Dormicum®

Midazolam

Composition

Active ingredient: midazolam as the maleate.

Excipients

Dormicum film-coated tablets 7.5 mg: excipients for coated tablets with lactose.

Dormicum film-coated tablets 15 mg: colourant: E 132 (indigo carmine), excipients for coated tablets with lactose.

Pharmaceutical form and quantity of active substance per unit

Dormicum film-coated tablets 7.5 mg:

White, oval, film-coated (scored) tablets containing 7.5 mg of midazolam.

Dormicum film-coated tablets 15 mg:

Light blue, oval, film-coated (scored) tablets containing 15 mg of midazolam.

Indications and potential uses

Short-term treatment of sleep disturbance. Like all hypnotics, Dormicum should be used only in cases of clinically significant insomnia.

Sleep pattern disturbances, difficulty in getting to sleep, or difficulty in getting back to sleep after premature waking.

Sedation in premedication before surgical or diagnostic procedures.

Dosage and administration

In general the lowest effective dose should always be used for as short a period as possible. Treatment should not be withdrawn abruptly.

Usual dosage

Standard dose: 7.5-15 mg is the usual dose in adults. In children and adolescents, the recommended dose for sedation in premedication is 0.2-0.5 mg/kg body weight (but to a maximum of 20 mg).

Special dosage instructions

In *elderly and frail patients*, the usual dose is 7.5 mg. Since the sedative effect is more marked in elderly patients, these patients may also be at increased risk of circulatory and respiratory depression. Dormicum should therefore be used with great caution in elderly patients and a lower dosage should be chosen if necessary.
This lower dose may also be suitable for patients with hepatic and/or renal impairment. Dormicum should be used with great caution in such patient groups. A lower dosage should be chosen if necessary. Treatment can be initiated with half a 7.5 mg film-coated tablet. In patients with severe renal failure, accumulation may occur of the main metabolite of midazolam, 1'-hydroxymidazolam glucuronide. This may cause more marked and prolonged sedation, up to and including clinically significant respiratory and circulatory depression. Dormicum should therefore be titrated with great caution in this patient population. The recommended dose is 7.5 mg and a lower dosage should be chosen if necessary.

The dose of 7.5 mg is generally also sufficient for situational sleep disturbances.

The above-mentioned dose may be increased to a maximum of 15 mg if treatment with the recommended dose and other measures such as improved sleep hygiene or treatment of the sleep-disturbing underlying disease remain ineffective.

For *premedication* of adults, 7.5 to 15 mg of Dormicum should be administered orally 30 to 60 minutes before the intended procedure, unless the parenteral route is preferred (see Dormicum ampoules).

Method and duration of use (mode of administration)

Because of its rapid onset of action, Dormicum should be swallowed whole with fluid immediately before retiring.

Dormicum can be taken at any time of day provided an uninterrupted period of at least 7–8 hours of sleep can be guaranteed thereafter. The risk of anterograde amnesia should be borne in mind (see *Undesirable effects*).

The maximum recommended dose should not be exceeded because this would increase the risk of central nervous system adverse effects, possibly including clinically significant respiratory and cardiovascular depression.

The duration of treatment should be as short as possible and should generally not exceed 2 weeks. A longer period of treatment may prove necessary, but this requires careful re-evaluation. Treatment should not be abruptly withdrawn. At the end of treatment it is recommended that Dormicum be withdrawn decrementally. How the tapering is performed should be tailored to the individual patient.

Contraindications

- Hypersensitivity to benzodiazepines or any of the excipients listed under *Composition*;
- Severe respiratory failure;
- Sleep disturbance in children and adolescents (1-18 years);
- Severe liver failure;
- Myasthenia;

– Sleep apnea syndrome;
– Cotreatment with ketoconazole, itraconazole, voriconazole and HIV protease inhibitors, including combinations of protease inhibitors containing ritonavir (see *Interactions*).

Warnings and precautions

Patients must be informed of the warnings and precautions:

Dormicum is not an approved monotherapy for psychosis and depression associated with insomnia (risk of suicide in these conditions). In such cases, priority should be given to treating the underlying disease.

