SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DORMICUM® 15 mg/3 mL Ampoules

DORMICUM® 5 mg/5 mL Ampoules

DORMICUM® 50 mg/10 mL Ampoules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DORMICUM contain 15 mg/3 mL, 5 mg/5 mL or 50 mg/10 mL midazolam per ampoule as the active substance.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DORMICUM 15 mg/3 mL: clear, practically colourless liquid in 3 mL colourless ampoules.

DORMICUM 5 mg/5 mL: clear, colourless to slightly yellow liquid in 5 mL colourless ampoules.

DORMICUM 50 mg/10 mL: clear, colourless to slightly yellow liquid in 10 mL colourless ampoules.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

DORMICUM is indicated:

- 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).

4.2. Posology and method of administration

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 section 4.4).

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.

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

Anaesthesia

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 ranges from 0,08 - 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.

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 - 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.

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.

***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 section 4.5).

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 - 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 - 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 - 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 - 0,12 mg/kg/hr (1 - 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 populations

Paediatric populations:

- 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 section 4.4).

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

- Patients with severe hepatic impairment should not be treated with DORMICUM (see section 4.3).
- The clinical effects in patients with hepatic impairment may be stronger and prolonged. In patients with mild to moderate hepatic impairment 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 (see section 4.4).

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). See section 6.2.

4.3. Contraindications

- Use in patients with known hypersensitivity to midazolam or any medicine from the benzodiazepines group or to any excipient within the medicine.
- Myasthenia gravis.
- Severe hepatic impairment. DORMICUM is not indicated to treat patients with severe hepatic impairment as it may cause encephalopathy (see section 4.4).
- Respiratory insufficiency.
- Sleep apnoea syndrome.
- Pregnancy and lactation (see section 4.6).

4.4. Special warnings and precautions for use

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 kidney function,
- patients with impaired hepatic function (DORMICUM is contraindicated in patients with severe hepatic impairment as it may precipitate or exacerbate encephalopathy),
- patients with impaired cardiac function, or
- paediatric patients with cardiovascular instability.

These higher risk patients require lower dosages and should be continuously monitored for early signs of alterations of vital functions (see section 4.2).

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 section 4.2).

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.

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 section 4.8).

Withdrawal symptom

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 section 4.8).

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 section 4.8).

Psychiatric and "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 section 4.8).

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 section 4.5. DORMICUM elimination may be delayed in patients receiving compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A4). See section 4.5.

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 section 4.5).

When midazolam is given as an intravenous infusion in combination with saquinavir, an initial dose reduction of midazolam of 50 % is recommended (see section 4.5).

It is advisable to lower doses of intravenous midazolam when co-administered with erythromycin (see section 4.5).

DORMICUM elimination may also be delayed in patients with liver dysfunction, low cardiac output and in neonates (see section 5.2).

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.

4.5. Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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.

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 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, isoniazid, HIV protease inhibitors (ritonavir), delavirdine, calcium channel blockers (e.g. verapamil, diltiazem), kinase inhibitors (e.g. imatinib, lapatinib, idelalisib), or the oestrogen receptor modulator, raloxifene and several herbal constituents (e.g. bergamottin, grapefruit). Ethinylestradiol combined with norgestrel or gestodene did not modify exposure to DORMICUM to a clinically significant degree.

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 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 combination of alcohol and DORMICUM should be avoided (see section 4.4).

See section 4.9 for warnings on 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 AchE inhibitor physostigmine, reversed the hypnotic effects of DORMICUM. Similarly, 250 mg of caffeine partly reversed the sedative effect of DORMICUM.

4.6. Pregnancy and lactation

Pregnancy

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

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

An increased risk of congenital malformation associated with the use of DORMICUM during the first trimester of pregnancy may occur.

If, exceptionally, it is considered by a medical practitioner that administration of DORMICUM during the last three months of pregnancy, or during labour, is essential, effects on the neonate such as irregularities in the foetal heart rate, hypothermia, hypotonia, poor sucking 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.

Lactation

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

4.7. Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or use machines. Prior to receiving DORMICUM, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The medical practitioner should decide when these activities may be resumed.

4.8. Undesirable effects

a. Summary of the safety profile: No text

b. Tabulated list of adverse reactions:

The side effects in the following table were reported post-marketing and are presented according to the MedDRA system organ classification. The frequency with which these side effects occur is not known (cannot be estimated from the available data).

