SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

Dormicum® 5 mg/5 mℓ ampoules

Dormicum® 15 mg/3 mℓ ampoules

Dormicum® 50 mg/10 mℓ ampoules

COMPOSITION

Dormicum contains 5 mg/5 mℓ, 15 mg/3 mℓ or 50 mg/10 mℓ midazolam per ampoule.

(8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a] [1,4] benzodiazepine) as the hydrochloride, per 5 mℓ, 3 mℓ or 10 mℓ ampoule respectively.

Excipients: sodium chloride, hydrochloric acid, sodium hydroxide, water for injections.

PHARMACOLOGICAL CLASSIFICATION

A 2.2 Sedatives, hypnotics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Midazolam, is a derivative of the imidazo-benzodiazepine group and has actions similar to those of the benzodiazepine class. The free base is a lipophilic substance with low solubility in water.

The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables midazolam to form water-soluble salts with acids. The pharmacological action of midazolam is characterised by rapid onset of action, rapid metabolic transformation and short duration.

Midazolam possesses sedative, sleep-inducing, anxiolytic, anticonvulsant effects and has a muscle-relaxant effect. After *IM* or *IV* administration, anterograde amnesia occurs.

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 gamma-aminobutyric acid (GABA) receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the post-synaptic transmembrane chloride ion flux.

Pharmacokinetic properties

Absorption after IM injection

Maximum plasma concentrations are reached within 30 minutes. Absolute bioavailability after *IM* injection is over 90 %.

Distribution

The course of the plasma concentrations shows a short distribution phase of 5 - 15 minutes, followed by an elimination phase. The volume of distribution at steady-state is 0,7 - 1,2 ℓ/kg. 96 - 98 % of midazolam is bound to plasma proteins, mainly albumin. Midazolam passes into the cerebro-spinal fluid and crosses the placenta slowly and enters foetal circulation. It also appears in breast milk. Midazolam is not a substrate for medicine transporters.

Metabolism

Midazolam is mostly eliminated by biotransformation. Midazolam is hydroxylated by the cytochrome P450 3A4 isozyme**.** α-Hydroxymidazolam, an active metabolite, is the major urinary and plasma metabolite. 60 - 80 % of the dose is excreted in urine as glucuroconjugated α-hydroxymidazolam. Plasma concentrations of α-hydroxymidazolam are 12 % of those of the parent compound. The fraction of the dose extracted by the liver has been estimated to be 30 - 60 %. α-Hydroxymidazolam is pharmacologically active, but contributes about 10 % to the effects of intravenous midazolam. There is no evidence of genetic polymorphism in the oxidative metabolism of midazolam.

Elimination

The elimination half-life of the parent substance is between 1,5 and 2,5 hours, Plasma clearance is in the region of 300 - 500 mℓ per minute in young healthy volunteers. When midazolam is given by *IV* infusion, its elimination kinetics does not differ from those following bolus injections. After

48 hours infusion elimination may be significantly prolonged. About 50 to 70 % of midazolam is eliminated by the kidneys in the form of a conjugate of the α-hydroxy-metabolite. Less than 1 % of the dose is recovered in urine as unchanged drug. The elimination half-life of the metabolite is shorter than 1 hour. Repeated administrations of midazolam do not induce drug-metabolising enzymes.

Pharmacokinetics in Special Populations

Elderly: In adults over 60 years of age, the elimination half-life may be prolonged by 8 - 9 hours.

Children: The elimination half-life after *IV* administration is shorter in children 3 - 10 years compared with that in adults. The difference is consistent with an increased metabolic clearance in children.

Neonates: In neonates the elimination half-life is on average 6 - 12 hours, probably due to liver immaturity, and the clearance is reduced. Neonates with asphyxia-related hepatic and renal impairment are at risk of generating unexpectedly high serum midazolam concentrations due to a significantly decreased and variable clearance. See WARNINGS AND SPECIAL PRECAUTIONS.

Obese: The mean half-life is greater in obese than non-obese patients (8,4 vs 2,7 hours). This is due to an increase of approximately 50 % in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese than non-obese patients.

Patients with hepatic impairment: The elimination half-life in cirrhotic patients may be longer and the clearance smaller, compared to those in healthy volunteers. See WARNINGS AND SPECIAL PRECAUTIONS.

Patients with renal impairment: The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

Critically ill patients: The elimination half-life of midazolam is prolonged in the critically ill.

Patients with cardiac insufficiency: The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects. See WARNINGS AND SPECIAL PRECAUTIONS.

INDICATIONS

- **Conscious (basal) sedation** before diagnostic or therapeutic procedures with, or without, local anaesthesia (*IV* administration).
- **Anaesthesia:**
  - Premedication before induction of anaesthesia, as part of a balanced technique.
  - Induction and maintenance of anaesthesia.
  - As an induction agent in adults in inhalation anaesthesia or a sedative component in combined anaesthesia, including total intravenous anaesthesia (*IV* injection, *IV* infusion).
- **Sedation in intensive care units**: Long-term sedation in intensive care units (*IV* administration as bolus injection or continuous infusion).

CONTRAINDICATIONS

Hypersensitivity to benzodiazepines or to any component of the product. Also see PREGNANCY AND LACTATION.

WARNINGS AND SPECIAL PRECAUTIONS

Dormicum ampoules should be used only when resuscitation facilities are available, as *IV* administration of Dormicum may depress myocardial contractility and cause apnoea.

When Dormicum is given with potent analgesics, the latter should be administered first so that the sedative effects of Dormicum can be safely titrated on top of any sedation caused by the analgesic.

Severe cardio-respiratory adverse events may occur. These include respiratory depression, apnoea and/or cardiac arrest. Such life-threatening incidents are more likely to occur in adults over 60 years of age, those with pre-existing respiratory insufficiency or impaired cardiac

function and in paediatric patients with cardiovascular instability, particularly when the injection is given too rapidly or when a high dosage is administered.

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

Conscious sedation should be provided by a medical practitioner experienced in the use of this technique.

Premedication: When Dormicum is used for premedication, adequate observation of the patient after administration is mandatory as inter-individual sensitivity varies and symptoms of overdose may occur.

