SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

Dormicum® 7,5 mg tablets

Dormicum® 15 mg tablets

COMPOSITION

Dormicum tablets contain midazolam maleate equivalent to 7,5 mg or 15 mg midazolam.

Excipients:

7,5 mg Tablets: lactose anhydrous, hypromellose, magnesium stearate, microcrystalline cellulose, pregelatinised starch, purified water, talc and titanium dioxide (CI 77891).

15 mg Tablets: carmellose sodium, lactose anhydrous, hypromellose, indigo carmine (CI 73015), macrogol, magnesium stearate, maize starch, microcrystalline cellulose, polyacrylate dispersion, purified water, talc and titanium dioxide (CI 77891).

PHARMACOLOGICAL CLASSIFICATION

A 2.2 Sedatives, hypnotics

PHARMACOLOGICAL ACTION

Midazolam is a benzodiazepine; it has anxiolytic, sedative and hypnotic characteristics as well as possible muscle relaxant and anticonvulsant characteristics.

Pharmacodynamics

Mechanism of action: Midazolam 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. Midazolam impairs psychomotor function after single and/or multiple doses.

It is believed that the effects of midazolam are mainly mediated via agonistic binding to gamma-aminobutyric acid receptors ($GABA_A$) in the central nervous system. 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: Due to the substantial first-pass effect, the absolute bioavailability of oral midazolam is linear only in the 7,5 - 20 mg oral dose range.

After a single administration of a midazolam 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.

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 minimal passage of midazolam into cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta and to enter foetal circulation. Midazolam is found in human milk.

Metabolism**:** Midazolam is almost entirely eliminated by biotransformation. Less than 1 % of the dose is recovered in the urine as unchanged drug. Midazolam is hydroxylated by cytochrome P450, CYP3A isozymes. Both isozymes, CYP3A4 and also CYP3A5 are actively involved in the hepatic oxidative metabolism of midazolam.

There are two main oxidised 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 form of 1'-hydroxymidazolam conjugate. Plasma concentrations of 1'-hydroxymidazolam may reach 30 - 50 % of 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 healthy young volunteers, the elimination half-life of midazolam ranges between 1,5 to 2,5 hours. Repeated administrations of midazolam do not induce drug-metabolising 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 of 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.

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 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 main 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

Dormicum is indicated:

- In short-term treatment of insomnia, when the disorder is severe, disabling, or subjecting the individual to extreme distress.
- In anaesthetic premedication.

CONTRAINDICATIONS

- Use in patients with known hypersensitivity to benzodiazepines or to any component of the product.
- Myasthenia gravis.
- Dormicum is not recommended for the primary treatment of psychotic illness.
- Dormicum, as a single treatment regime, should not be used to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).
- Severe hepatic impairment.
- Dormicum is not suitable for use in children.
- Respiratory insufficiency.
- Sleep apnoea syndrome.
- Concomitant therapy with ketoconazole, itraconazole, voriconazole, HIV protease inhibitors including ritonavir boosted protease inhibitors formulations. See INTERACTIONS.
- Galactose intolerance.

WARNINGS AND SPECIAL PRECAUTIONS

Tolerance: Some loss of efficacy of the hypnotic effects of short acting benzodiazepines, such as Dormicum, may develop after repeated use for a few weeks.

Dependence: Use of Dormicum may lead to physical and psychological dependence. Discontinuation of therapy may result in withdrawal or rebound phenomena. Psychological dependence may occur. Abuse has been reported in poly-drug abusers.

Once physical dependence has developed, abrupt termination will be accompanied by withdrawal symptoms. These 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 epileptic seizures.

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 DOSAGE AND DIRECTIONS FOR USE and INTERACTIONS.

***Rebound insomnia*:** A transient syndrome, whereby the symptoms that led to treatment with Dormicum, recur in an enhanced form, may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.

Duration of treatment: The duration of treatment should be as short as possible. See DOSAGE AND DIRECTIONS FOR USE, 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 explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while Dormicum is being discontinued.

There are indications that, in the case of Dormicum, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Amnesia: Dormicum may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore, to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7 - 8 hours. See SIDE EFFECTS.

Psychiatric and "paradoxical" reactions: Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur when using Dormicum and other benzodiazepine-like agents. Should this occur Dormicum should be discontinued. They are more likely to occur in children and 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 Dormicum like cardio-respiratory depression. Thus Dormicum should be used very carefully in these patient populations and if needed a lower dose should be considered.

Benzodiazepines, including Dormicum, are not indicated for the treatment of patients with severe hepatic insufficiency as it may precipitate encephalopathy.

Dormicum is not recommended for the primary treatment of psychotic illness.

Dormicum should not be used alone to treat depression or anxiety associated with depression as suicide may occur in such patients.

The concomitant use of Dormicum with alcohol or/and central nervous system depressants should be avoided. Such concomitant use increases the clinical effects of Dormicum possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression. See INTERACTIONS.

Dormicum should be used with extreme caution in patients with a history of alcohol or drug abuse.

Co-medication with medicines that alter CYP3A activity: Dormicum 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 INTERACTIONS.

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

Effects on ability to drive or to use machines: Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. See INTERACTIONS.

INTERACTIONS

Pharmacokinetic Interaction*:* See CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS.

Because Dormicum 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 Dormicum.

