Dormicum®
Midazolam Maleate BP

1. DESCRIPTION
1.1 Therapeutic / Pharmacologic Class of Drug: Dormicum® Tablet is a sleep-inducing agent belonging to the benzodiazepines.
1.2 Type of Dosage Form: Tablets.
1.3 Route of Administration: Oral use.
1.4 Sterile / Radioactive Statement: Not applicable.
1.5 Composition: Each tablet contains Midazolam 7.5 mg as Midazolam Maleate BP.

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
Duration of treatment 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 reevaluation 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 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.

Premedication: 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: 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 7.5 mg. (see 3.2.5 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 impairment as they may cause encephalopathy).
- Sleep apnea syndrome.
- Known hypersensitivity to benzodiazepines or to any of their formulation excipients.
- Myasthenia gravis.

Dormicum® tablets should not be given to children, 12 years of age and under, 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 (ketoconazole, itraconazole, voriconazole, HIV protease inhibitors including ritonavir-boosted formulations, and the HCV protease inhibitors boceprevir and telaprevir (see 2.4.5 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. Extension beyond this period should not take place without reevaluation of the situation.

Rebound insomnia: When discontinuing Dormicum® 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 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 have an uninterrupted sleep of 7-8 hours (see 2.6 Undesirable effects).

Residual effects: Provided the oral dose of Dormicum® 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 Dormicum® tablet in standard patients as confirmed by clinical observations using sensitive pharmacological methods.

Psychiatric and 'paradoxical' reactions: Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, and more rarely, delusion, anger, nightmares, hallucinations, psychoses, 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). 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 Dormicum® with alcohol or /and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Dormicum® possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardio-vascular depression (see 2.4.5 Interactions with other Medicinal Products and other Forms of Interactions).

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 alter CYP3A activity: Midazolam pharmacokinetics is altered in patients receiving concomitantly compounds that inhibit or induce CYP3A. Consequently the clinical and adverse effects may be increased or decreased respectively (see 2.4.5 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.

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 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, diarrhea, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or convulsions. Since the risk of withdrawal phenomena / rebound insomnia is higher after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually {see 2.2 Dosage and
inappropriate behaviour and other adverse behavioural effects are known to occur. Should this be the case, 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 2.4.1 General (Warnings and Precautions)}. Psychological drug dependence may occur. Abuse has been reported in poly-drug abusers.

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: 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.

2.6.2.1 Laboratory Abnormalities
No text.

2.7 Overdose
Symptoms: Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Dormicum® is seldom life-threatening, if the drug is taken alone, but may lead to areflexia, apnea, hypotonia, hypotension, cardiorespiratory depression and rare cases to 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 (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 drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil (Anexate®), for further information on the correct use of this drug.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 Pharmacodynamic Properties
3.1.1 Mechanism of Action
Dormicum® has a hypnotic and sedative effect characterized by a rapid onset and short duration of action. It also exerts anxiolytic, anticonvulsant and muscle-relaxant effects. Dormicum® 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.

3.1.2 Clinical / Efficacy Studies
No text.

3.2 Pharmacokinetic Properties
3.2.1 Absorption
Midazolam is absorbed rapidly and completely after oral administration. Due to the substantial first-pass effect, the absolute bioavailability of oral midazolam ranges 30-70%. Midazolam exhibits linear pharmacokinetics following oral doses of 7.5-20 mg. After a single administration of a Dormicum® 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, pointing to a reduced absorption rate of midazolam. The absorption half-life is 5-20 minutes.

3.2.2 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 0.7-1.21 / kg. 96-98% of midazolam is bound to plasma

Administration and 2.4.1 General (Warnings and Precautions)}.

2.4.3 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 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 2.4.5 Interactions with other Medicinal Products and other Forms of Interaction).

2.4.4 Laboratory Tests
No text.

2.4.5 Interactions with other Medicinal Products and other Forms of Interaction
Pharmacokinetic Drug-Drug Interaction (DDI) {See 2.3 Contraindications and 2.4.1 General (Warnings and Precautions)}. Midazolam is almost exclusively metabolized 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 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 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. Ethinyloestradiol 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 administered 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.