High-risk patients: Special caution should be exercised when administering Dormicum parenterally to patients representing a higher risk group:

- adults over 60 years of age
- debilitated or chronically ill patients
- patients with impaired respiratory insufficiency
- patients with impaired kidney function
- patients with impaired hepatic function (Dormicum may precipitate or exacerbate encephalopathy in patients with severe hepatic impairment)
- patients with impaired cardiac function
- paediatric patients with cardiovascular instability

These higher risk patients require lower dosages. See DOSAGE AND DIRECTIONS FOR USE and should be continuously monitored for early signs of alterations of vital functions.

Particular care should be taken when administering Dormicum to a patient with myasthenia gravis, owing to pre-existing muscle weakness.

After parenteral administration of Dormicum, patients should not be discharged from hospital for at least four hours. They must then be accompanied by a responsible person. Prior to receiving Dormicum, patients should be warned not to drive a vehicle or operate machinery for at least twelve hours thereafter.

Special care must be taken when Dormicum is used during labour and delivery, as high single doses may produce respiratory depression, irregularities in the foetal heart rate and hypotonia, poor sucking and hypothermia in the neonate.

Usage in Pre-term Infants and Neonates

Due to an increased risk of apnoea, extreme caution is advised when sedating pre-term and former pre-term patients without trachea intubation. Careful monitoring of respiratory rate and oxygen saturation is required, see DOSAGE AND DIRECTIONS FOR USE.

Rapid injection should be avoided in neonates as they are vulnerable to profound and/or prolonged respiratory effects of Dormicum.

Dormicum administered rapidly as an intravenous injection (less than 2 minutes) has been associated with severe hypotension in neonates, particularly when the patient has also received fentanyl. Likewise, severe hypotension has been observed in neonates receiving a continuous infusion of midazolam who then receive a rapid intravenous injection of fentanyl. Seizures have been reported in several neonates following rapid intravenous administration.

The neonate also has reduced and/or immature organ function and is vulnerable to profound and/or prolonged respiratory effects of Dormicum.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small term infants. There have been rare reports of death, primarily in pre-term infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications (including Dormicum) containing this preservative must take into account the total amount of benzyl alcohol administered. The recommended dosage range of Dormicum for preterm and term infants includes amounts of benzyl alcohol well below that associated with toxicity; however, the amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this

preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources.

Special Precautions

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

Tolerance: Loss of efficacy has been reported when Dormicum has been used as prolonged sedation in intensive care units (ICU).

Dependence: When Dormicum is used in long-term sedation physical dependence on Dormicum may develop, which is related to the dose and duration of treatment. See SIDE EFFECTS.

Withdrawal symptoms: Abrupt termination of the treatment after prolonged administration will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, diarrhoea, muscle pain, extreme anxiety, tension, sleep disturbances, restlessness, confusion, irritability, rebound insomnia, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended that the dose be gradually decreased. See SIDE EFFECTS.

Amnesia: Dormicum causes anterograde amnesia which may occur at therapeutic doses, with the risk increasing at higher dosages. Prolonged amnesia can present problems in outpatients who are scheduled for discharge following intervention. After receiving Dormicum parenterally, patients should be discharged from hospital or consulting room after at least four hours and only if accompanied by an attendant. See SIDE EFFECTS.

Paradoxical reactions: Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, may occur with the use of Dormicum. The highest incidence of susceptibility to such reactions has been reported among children and the elderly. Should such symptoms suggestive of paradoxical reaction occur, the response to Dormicum should be evaluated before proceeding. See SIDE EFFECTS.

Altered Elimination: Dormicum elimination may also be altered in patients receiving compounds that inhibit or induce CYP3A4, and the dose of Dormicum may need to be adjusted accordingly. See INTERACTIONS.

Dormicum elimination may be delayed in patients receiving compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4). See INTERACTIONS.

Sleep apnoea: Dormicum should be used with extreme caution in patients with sleep apnoea syndrome and patients should be regularly monitored.

The concomitant use of Dormicum with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Dormicum possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression. See INTERACTIONS.

When midazolam is given as an intravenous infusion in combination with saquinavir, an initial dose reduction of midazolam of 50 % is recommended. See INTERACTIONS.

It is advisable to lower doses of intravenous midazolam when co-administered with erythromycin. See INTERACTIONS.

Dormicum elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates. See *Pharmacokinetics in Special Populations*.

Adverse haemodynamic events have been reported in paediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.

Routine intravenous Dormicum induction is not recommended in children under 7 years of age.

Effects on the ability to drive or use machines*:* Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive a vehicle or operate machines. Prior to receiving Dormicum, the patient should be warned not to drive a vehicle or operate a machine until fully recovered.

Incompatibilities: Do not dilute Dormicum ampoule solutions with Macrodex 6 % in dextrose. Do not mix Dormicum ampoule solutions in alkaline injections. Dormicum precipitates in sodium bicarbonate.

INTERACTIONS

Pharmacokinetic Medicine-Medicine Interaction

Dormicum is almost exclusively metabolised by cytochrome P450 3A4 (CYP3A4). Inhibitors and inducers of CYP3A have the potential to increase and decrease the plasma concentrations, and subsequently pharmacodynamic effects of Dormicum. No other mechanism than modulation of CYP3A activity has been proven as a source of clinically relevant pharmacokinetic medicine interaction with Dormicum. However acute protein displacement from albumin is a theoretical possibility of medicine interaction with medicines with rather high therapeutic serum concentrations as it has been hypothesized e.g. for valproic acid (see below). Dormicum is not known to change the pharmacokinetics of other medicines.

It is recommended to carefully monitor the clinical effects and vital signs during the use of Dormicum taking into account the clinical effects of Dormicum might be stronger and also last longer after administration of a CYP3A inhibiting medicine. Depending on the magnitude of the CYP3A inhibiting effect the dose of Dormicum may be largely reduced. Conversely administration of a CYP3A inducing medicine may lead to a higher dose of Dormicum required to achieve the desired effect.

In case of CYP3A induction and irreversible inhibition (so-called mechanism based inhibition), the effect on the pharmacokinetics of Dormicum may persist for several days up to a few weeks after administration of the CYP3A inhibitor. Examples for mechanism-based CYP3A inhibitors include antibacterials (e.g. clarithromycin, erythromycin, isoniazid); anti-HIV agents (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, and several herbal constituents (e.g. bergamottin (grapefruit)). In contrast to the other mechanism-based inhibitors,

ethinylestradiol combined with norgestrel or gestodene when used for oral contraception and grapefruit juice (200 mℓ) did not relevantly change the plasma concentrations of *IV* Dormicum.