When co-administered with a CYP3A inhibitor, the clinical effects of oral Dormicum may be stronger and also last longer and a lower dose may be required. Conversely the effect of Dormicum 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 reversible inhibition (so-called mechanism based inhibition), the effect of the pharmacokinetics of Dormicum may persist for several days up to a few weeks after administration of the CYP3A modulator. Examples include: clarithromycin, erythromycin, HIV protease inhibitors, verapamil, diltiazem.

During co-administration with ethinyl estradiol/norgestrol (mechanism based inhibitors) used as oral contraceptives, the exposure to Dormicum 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 Dormicum.

Very strong inhibitors: Dormicum 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.

Combination of Dormicum administered orally with very strong CYP3A inhibitors is contraindicated. See CONTRAINDICATIONS.

Strong inhibitors: Dormicum AUC increased by 5 to 10-fold and C_{max} increased > 3-fold.

Moderate inhibitors: Dormicum 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.

Combination of Dormicum with strong and moderate CYP3A inhibitors requires a careful evaluation of the patient condition that could make the patient in particular sensitive to the potential clinical side effects of Dormicum. See WARNINGS AND SPECIAL PRECAUTIONS.

Weak inhibitors: Dormicum 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.

Concomitant administration of Dormicum with weak CYP3A inhibitors does usually not lead to a relevant change of Dormicum clinical effect.

Medicines that induce CYP3A: Patients receiving a combination of Dormicum with CYP3A inducers may require a higher Dormicum dose in particular if Dormicum 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 Interactions

The co-administration of Dormicum 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 medicines. Dormicum decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

Enhanced side effects such as sedation and cardio-respiratory depression may also occur when Dormicum is co-administered with any centrally acting depressants including alcohol. The combined influence of alcohol and Dormicum should be avoided. See WARNINGS AND SPECIAL PRECAUTIONS.

See KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT for warning of other central nervous system depressants, including alcohol.

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

PREGNANCY AND LACTATION

Insufficient data are available on Dormicum to assess its safety during pregnancy. Benzodiazepines, including Dormicum, should be avoided in pregnancy unless there is no safer alternative.

If Dormicum is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of Dormicum if she intends to become or suspects that she is pregnant.

If, exceptionally, it is considered by a physician that administration of Dormicum during the last three months of pregnancy, or during labour, is essential, effects on the neonate such as hypothermia, hypotonia and moderate respiratory depression can be expected, due to the pharmacological action of the product.

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.

Dormicum is excreted in breast milk. Do not use during lactation.

DOSAGE AND DIRECTIONS FOR USE

Patients should be advised to take Dormicum for short-term treatment only.

Generally the duration of treatment varies from a few days to a maximum of two weeks. The tapering off process should be tailored to the individual. Treatment with Dormicum should not be terminated abruptly.

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. Dormicum should be taken just before going to bed.

Dose for insomnia

Adults - Initial dose: 7,5 mg

Dosage range: 7,5 mg - 15 mg

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded because of the increased risk of unacceptable CNS adverse effects, possibly including

clinically relevant respiratory and cardiovascular depression. Patients with impaired liver function should have a reduced dose.

In premedication, a 15 mg Dormicum tablet should be given orally, 30 - 60 minutes before the operation, unless the parenteral route is preferred.

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 impaired hepatic impairment: In patients with impaired liver function the recommended dose is 7,5 mg. Dormicum should be used very carefully in patients with hepatic impairment. If necessary a lower dose should be considered.

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. Dormicum 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.

SIDE 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 Dormicum should be discontinued. These effects are more likely to occur in the elderly.

Dependence: Use (even at therapeutic doses) may lead to development of physical dependence: discontinuation of therapy may result in withdrawal or rebound phenomena including rebound insomnia, mood changes, anxiety and restlessness. See WARNINGS AND SPECIAL PRECAUTIONS. Psychic drug dependence may occur. Abuse have been reported in poly-drug users.

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 post-operative sedation.

Anterograde amnesia may occur with therapeutic doses, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour. See WARNINGS AND SPECIAL 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: An increased risk for falls and fractures have been reported in the elderly benzodiazepine users.

Respiratory Disorders: Respiratory depression was reported.

Cardiac Disorders: Cardiac failure including cardiac arrest was reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms: Benzodiazepines, including Dormicum, commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Dormicum is seldom life-threatening, if the medicine is taken alone, but may lead to areflexia, apnoea, hypotonia, hypotension, cardio-respiratory 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, including Dormicum, 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 cardio-respiratory 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 affects 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 package insert for flumazenil, for further information on the correct use of this product.

IDENTIFICATION

Dormicum 7,5 mg: White to almost white, oval, cylindrical, biconvex film-coated tablets. Imprint: upper surface 'Roche 7,5'; lower surface scored.

Dormicum 15 mg: Grey-blue, oval, cylindrical, biconvex, film-coated tablets. Imprint: upper surface 'Roche 15'; lower surface scored.

PRESENTATION

Dormicum 7,5 mg tablets: blister packs of 20's, 30's and 90's.

Dormicum 15 mg tablets: blister packs of 20's, 30's and 90's.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Protect from light and moisture. Store in outer container until required for use. Store out of reach of children.

REGISTRATION NUMBERS

Dormicum 7,5 mg tablets: 27/2.2/0078

Dormicum 15 mg tablets: R/2.2/123

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

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Illovo

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Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

DATE OF PUBLICATION OF THE PACKAGE INSERT

Registration: 7,5 mg – Jan 1993; 15 mg – Aug 1984

Last revision: 1 October 2010