Combination of midazolam administered orally with very strong CYP3A inhibitors is contraindicated (see 2.3 Contraindications).
- *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 2.3 Contraindications).
- *Moderate inhibitors:* Midazolam AUC increased by 2 to 5-fold. The following drugs fall into this category: e.g., fluconazole, clarithromycin, 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 2.4.1 General (Warnings and Precautions)}.
- *Weak inhibitors:* Midazolam AUC increased by 1.25 to < 2-fold. The following drugs 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. Concomitant administration of midazolam with weak CYP3A inhibitors does not usually lead to a relevant change of midazolam clinical effect.

Drugs 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 (≥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. 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 2.4.1 General (Warnings and Precautions)}. See section 2.7 Overdose for warning of other central nervous system depressants, including alcohol. Drugs increasing alertness / memory like the AchE inhibitor physostigmine reversed the hypnotic effects of midazolam. Similarly, 250 mg of caffeine partly reversed the sedative effect of midazolam.

2.5 Use in Special Populations
2.5.1 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. An increased risk of congenital malformation 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.

2.5.2 Labour and Delivery
See 2.5.1 Pregnancy.

2.5.3 Nursing Mothers
Since midazolam passes into breast milk, Dormicum® should not be administered to breast-feeding mothers.

2.5.4 Pediatric Use
See 2.3 Contraindications.

2.5.5 Geriatric Use
See 2.2.1 Special Dosage Instructions and 2.4.1 General (Warning and Precautions).

2.5.6 Renal Impairment
There is a greater likelihood of adverse drug reactions in patients with severe kidney disease. (see 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations).

2.5.7 Hepatic Impairment
See 2.2.1 Special Dosage Instructions and 2.3 Contraindications.

2.6 Undesirable Effects
2.6.1 Clinical Trials
No text.

2.6.1.1 Laboratory Abnormalities
No text.

2.6.2 Post-Marketing
Immune System Disorders: Hypersensitivity reactions and angioedema may occur in susceptible individuals.

Psychiatric Disorders: Confusional state, disorientation, emotionaland 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,
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.

3.2.3 Metabolism
Midazolam is almost entirely eliminated by biotransformation. Midazolam is hydroxylated by Cytochrome P450, CYP3A isozymes. Both isozymes, CYP3A4 and also CYP3A5 are actively involved in the two key pathways for the hepatic oxidative metabolism of midazolam. The metabolism of midazolam after oral administration relies to a comparable extent on intestinal CYP3A and on hepatic CYP3A. There are two main oxidized metabolites 1'-hydroxymidazolam (also named α-hydroxymidazolam) and 4-hydroxymidazolam. 1'-hydroxymidazolam is the major urinary and plasma metabolite. 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.

3.2.4 Elimination
In young healthy volunteers, the elimination half-life of midazolam ranges from 1.5 to 2.5 hours. The elimination half-life of 1'-hydroxymidazolam is shorter than 1 hour, 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. 60-80% of the dose is glucuronidated and excreted in the urine in the form of 1'-hydroxymidazolam conjugate. Midazolam is a non-accumulating drug when given once daily. Repeated administrations of midazolam do not induce drug-metabolizing enzymes.

3.2.5 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 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 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.

3.3 Preclinical Safety
3.3.1 Carcinogenicity
No text.

3.3.2 Mutagenicity
No text.

3.3.3 Impairment of Fertility
No text.

3.3.4 Teratogenicity
No text.

3.3.5 Other
No text.

4. PHARMACEUTICAL PARTICULARS
4.1 Storage
This medicine should not be used after the expiry date (EXP) shown on the pack.

Do not store above 30ºC, protect from light & moisture.

Medicine: Keep out of reach of children.

4.2 Special Instructions for Use, Handling and Disposal
No text.

5. Packs
Dormicum® 7.5 mg Tablet: Each box contains 30 (3 x 10's) tablet.

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RADIANT PHARMACEUTICALS
Manufactured by
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B-34 & B-46, BSCIC Industrial Estate
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ডরমিকাম®
মিডাজোলাম মেলিয়েট বিপি

উপস্থাপনঃ
প্রতি ট্যাবলেটে আছে মিডাজোলাম মেলিয়েট বিপি যা ৭.৫ মিগ্রা মিডাজোলাম এর সমতুল্য।

তাই ওষুধ প্রত্যাহার পরবর্তী অবাঞ্চিত প্রতিক্রিয়া এড়ানোর জন্য ওষুধ ব্যবহারের মাত্রা ধীরে ধীরে কমিয়ে এনে ওষুধ সেবন বন্ধ করতে হবে।