The range of the inhibiting/inducing potency of medicines is wide. The antifungal ketoconazole, a very potent CYP3A inhibitor, increased the plasma concentrations of *IV* Dormicum by about 5-fold. The tuberculostatic medicine rifampicin belongs to the strongest inducers of CYP3A and its co-administration resulted in a decrease in the plasma concentrations of intravenous Dormicum by about 60 %.

The mode of Dormicum use also determines the magnitude of change in its pharmacokinetics due to CYP3A modulation: (i) The change in plasma concentrations is expected to be less for intravenous compared to oral administration of Dormicum because CYP3A modulation not only affects the systemic clearance, but also the bioavailability of oral Dormicum. (ii) There are no studies available having investigated the effect of CYP3A modulation on the pharmacokinetics of Dormicum after rectal and intramuscular administration, respectively. As after rectal administration the medicine partly bypasses the liver and the expression of CYP3A in the colon is less compared to the upper gastrointestinal tract. It is expected that the change in Dormicum plasma concentrations due to CYP3A modulation will be less for the rectal than for the oral route of administration. As after intramuscular administration the medicine directly enters the systemic circulation, it is expected that the effects of CYP3A modulation will be similar to those for intravenous Dormicum. (iii) In line with the pharmacokinetic principles, clinical studies have shown that after *IV* single dose of Dormicum, the change in maximal clinical effect due to CYP3A modulation will be minor while the duration of effect may be prolonged. However, after prolonged dosing of Dormicum, both the magnitude and the duration of effect will be increased in the presence of CYP3A inhibition.

The following listing gives examples of clinical pharmacokinetic medicine-medicine interactions with Dormicum after intravenous administration. Importantly, any medicine shown to possess CYP3A modulating effects *in vivo* and *in vitro*, respectively, has the potential to change the plasma concentrations of Dormicum and therefore its effects. The listing includes information from clinical medicine-medicine interaction studies for oral Dormicum where no information on

intravenous Dormicum is available. However, as outlined above the change in plasma concentrations is expected to be less for intravenous compared to oral Dormicum.

Medicines that inhibit CYP3A

Azole antifungals

- *Ketoconazole and voriconazole* increased the plasma concentrations of intravenous Dormicum by 5-fold and by 3-4 fold respectively while the terminal half-life increased by about 3-fold. If parenteral Dormicum is co-administered with these strong CYP3A inhibitors, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dosage adjustment should be considered, especially if more than a single dose of *IV* Dormicum is administered.
- *Fluconazole and itraconazole* both increased the plasma concentrations of intravenous Dormicum by 2 - 3-fold associated with an increase in terminal half-life by 2,4-fold for itraconazole and 1,5-fold for fluconazole, respectively.
- *Posaconazole* increased the plasma concentrations of intravenous Dormicum by about 2-fold.

Macrolide antibiotics

- *Erythromycin* resulted in an increase in plasma concentrations of intravenous Dormicum by about 1,6 - 2-fold associated with an increase in Dormicum's terminal half-life by 1,5 - 1,8-fold.
- *Clarithromycin* increased Dormicum's plasma concentrations by up to 2,5-fold associated with an increase in terminal half-life by 1,5 - 2-fold.

Additional information from oral Dormicum

- *Telithromycin* increased the plasma levels of oral Dormicum by 6-fold.
- *Roxithromycin*: The roxithromycin effects on Dormicum's pharmacokinetics are less compared to erythromycin and clarithromycin. After oral administration, the plasma concentrations of Dormicum were increased by about 50 % compared to a 4,4 and 2,6-fold increase caused by erythromycin and clarithromycin, respectively. The mild effect on the

terminal half-life of Dormicum by about 30 % indicates that the effects of roxithromycin on intravenous Dormicum may be minor.

Intravenous anaesthetics

- Disposition of intravenous Dormicum was also changed by intravenous propofol (AUC and half-life increased by 1,6-fold.

Protease inhibitors

- *Saquinavir and other HIV protease inhibitors*: Upon co-administration with ritonavir boosted lopinavir, the plasma concentrations of intravenous Dormicum increased by 5,4-fold, associated with a similar increase in terminal half-life. If parenteral Dormicum is co-administered with HIV protease inhibitors, treatment setting should follow the description in the section above for ketoconazole within azole antifungals.
- *HCV protease inhibitors*: Boceprevir and telaprevir reduce Dormicum clearance. This effect resulted in a 3,4-fold increase of Dormicum AUC after *IV* administration and prolonged its elimination half-life 4-fold.

Histamine receptor 2 antagonists

- *Cimetidine* increased the steady state plasma concentrations of Dormicum by 26 %.

Calcium-channel blockers

- *Diltiazem*: A single dose of diltiazem increased the plasma concentrations of intravenous Dormicum by about 25 % and the terminal half-life was prolonged by about 43 %.

Additional information from oral Dormicum

- *Verapamil/diltiazem* increased the plasma concentrations of oral Dormicum by 3- and 4-fold, respectively. The terminal half-life of Dormicum was increased by 41 % and 49 % respectively. The dose of Dormicum should be reduced during concomitant treatment with verapamil and diltiazem.

Various medicines/Herbs

- *Atorvastatin* showed an about 1,4-fold increase in plasma concentrations of *IV* Dormicum compared to control group.

- *Intravenous fentanyl* is a weak inhibitor of Dormicum's elimination: AUC and half-life of *IV* Dormicum were increased by 1,5-fold in presence of fentanyl.

Additional information from oral Dormicum

- *Fluvoxamine* showed a mild increase in plasma concentrations of oral Dormicum (28 %) while the terminal half-life doubled.
- *Nefazodone* increased the plasma concentrations of oral Dormicum by 4,6-fold with an increase in terminal half-life by 1,6-fold.
- *Tyrosine kinase inhibitors* have been shown either *in vitro* (imatinib, lapatinib) or after oral administration *in vivo* (idelalisib) to be potent inhibitors of CYP3A4. After concomitant administration of idelalisib, oral Dormicum exposure was increased on average 5,4-fold.
- *Neurokinin (NK1) receptor antagonists (aprepitant, netupitant, casopitant)* dose dependently increased the plasma concentrations of oral Dormicum up to about 2,5-3,5-fold and increased terminal half-life by approximately 1,5-2-fold.
- *Chlorzoxazone* decreased the ratio of the CYP3A generated metabolite α-hydroxy-midazolam to Dormicum indicating a CYP3A inhibiting effect of chlorzoxazone.
- For a number of medicines or herbal medicines, a weak interaction with Dormicum's elimination was observed with concomitant changes in its exposure (< 2-fold change in AUC) (*bicalutamide, everolimus, ciclosporin, simeprevir, propiverine, berberine* as also contained in *goldenseal.* These weak interactions are expected to be further attenuated after *IV* administration.

