Dormicum®
Midazolam

1. DESCRIPTION

1.1. Therapeutic/ Pharmacologic Class of Drug

Dormicum tablet is a sleep-inducing agent belonging to the benzodiazepines.

ATC code: N05CD08

1.2. Type of Dosage Form

Tablets.

1.3. Route of Administration

Oral use.

1.4. Sterile / Radioactive Statement

Not applicable.

1.5. Qualitative and Quantitative Composition

Active ingredient: midazolam as the maleate. Tablets containing midazolam maleate equivalent to 7.5 mg and 15 mg of midazolam.

Excipients: described as per local requirements (Dormicum tablets contain unhydrolysed lactose. For warning related to lactose monohydrate, see 2.4.1 General (Warnings and Precautions)).

2. CLINICAL PARTICULARS

2.1. Therapeutic 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.

2.2. Dosage and Administration

Dosage and treatment duration should be as short as possible. Generally the duration of treatment varies from a few days to a maximum of 2 weeks. The tapering-off process should be tailored to the individual. Treatment with Dormicum should not be terminated abruptly (see 2.4.2 Drug Abuse and Dependence).

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. Owing to the rapid onset of action Dormicum tablets should be taken immediately before going to sleep, and swallowed whole with fluid. Dormicum can be taken 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 addiction, respiratory and cardiovascular depression.

Premeicadation

In premedication, Dormicum should be given 30–60 minutes before the procedure.

2.2.1. Special Dosage Instructions

Elderly and/or debilitated patients

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

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

Patients with hepatic impairment

In patients with severe hepatic impairment should not be treated with Dormicum (see section 2.3 Contraindications). In patients with mild to moderate hepatic impairment, the lowest dose possible should be considered; not exceeding 7.5mg (see 2.3.5 Pharmacokinetics in Special Populations).

Patients with renal impairment

In patients with severe renal impairment, Dormicum may be accompanied by more pronounced and prolonged sedation possibly including clinically relevant respiratory and cardiovascular depression. Dormicum 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 3.2.5 Pharmacokinetics in Special Populations).

2.3. Contraindications

Dormicum must not be used in patients with:

- Severe respiratory insufficiency;
- Severe hepatic impairment (benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may cause encephalopathy);
- Sleep apnea syndrome;

- Known hypersensitivity to benzodiazepines or to any of their components;
- Mysyathria gravis;

Dormicum tablets should not be given to children because the available strengths of tablets do not allow for appropriate dosing in this patient population.

Dormicum tablets should not be given to patients receiving concomitant therapy with very strong CYP3A inducers or inhibitors (ketonazole, itraconazole, voriconazole, HIV protease inhibitors including ritonavir-boosted formulations and the HCV protease inhibitors boceprevir and telaprevir (see 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).

2.4. Warnings and Precautions

2.4.1. General

Information should be given to the patients about following warnings and precautions.

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 2.2 Dosage and Administration), and should not exceed 2 weeks. The tapering-off process should be tailored to the individual. Extention beyond this period should not take place without re-evaluation of the patient’s status.

Rebound insomnia

When discontinuing Dormicum therapy, insomnia may recur, 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 increased when these activities may be resumed.

Anxiety

Dormicum 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 sleep undisturbed for 6 hours after abrupt discontinuation of treatment. Therefore, it is recommended that the dosage of Dormicum is decreased gradually (see 2.4.2 Drug Abuse and Dependence).

Amnesia

Dormicum 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 sleep undisturbed for 6 hours after abrupt discontinuation of treatment. Therefore, it is recommended that the dosage of Dormicum is decreased gradually (see 2.4.2 Drug Abuse and Dependence).

Psychiatric and ‘paradoxical’ reactions

Paradoxic 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 drug 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 Dormicum should be used very carefully in these patient populations and if needed a lower dose should be considered (see 2.2.1 Special Dosage Instructions).

Dormicum tablets should be used very carefully in these patient populations and titrated for the desired effect. The lowest dose should be considered, not exceeding 7.5 mg, (see 2.2.1 Special Dosage Instructions).

Concomitant use of alcohol / CNS depressants

The concomitant use of Dormicum with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Dormicum. This may include severe sedation that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression (see 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).

Medical history of alcohol or drug abuse

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

Co-medication with drugs that later CYP3A activity

Midazolam pharmacokinetics is altered in patients receiving concomitant therapy with very strong CYP3A inducers (see 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction). Consequently the clinical and adverse effects may be increased or decreased respectively (see 2.4.4 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 medicinal product.

2.4.2. Drug Abuse and Dependence

Dependence

Use of Dormicum may lead to the development of physical and psychological dependence. The risk of dependence increases with the dose and duration of treatment; it is also greater in patients with a medical history of alcohol or drug abuse.

Withdrawal

Withdrawal symptoms may consist of headaches, diarrhea, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: severe insomnia, increased or decreased respectively (see 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).

2.4.3. Ability to Drive and Use Machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. Prior to receiving Dormicum, 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 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).

2.4.4. Interactions with other Medicinal Products

2.4.4.1. Pharmacokinetic Drug-Drug Interaction (DDI) (See 2.3 Contraindications and 2.4.1 General (Warnings and Precautions))

Some 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 stronger and also longer lasting and a lower dose may be required. Conversely the effect of midazolam may be weaker and last shorter when co-administered with a CYP3A inducer and a higher dose 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 inducing/ inhibiting agent. Examples of mechanism-based CYP3A inhibitors include antibacterial drugs (e.g., clarithromycin, erythromycin, isonazid), anti-retrovirals (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 bicalutamide.

Ethinylestradiol combined with norgestrel 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 used concomitantly with oral midazolam:

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

- Moderate inhibitors: Combination of midazolam administered orally with very strong CYP3A inhibitors is contraindicated (see 2.3 Contraindications).
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 in treatment were observed.
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 pharmacologically mildly active 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 and titrated to the desired effect (see section 2.2.1 Special Dosage Instructions).

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.

4. PHARMACEUTICAL PARTICULARS

4.2. Storage
Dormicum Film-Coated Tablets 15 mg: Store in the original container and keep blisters in outer carton in order to protect from light.

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

5. PACKS

| Tablets 7.5 mg (white) | 10 |
| Tablets 15 mg (blue)   | 10, 20, 30, 100 |

Not all pack sizes are available for sale.

| Medicine: keep out of reach of children |

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