available on midazolam to assess its safety during pregnancy. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance 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.

Nursing Mothers

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

Adverse Effects

Post Marketing

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

Psychiatric Disorders: Confusional state, emotional disorder. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. Libido disorders have been reported occasionally.

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

Paradoxical reactions such as restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur with benzodiazepines or benzodiazepine-like agents. 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. 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.

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 disappear with repeated administration.

Injury, Poisoning and Procedural Complications: An increased risk for falls and fractures has been reported in elderly benzodiazepine users.

Respiratory Disorders: Respiratory depression was reported.

Cardiac Disorders: Cardiac failure including cardiac arrest was reported.

Overdosage

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. 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, 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.

Medicine classification

Controlled Drug (C5)

Presentation and Storage

Hypnovel tablets 7.5mg in blister packs of 100.

Store below 30°C.

Protect from heat and light.



This medicine should not be used after the expiry date shown on the pack.

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