Medicines that induce CYP3A

- *Rifampicin* decreased the plasma concentrations of intravenous Dormicum by about 60 % after 7 days of rifampicin 600 mg once daily. The terminal half-life decreased by about 50 - 60 %.
- *Ticagrelor* is a weak CYP3A inducer but has only small effects on intravenously administered Dormicum (-12 %) and 4-hydroxy-midazolam (-23 %) exposures.

Additional information from oral Dormicum

- *Carbamazepine/phenytoin*: Repeat dosages of carbamazepine or phenytoin resulted in a decrease in plasma concentrations of oral Dormicum by up to 90 % and a shortening of the terminal half-life by about 60 %.
- The very strong CYP3A4 induction seen after *mitotane* or *enzalutamide* resulted in a profound and long-lasting decrease of Dormicum levels in cancer patients. AUC of orally administered Dormicum was reduced to 5 % and 14 % of normal values respectively.
- *Clobazam* and *efavirenz* are weak inducers of Dormicum metabolism and reduce the AUC of the parent compound by approximately 30 %. There is a resulting 4-5-fold increase in the ratio of the active metabolite (α-hydroxymidazolam) to the parent compound but the clinical significance of this is unknown.
- *Vemurafenib* modulates CYP isozymes and inhibits CYP3A4 mildly: Repeat-dose administration resulted in a mean decrease of oral Dormicum exposure of 32 % (up to 80 % in individuals).

Herbs and food

- *Echinacea purpurea root* extract decreased plasma concentrations of *IV* Dormicum by 20 % associated with a decrease in half-life by about 42 %.
- *St John's wort* decreased plasma concentrations of Dormicum by about 20 - 40 % associated with a decrease in terminal half-life of about 15 - 17 %.

Additional information from oral Dormicum

- *Quercetin* (also contained in Gingko biloba) and *Panax ginseng* both have weak enzyme inducing effects and reduced exposure to Dormcium after its oral administration to the extent of 20 - 30 %.

Acute protein displacement

- *Valproic acid*: In one publication protein displacement of Dormicum by valproic acid was discussed as a potential mechanism of medicine-medicine interaction. The clinical relevance of this study is considered very limited because of methodological concerns. However, due to the high therapeutic plasma concentration of valproic acid the protein displacement of

Dormicum in the acute dose setting, resulting in more apparent clinical effect of Dormicum, cannot be excluded.

Pharmacodynamic Medicine-Medicine Interactions

The co-administration of Dormicum 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 medicines. Dormicum decreased the minimum alveolar concentration (MAC) of the inhalational anaesthetic, halothane.

Enhanced effects on sedation, respiration and haemodynamics may occur when Dormicum is co-administered with any centrally acting depressants including alcohol, therefore adequate monitoring of vital signs has to be established. Alcohol should also be avoided in patients receiving Dormicum. 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.

It has been shown that spinal anaesthesia can increase the sedative effect of *IV* Dormicum. The Dormicum dose may therefore be reduced. Also, when lidocaine and bupivacaine, respectively, were administered intramuscularly, the dose of *IV* Dormicum required for sedation was reduced.

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

PREGNANCY AND LACTATION

Midazolam has been shown to cross the placenta and to enter foetal circulation.

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

The administration of Dormicum 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 received 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.

An increased risk of congenital malformation associated with the use of benzodiazepines, including Dormicum, during the first trimester of pregnancy has been reported.

Dormicum passes into breast milk and should not be administered to breast feeding mothers. Nursing mothers should be advised to discontinue breast feeding for 24 hours following administration of Dormicum.

DOSAGE AND DIRECTIONS FOR USE

Standard dosages are provided in the table below. Additional details are given in the text following the table.

Table 1: Standard Dosage

Indication	**Adults < 60 years**	**Adults ≥ 60 years, debilitated, chronically ill, patients**	**Paediatrics**
Conscious (basal) sedation	***IV*** Initial dose: 2,5 mg Titration doses: 1 mg Total dose: 3,5 - 7,5 mg	***IV*** Initial dose: 1,25 mg Titration doses: 0,5 mg Total dose: ≤ 3,5 mg	***IV 6 months – 5 years***: Initial dose: 0,05 - 0,1 mg/kg Total dose: ≤ 6 mg

			IV 6 - 12 years: Initial dose: 0,025 - 0,05 mg/kg Total dose: < 10 mg **12 - 16 years**: As adults ***IM 1 - 15 years***: 0,1 - 0,15 mg/kg
Anaesthesia premedication	***IM*** 0,07 - 0,1 mg/kg		***IM 1 - 15 years***: 0,08 - 0,2 mg/kg
Anaesthesia induction	***IV*** 0,3 - 0,35 mg/kg without premedication	***IV*** 0,2 - 0,25 mg/kg without premedication	Not indicated in paediatrics
Maintenance	***IV*** Intermittent doses of 0,03 - 0,1 mg/kg or continuous infusion of 0,03 - 0,1 mg/kg/hr	***IV*** Lower doses than recommended for adults < 60 years	***IM*** for Ataralgesia 0,15 - 0,20 mg/kg

Sedation in ICU	***IV*** Loading dose: 0,03 - 0,3 mg/kg in increments of 1 - 2,5 mg Maintenance dose: 0,03 - 0,2 mg/kg/hr	***IV*** **< 32 weeks gestational age**: 0,03 mg/kg/hr ***IV*** **> 32 weeks gestational age up to 6 months**: 0,06 mg/kg/hr ***IV*** **> 6 months of age**: Loading dose: 0,05 - 0,2 mg/kg Maintenance dose: 0,06 - 0,12 mg/kg/hr

Standard dosage

Dormicum requires slow administration and individualisation of dosage. The dose should be titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication.

In adults over 60 years of age, especially those with organic cerebral changes or impaired cardiac and respiratory function, paediatric and in debilitated or chronically ill patients, the dosage should be determined with caution, the special factors relating to each patient being taken into consideration. See WARNINGS AND SPECIAL PRECAUTIONS.

a. Conscious (basal) sedation

For basal (conscious) sedation prior to diagnostic or surgical intervention, Dormicum is administered *IV*. The dose must be individualised and titrated and should not be administered by rapid or single bolus injection. If necessary, subsequent doses may be administered

according to individual need. The medicine takes effect in about 2 minutes after the injection has been given. Mean time to maximum effect is 2,4 minutes.