Frequency categories are as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

MedDRA SOC	**Adverse reaction (Frequency not known)**
Immune system disorders	Hypersensitivity, angioedema, anaphylactic shock
Psychiatric disorders	Confusional state, emotional and mood disturbances Paradoxical reactions: restlessness, agitation, psychomotor hyperactivity, irritability, aggression, delusion, anger, nightmare, hallucination Dependence: drug dependence, withdrawal syndrome, substance abuse

Nervous system disorders	Somnolence, headache, dizziness, depressed level of consciousness, ataxia, anterograde amnesia, convulsions Premedication: impact on post-operative sedation
Cardiac disorders	Cardiac failure, cardiac arrest
Vascular disorders	Thrombophlebitis, thrombosis, hypotension, vasodilation.
Respiratory, thoracic and mediastinal disorders	Respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm, hiccups
Gastrointestinal disorders	Nausea, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders	Skin rash, urticaria, pruritus, erythema on injection site
General disorders and administration site conditions	Fatigue, pain on injection site
Injury, poisoning and procedural complications	Fall, fracture

c. Description of selected adverse reactions:

Psychiatric Disorders: The use of the product should be discontinued if paradoxical reactions occur. These effects are more likely to occur in the elderly (see section 4.4). Abuse has been reported in poly-drug abusers.

Nervous System Disorders: These adverse events occur predominantly at the start of therapy and usually disappear with repeated administration. The duration 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. 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 section 4.4).

Respiratory, Thoracic and Mediastinal Disorders: Disorders: Severe cardio-respiratory adverse events have occurred. 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 section 4.4).

Injury, Poisoning and Procedural Complications: The risk of falls and fractures is increased in DORMICUM users taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Patients and Healthcare professionals can contact Pharmaco directly for assistance with reporting adverse events on +27 (0) 11 784 00 77.

4.9. Overdose

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 professional information for flumazenil, for further information on the correct use of this medicine.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives (benzodiazepine derivatives), ATC code: N05CD08.

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

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.

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.

5.2. Pharmacokinetic properties

***Absorption**:*

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. 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. Midazolam is not a substrate for medicine transporters.

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 are 12 % those of the parent compound. 1'-hydroxymidazolam is pharmacologically active, but contributes only minimally (about 10 %) to the effects of intravenous midazolam.

Elimination

In healthy young volunteers, the elimination half-life of midazolam ranges between 1,5 - 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. When midazolam is given by *IV* infusion, its elimination kinetics does not differ from those following bolus injections.

Pharmacokinetics in special populations

Elderly

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

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 section 4.4).

Patients with renal impairment

The pharmacokinetics of midazolam are not altered in patients with severe renal impairment. However the 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.

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 (8,4 hours vs 2,7 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 section 4.4).

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 section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

DORMICUM contain midazolam as the active substance.

Excipients:

Sodium chloride, hydrochloric acid, sodium hydroxide, water for injections.

6.2. Incompatibilities

The DORMICUM ampoule solution should not be diluted with Macrodex 6 % in dextrose or mixed with alkaline injections. DORMICUM precipitates in sodium bicarbonate. To avoid potential incompatibility with other solutions, DORMICUM ampoule solution must not be mixed with other solutions except those mentioned in section 4.2.

6.3. Shelf life

DORMICUM 15 mg/3 mL: 60 months

DORMICUM 5 mg/5 mL: 60 months

DORMICUM 50 mg/10 mL: 60 months

6.4. Special precautions for storage

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.

6.5. Nature and contents of container

DORMICUM 15 mg/3 mL ampoule: 5

DORMICUM 5 mg/5 mL ampoule: 5

DORMICUM 50 mg/10 mL ampoule: 1

Not all packs may be marketed.

6.6. Special precautions for disposal and other handling

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.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd.

3 Sandown Valley Crescent

South Tower, First Floor

Sandton 2196, Gauteng

South Africa

Ethical assistance Line: +27 (0) 784 00 77

8. REGISTRATION NUMBER(S)

DORMICUM 15 mg/3 mL ampoules: Q/2.2/286

DORMICUM 5 mg/5 mL ampoules: T/2.2/207

DORMICUM 50 mg/10 mL ampoules: Y/2.2/325

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

Last revision: 2022-08-25

DORMICUM 15 mg/3 mL	
NAMIBIA Reg. No. 90/2.2/001404	NS3

DORMICUM 5 mg/5 mL	
NAMIBIA Reg. No. 90/2.2/001405	NS3