Adults: The *IV* injection of Dormicum should be given slowly at a rate of approximately 1 mg in 30 seconds.

In adults below the age of 60, the initial dose is 2,5 mg given 5 - 10 minutes before starting the procedure. Further doses of 1 mg may be given as necessary. Mean total doses have been found to range from 3,5 - 7,5 mg. A total dose greater than 5,0 mg is not usually necessary.

In adults over 60 years of age, debilitated or chronically ill patients, the initial and further doses must be halved. Additional Dormicum should be titrated very slowly and carefully. A total dose of more than 3,5 mg is not usually necessary.

Children IM: In children the dose is 0,1 - 0,15 mg/kg given 5 - 10 minutes before the start of the procedure. For more anxious patients up to 0,5 mg/kg may be given. A total dose greater than 10,0 mg is not usually necessary.

Children IV: Dormicum should be titrated slowly to the desired clinical effect. The initial dose of Dormicum should be administered over 2 - 3 minutes. An additional 2 - 3 minutes must be waited to fully evaluate the sedative effect before initiating a procedure or repeating a dose. If further sedation is necessary, continue titrating with small increments until the appropriate level of sedation is achieved. Infants and children less than 5 years of age may require substantially higher doses than children and adolescents.

1. *Paediatric patients less than 6 months of age:* limited information is available in non-intubated paediatric patients less than 6 months of age. These patients are particularly vulnerable to airway obstruction and hypoventilation, therefore titration with small increments to the clinical effect and careful monitoring are essential.
2. *Paediatric patients 6 months to 5 years of age:* initial dose of 0,05 - 0,1 mg/kg. A total dose of up to 0,6 mg/kg may be necessary to reach the desired endpoint, but should not exceed 6 mg.
3. *Paediatric patients 6 - 12 years of age:* initial dose 0,025 - 0,05 mg/kg. A total dose up to 0,4 mg/kg, to a maximum of 10 mg.

4. *Paediatric patients 12 - 16 years of age:* as for adults.

b. Anaesthesia

b. i). Premedication

Premedication with Dormicum given shortly before a procedure produces sedation (induction of sleepiness or drowsiness and relief of apprehension), and pre-operative impairment of memory. Dormicum may be administered in combination with anticholinergics. For this indication, Dormicum should be administered *IM,* deep into a large muscle mass 20 - 60 minutes before induction of anaesthesia.

Adults below the age of 60: 0,07 - 0,1 mg/kg bodyweight *IM* according to general condition of the patient. Usual dose is about 5 mg.

Children: In children between ages 1 - 15, proportionally higher doses are required than in adults in relation to bodyweight. The dose range from 0,08 to 0,2 mg/kg of Dormicum administered *IM* has been shown to be effective and safe. These doses should be administered into a large muscle mass 30 - 60 minutes before induction of anaesthesia.

b. ii). Induction

Adults: If Dormicum is used for induction of anaesthesia before other anaesthetic agents have been administered, the individual response is variable. The dose of all the agents should be titrated to the desired effect, at times as low as 25 % of the usual initial dose of the individual agents.

The desired level of anaesthesia is reached by stepwise titration. The intravenous induction dose of Dormicum should be given slowly, in increments. Each increment of not more than 5 mg should be injected over 20 - 30 seconds, allowing 2 minutes between successive increments.

In non-premedicated adults below the age of 60, the dose may be higher (0,3 to 0,35 mg/kg), administered *IV* over 20 - 30 seconds and allowing 2 minutes for effect. If needed to complete induction, increments of approximately 25 % of the patient's initial dose may be used. Induction may instead be completed with volatile liquid inhalation anaesthetics. In resistant cases, a total dose of up to 0,6 mg/kg may be used for induction, but such larger doses may prolong recovery.

Non-premedicated elderly patients usually require less Dormicum for induction; an initial dose of 0,3 mg/kg is recommended. Non-premedicated patients with severe systemic disease or other debilitation usually require less Dormicum for induction. An initial dose of 0,2 - 0,25 mg/kg will usually suffice; in some cases as little as 0,15 mg/kg may suffice. In adults over 60 years of age, debilitated and chronically ill patients, lower doses will be required.

Children: Dormicum is not recommended for the induction of anaesthesia in children, as experience is limited.

b.iii) Maintenance

Adults: The maintenance of the desired level of unconsciousness can be achieved either by further intermittent small *IV* doses (range between 0,03 and 0,1 mg/kg) or continuous infusion of *IV* Dormicum (range between 0,03 and 0,1 mg/kg/hr), typically in combination with analgesics. The dose and the interval between doses vary according to the patient's individual reaction.

In high-risk surgical patients, adults over 60 years, debilitated and chronically ill patients, lower maintenance doses will be required.

Children: In children receiving ketamine for anaesthesia (ataralgesia), an *IM* dose of Dormicum of 0,15 - 0,20 mg/kg is recommended. A sufficiently deep level of sleep is generally achieved after 2 - 3 minutes.

c. IV Sedation in intensive care units (ICU):

The desired level of sedation is reached by stepwise titration of Dormicum followed by either continuous infusion or intermittent bolus, according to clinical need, physical status, age and concomitant medication. See INTERACTIONS.

Adults: The intravenous loading dose should be given slowly in increments. Each increment of 1 to 2,5 mg should be injected over 20 - 30 seconds allowing 2 minutes between successive increments. The intravenous loading dose can range from 0,03 to 0,3 mg/kg, but a total dose greater than 15 mg is usually not necessary.

The loading dose should be reduced or omitted in hypovolaemic, vasoconstricted or hypothermic patients.

When Dormicum is given with potent analgesics, the latter should be administered first so that sedative effects of Dormicum can safely be titrated on top of any sedation caused by the analgesic.

The maintenance dose ranges from 0,03 to 0,2 mg/kg/hr. In hypovolaemic, vasoconstricted or hypothermic patients the maintenance dose should be reduced, at times to as low as 25 % of the usual dose. The level of sedation should be assessed regularly if the patient's condition permits.

Children: 0,05 to 0,2 mg/kg *IV* administered over at least 2 - 3 minutes to establish the desired clinical effect (Dormicum should not be administered as a rapid intravenous dose), followed by a continuous *IV* infusion at 0,06 to 0,12 mg/kg/hr (1 to 2 µg/kg/min). The rate of infusion can be increased or decreased (generally by 25 % of the initial or subsequent infusion rate) as required, or supplemental *IV* doses of Dormicum can be administered to increase or maintain the desired effect.

When initiating an infusion with Dormicum in haemodynamically compromised patients, the usual loading dose should be titrated in small increments and the patient monitored for haemodynamic instability e.g. hypotension. These patients are also vulnerable to the respiratory depressant effect of Dormicum and require careful monitoring of respiratory rate and oxygen saturation.

Neonates: Dormicum should be given as a continuous *IV* infusion, starting at 0,03 mg/kg/hr (0,5 µg/kg/min) in neonates < 32 weeks old or 0,06 mg/kg/hr (1 µg/kg/min) in neonates > 32 weeks old. Intravenous loading doses should not be used in neonates, rather the infusion may be run more rapidly for the first several hours to establish therapeutic plasma levels. The rate of infusion should be carefully and frequently reassessed, particularly after the first 24 hours so as to administer the lowest possible effective dose and reduce the potential for medicine accumulation. Careful monitoring of respiratory rate and oxygen saturation is required.

Special dosage instructions:

Paediatric Use

- In preterm newborn infants, and paediatrics less than 15 kg of body weight, Dormicum solutions with concentrations higher than 1 mg/mℓ are not recommended. Higher concentrations should be diluted to 1 mg/mℓ.
- *IV* administration in paediatric patients less than 6 months of age is not recommended with exception in ICU as they are vulnerable to airway obstruction and hypoventilation.
- Dormicum is not indicated in children in induction of anaesthesia and as a sedative component in combined anaesthesia as limited data is available.

Geriatric Use

Geriatric patients ≥ 60 years, require lower dosages and should be continuously monitored for early signs of alterations of vital functions. See WARNINGS AND SPECIAL PRECAUTIONS.

Renal Impairment

There is a greater likelihood of adverse drug reactions in patients with severe renal impairment. Dormicum should therefore be dosed carefully in this patient population and titrated for the desired effect.

In patients with chronic renal disease, it has been shown that α-hydroxymidazolam accumulates and could contribute to the clinical effects of Dormicum resulting in prolonged sedation.

Hepatic Impairment

The clinical effects in patients with hepatic impairment may be stronger and prolonged. The dose of Dormicum may have to be reduced and vital signs should be monitored.

Hepatic impairment reduces the clearance of *IV* Dormicum with a subsequent increase in terminal half-life. **[**~~Therefore the clinical effect may be stronger and prolonged. The required dose of Dormicum may be reduced and proper monitoring of vital signs should be established~~.**]**

See WARNINGS AND SPECIAL PRECAUTIONS.

Table 2: Time to awaken (hr) following cessation of the Dormicum infusion.

		Time to awaken (min)	
	No of patients	Mean ± SD	range
All patients	37	27,8 ± 37,2	0 - 140

Patients without renal or hepatic dysfunction	24	13,6 ± 16,4	0 - 58
Patients with renal dysfunction without liver dysfunction	9	44,6 ± 42,5	2 - 120
Patients with renal failure and liver disease	2	-	124 - 140

Compatibility with infusion solutions: The Dormicum ampoule solution can be diluted with sodium chloride 0,9 %, dextrose 5 %, dextrose 10 %, levulose 5 %, Ringer's solution and Hartmann's solution in a mixing ratio of 15 mg Dormicum per 100 - 1 000 mℓ infusion solution. These solutions remain physically and chemically stable for 24 hours at room temperature (or three days at 5 °C).

The Dormicum ampoule solution should not be diluted with Macrodex 6 % in dextrose or mixed with alkaline injections.

To avoid potential incompatibility with other solutions, Dormicum ampoule solution must not be mixed with other solutions except those mentioned above.

SIDE EFFECTS

The following side effects have been reported (very rarely) when Dormicum was injected:

Immune System Disorders: Generalised hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), angioedema, anaphylactic shock.

Psychiatric Disorders: Confusional state, euphoric mood, hallucinations.

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault have been reported particularly among children and the elderly. See WARNINGS AND SPECIAL PRECAUTIONS. Use of Dormicum, even in therapeutic doses, may lead to the development of physical dependence. After prolonged *IV* administration, discontinuation, especially abrupt discontinuation, may be accompanied by

withdrawal symptoms, including withdrawal convulsions. See WARNINGS AND SPECIAL PRECAUTIONS.

Abuse has been reported in poly-drug abusers.

Nervous System Disorders: Prolonged sedation, decreased alertness, headache, dizziness, ataxia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

Convulsions have been reported in premature infants and neonates.

Cardiac disorders: Severe cardio-respiratory adverse events have occurred. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects. Such life-threatening incidents are more likely to occur in adults older than 60 years and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered. See WARNINGS AND SPECIAL PRECAUTIONS.

Respiratory Disorders: Severe cardio-respiratory adverse events have occurred. These have included respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm. Such life-threatening incidents are more likely to occur in adults older than 60 years and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered. See WARNINGS AND SPECIAL PRECAUTIONS. Hiccup.

Gastrointestinal System Disorders: Nausea, vomiting, constipation, dry mouth.

Skin and Appendages Disorders: Skin rash, urticaria, pruritus.

General and Application Site Disorders: Erythema and pain on injection site, thrombophlebitis, thrombosis.

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users, including Dormicum. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms: Benzodiazepines such as 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, 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 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 it's 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 package insert for flumazenil, for further information on the correct use of this product.

IDENTIFICATION

Dormicum ampoules 5 mg/5 mℓ: clear, colourless to slightly yellow liquid in 5 mℓ colourless ampoules.

Dormicum ampoules 15 mg/3 mℓ: clear, practically colourless liquid in 3 mℓ colourless ampoules.

Dormicum ampoules 50 mg/10 mℓ: clear, colourless to slightly yellow liquid in 10 mℓ colourless ampoules.

PRESENTATION

Dormicum ampoules 5 mg/5 mℓ : 5

Dormicum ampoules 15 mg/3 mℓ : 5

Dormicum ampoules 50 mg/10 mℓ: 1

STORAGE INSTRUCTIONS

Store at or below 30 °C. Keep ampoule in outer carton in order to protect from light.

Dormicum ampoules should not be frozen because they can burst. Furthermore, precipitation can occur which dissolves on shaking at room temperature.

Store out of reach of children.

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

Dormicum ampoules are for single use only. Discard any unused solution.

The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

REGISTRATION NUMBERS

Dormicum ampoules 5 mg/5 mℓ : T/2.2/207

Dormicum ampoules 15 mg/3 mℓ : Q/2.2/286

Dormicum ampoules 50 mg/10 mℓ: Y/2.2/325

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

Roche Products (Pty) Ltd

24 Fricker Road

Illovo

Gauteng

South Africa

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

DATE OF PUBLICATION OF THE PACKAGE INSERT

Registration: 5 mg/5 mℓ - Aug 1986; 15 mg/3 mℓ - Jul 1985; 50 mg/10 mℓ - Aug 1991

Last revision: 7 December 2019

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S5

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

Dormicum® 5 mg/5 mℓ ampoules

Dormicum® 15 mg/3 mℓ ampoules

Dormicum® 50 mg/10 mℓ ampoules

Read all of the leaflet carefully before you are given Dormicum

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- Dormicum has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT DORMICUM CONTAINS

Dormicum contains 5 mg/5 mℓ, 15 mg/3 mℓ or 50 mg/10 mℓ midazolam active substance per ampoule, respectively.

The other ingredients are: sodium chloride, hydrochloric acid, sodium hydroxide, water for injection.

WHAT DORMICUM IS USED FOR

Dormicum contains a medicine called midazolam. This belongs to a group of medicines called “benzodiazepines”.

Dormicum works quickly to make you feel sleepy or to put you to sleep. It also makes you calm and relaxes your muscles.

Dormicum is used for:

- Anaesthesia in adults.

- Sedation of adults and children, in intensive care units.
- Conscious sedation (an awake but very relaxed state of calm or drowsiness during a medical test or procedure) in adults and children.
- Premedication (medicine used to cause relaxation, calm and drowsiness before an anaesthetic) in adults and children.

BEFORE YOU ARE GIVEN DORMICUM

You must not be given Dormicum if:

- You are allergic (hypersensitive) to midazolam or any of the other ingredients of this medicine.
- You are allergic to other benzodiazepine medicines, such as diazepam or nitrazepam.
- You have severe breathing problems **and** you are going to have Dormicum for "conscious sedation".

You must not be given Dormicum if any of the above apply to you. If you are not sure, talk to your doctor or nurse before you are given this medicine.

Take special care with Dormicum:

Check with your doctor or nurse before you are given Dormicum if:

- You are over 60 years of age.
- You have a long term illness, such as breathing problems or kidney, liver or heart problems.
- You have an illness that makes you feel very weak, run down or short of energy.
- You have something called "myasthenia gravis" where your muscles are weak.
- You have ever had alcohol problems.
- You have ever had drug problems.
- If you have sleep apnoea (repetitive periods without breathing, occurring during sleep).
- Dormicum can cause withdrawal symptoms if it is stopped abruptly. See "How Dormicum is given, Effects with Dormicum is stopped" below.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before you are given Dormicum.

If your child is going to be given this medicine:

- Talk to your doctor or nurse if any of the above applies to your child. In particular, tell your doctor or nurse if your child has heart or breathing problems, as your child will have to be monitored while Dormicum is being administered.

Using Dormicum with food and drink:

Drinking alcohol: Do not drink alcohol if you have been given Dormicum. This is because it may make you feel very sleepy and cause problems with your breathing.

Pregnancy and Breast feeding

- Talk to your doctor before you are given Dormicum if you are pregnant or think you may be pregnant. Your doctor will decide if this medicine is suitable for you.
- Dormicum can cause harm to the foetus (unborn baby), if taken by a pregnant woman.
- After you have been given Dormicum, do not breast feed for 24 hours. This is because Dormicum may pass into your breast milk.

If you are pregnant or breast feeding your baby please consult your doctor, pharmacist or other health care professional for advice before being given Dormicum.

Driving and using machinery

- After having Dormicum, do not drive or use tools or machines until your doctor says you can.
- This is because Dormicum may make you feel sleepy or forgetful. It may also affect your concentration and co-ordination. This may affect you being able to drive or use tools and machines.
- After your treatment, you must be taken home by an adult who can look after you.

Important information about some of the ingredients of Dormicum

Dormicum is essentially "sodium free" as it contains less than 1 mmol sodium (23 mg) per small glass bottle (ampoule).

Taking other medicines with Dormicum:

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)

Dormicum can affect the way some other medicines work. Also some medicines can affect the way Dormicum works.

In particular tell your doctor or nurse if you are taking any of the following medicines:

- Medicines for depression.
- Hypnotic medicines (to make you sleep).
- Sedatives (to make you feel calm or sleepy).
- Tranquilliser medicines (for anxiety or to help you sleep).
- Carbamezapine or phenytoin (these may be used for fits or seizures).
- Rifampicin (for tuberculosis).
- Medicines for HIV called "protease inhibitors" (such as saquinavir, ritonavir).
- Medicines for hepatitis C such as boceprevir and telaprevir.
- Medicines used in the treatment of leukemia and other cancers, such as imatinib, lapatinib.
- Neurokinin receptor antagonists such as aprepitant, netupitant, casopitant.
- Oral contraceptive medicines such as ethinylestradiol combined with norgestrel or gestodene.
- Oestrogen receptor modulators such as raloxifene.
- Antibiotics called "macrolides", such as erythromycin, telithromycin or clarithromycin.
- Medicines to treat fungal infections, such as ketoconazole, voriconazole, fluconizole, itraconazole, posaconazole.
- Strong pain killers.
- Atorvastatin (for high cholesterol).
- Antihistamines (for allergic reactions).

- Herbal medicines such as St John's Wort, berberine, goldenseal, Echinacea purpurea root, Quercetin or Panax ginseng.
- Medicines for cancer such as mitotane or enzalutamide.
- Medicines for high blood pressure called "calcium channel blockers", such as diltiazem.
- Intravenous anaesthetics such as propofol.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before you are given Dormicum.

HOW DORMICUM IS GIVEN

Dormicum will be given to you by a doctor or nurse. It will be given to you in a place that has the equipment needed to monitor you and to treat any side effects. This might be a hospital, clinic or doctor's surgery. In particular, your breathing, heart and circulation will be monitored.

Dormicum is not recommended for use for infants and babies under 6 months of age. However, if the doctor feels that it is necessary, it can be given to an infant or baby under 6 months who is in intensive care.

How Dormicum will be given to you

You will be given Dormicum in one of the following ways:

- By slow injection into a vein (intravenous injection).
- Through a drip into one of your veins (intravenous infusion).
- By injection into a muscle (intramuscular injection).

How much Dormicum will be given to you

The dose of Dormicum varies from one patient to another. Your doctor will work out how much to give you. It depends on your age, weight, and general health. It also depends on what you need the medicine for, how you respond to treatment, and whether you are going to be given other medicines at the same time.

After being given Dormicum

After your treatment, you must be taken home by an adult who is able to look after you. This is because Dormicum may make you sleepy or forgetful. It may also affect your concentration and co-ordination.

If you are given Dormicum for a long time, such as in intensive care, your body may start to get used to the medicine. This means it may not work as well.

If you have the impression that the effect of Dormicum is too strong or too weak, talk to your doctor, nurse or pharmacist.

If you are given too much Dormicum

Your medicine will be given to you by a doctor or a nurse. If you are given too much my mistake, you may notice the following:

- Feeling sleepy and losing your co-ordination and reflexes.
- Problems with speaking and unusual eye movements.
- Low blood pressure. This may make you feel dizzy or light-headed.
- Slow or stopping of your breathing and heart beat and being unconscious (coma).

Long term use of Dormicum for sedation in intensive care

If you are given Dormicum for a long time, the following may happen:

- It may start to work less well.
- You may become dependent on the medicine and get withdrawal symptoms when you stop having it. See “Stopping Dormicum” below.

Effects when treatment with Dormicum is stopped

If you are given Dormicum for a long time, such as in intensive care, you may get withdrawal symptoms when Dormicum is stopped. These include:

- Mood changes.

- Fits (convulsions).
- Headache.
- Diarrhoea,
- Muscle pain.
- Problems with sleeping (insomnia).
- Feeling very worried (anxious), tense, restless, confused or bad tempered (irritable).
- Seeing and possible hearing things that are not really there (hallucinations).

Your doctor will lower your dose gradually. This will help to stop withdrawal symptoms from happening to you.

POSSIBLE SIDE EFFECTS

Dormicum can cause side effects. The following side effects have been reported.

Stop having Dormicum and see a doctor straight away if you notice any of the following side effects. They can be life-threatening and you may need urgent medical treatment:

- A severe allergic reaction (anaphylactic shock). The signs may include a sudden rash, itching or lumpy rash (hives) and swelling of the face, lips, tongue or other parts of the body. You may also have shortness of breath, wheezing or trouble breathing.
- Heart attack (cardiac arrest). The signs may include chest pain.
- Breathing problems, sometimes causing the breathing to become laboured.
- Muscle spasm around the voice box, causing choking.

The side effects are also more likely if the injection is given too fast or at a high dose.

Other possible side effects:

Nervous system and mental problems

- Being less alert.
- Feeling confused.
- Feeling very happy or excited (euphoria).

- Feeling tired or sleepy or being sedated for a long time.
- Seeing or possibly hearing things that are not really there (hallucinations).
- Headache.
- Feeling dizzy.
- Difficulty co-ordinating muscles.
- Fits (convulsions) in premature and new-born babies.
- Temporary memory loss. How long this lasts depends on how much Dormicum you were given. Occasionally this has lasted for a long time.
- Feeling agitated, restless, angry or aggressive. You may also have muscle spasms or shaking of your muscles that you cannot control (tremors). These effects are more likely if you have been given a high dose of Dormicum or if it has been given too quickly. It is also more likely in children and elderly people.

Heart and circulation

- Fainting.
- Slow heart rate.
- Redness of the face and neck (flushing).
- Low blood pressure. This may make you feel dizzy or light-headed.

Breathing

- Hiccups.
- Being short of breath.

Mouth, stomach and gut

- Dry mouth.
- Constipation.
- Feeling sick (nausea) or being sick (vomiting).

Skin

- Feeling itchy.
- Rash, including a lumpy rash (hives).

- Redness, pain, blood clots or swelling of the skin where the injection was given.

Injury

- Patients taking Dormicum are at risk of falling and breaking bones. This risk is increased in the elderly and those taking other sedatives (including alcohol).

General

- Allergic reactions including skin rash and wheezing.
- Angioedema (an allergic skin disease characterised by patches of confined swelling involving the skin, the layers beneath the skin or mucous membranes).
- Withdrawal symptoms. See "Stopping Dormicum" above.

Elderly people

- Life-threatening side effects are also more likely to happen in adults over 60 years.

If you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

Not all side effects reported for Dormicum are included in this leaflet. Should your general health worsen, or if you experience any untoward effects while being given Dormicum, please consult your doctor, pharmacist or other health care professional for advice.

STORING AND DISPOSING OF DORMICUM

Store at or below 30 °C. Keep ampoule in outer carton in order to protect from light.

Dormicum ampoules should not be frozen because they can burst. Furthermore, precipitation can occur which dissolves on shaking at room temperature.

Store out of reach of children.

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

PRESENTATION OF DORMICUM

Dormicum ampoules 5 mg/5 mℓ : 5

Dormicum ampoules 15 mg/3 mℓ : 5

Dormicum ampoules 50 mg/10 mℓ: 1

IDENTIFICATION OF DORMICUM

Dormicum ampoules 5 mg/5 mℓ: clear, colourless to slightly yellow liquid in 5 mℓ colourless ampoules.

Dormicum ampoules 15 mg/3 mℓ: clear, practically colourless liquid in 3 mℓ colourless ampoules.

Dormicum ampoules 50 mg/10 mℓ: clear, colourless to slightly yellow liquid in 10 mℓ colourless ampoules.

REGISTRATION NUMBERS

Dormicum ampoules 5 mg/5 mℓ : T/2.2/207

Dormicum ampoules 15 mg/3 mℓ : Q/2.2/286

Dormicum ampoules 50 mg/10 mℓ : Y/2.2/325

NAME AND ADDRESS OF REGISTRATION HOLDER

Roche Products (Pty) Ltd

24 Fricker Road

Illovo

Gauteng

South Africa

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

DATE OF PUBLICATION

Registration: 5 mg/5 mℓ - Aug 1986; 15 mg/3 mℓ - Jul 1985; 50 mg/10 mℓ - Aug 1991

Last revision: 7 Dec 2019