Benzodiazepines should be used only with extreme caution in patients with a history of alcohol and/or prescription drug abuse.

As with other sedating medications, dosing should be cautious in patients with organic brain changes, patients in respiratory failure, patients in poor general health and patients under unusual mental stress (increased drug sensitivity).

Coadministration of oral midazolam with nefazodone, fluconazole or erythromycin is not recommended (see *Interactions*).

Elimination of the drug may be delayed during concomitant treatment with central nervous system depressants and compounds that inhibit certain hepatic enzymes (particularly cytochrome P450 3A), such as erythromycin, saquinavir, cimetidine, or nefazodone (see *Contraindications* and *Interactions*). The midazolam dose must be carefully adjusted: reduced during cotreatment with erythromycin, diltiazem, verapamil and saquinavir; increased during cotreatment with carbamazepine, phenytoin and rifampicin (see *Interactions*).

The patient should be warned against simultaneous consumption of alcohol, as the combination can potentiate the undesirable effects of both substances.

As interactions between Dormicum, on the one hand, and alcohol or other medications acting on the CNS, on the other, may disrupt normal behaviour, the consumption of alcohol before or while using Dormicum should be avoided. Avoid administering Dormicum to patients receiving other centrally acting medications (see *Interactions*).

Tolerance

Some loss of hypnotic efficacy may occur with short-acting benzodiazepines after repeated use over several weeks.

Rebound sleep disturbance

Sleep disturbance may recur on withdrawal of Dormicum therapy, and may even be more marked than before starting treatment (“rebound sleep disturbance”). Rebound sleep disturbances are generally only transient, but they may be associated with other reactions, such as mood swings, anxiety and nervousness. The risk of rebound sleep disturbance is

increased by abrupt treatment withdrawal. Hence the recommendation that the dose of Dormicum be reduced gradually.

Amnesia

Dormicum may cause anterograde amnesia, typically for the first few hours after dosing. To reduce the risk of such amnesia, patients should ensure that they can sleep uninterruptedly for 7–8 hours after dosing.

Residual effects

When the oral dose of Dormicum does not exceed 15 mg/day and an uninterrupted sleep duration of 7–8 hours is guaranteed after dosing, no residual effect is observed after oral Dormicum administration in normal patients. This has been confirmed by clinical observations made using sensitive pharmacological methods.

Psychiatric and paradoxical reactions

Paradoxical reactions can occur during treatment with benzodiazepines. These reactions include: nervousness, agitation, irritability and aggression, also more rarely delusional ideas, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other unwanted behavioural disturbances. Treatment should be withdrawn should such reactions occur. Such reactions may occur more frequently in elderly patients and children.

Special patient groups

The usual dose is 7.5 mg for elderly and/or frail patients as well as those with respiratory or cardiovascular insufficiency. The probability of unwanted effects, such as respiratory or circulatory depression, is higher with midazolam in such patients. Dormicum must therefore be used with great caution in these patient groups; if necessary, a lower dosage must be chosen.

Patients with hepatic impairment

Dormicum must be used with caution in these patient groups due to the change in its pharmacokinetics (prolongation of the elimination half-life, increase in bioavailability).

Obese patients

The volume of distribution of midazolam is increased in obese patients, leading to a prolongation of the elimination half-life. This may require longer monitoring of this group of patients after surgery.

Concomitant use of alcohol/CNS depressants

Avoid the concomitant use of Dormicum with alcohol and/or CNS depressants. Such a combination potentiates the clinical effect of Dormicum and may cause severe sedation and clinically significant respiratory and/or cardiovascular depression (see *Interactions*).

History of alcohol or prescription drug abuse

Dormicum must be used with very great caution in patients with a history of alcohol, prescription drug or street drug abuse.

Concomitant use of substances that alter CYP3A4 activity
Concomitant use of substances that inhibit or induce CYP3A4 alters the pharmacokinetics of midazolam. As a consequence the clinical and undesirable effects may be increased or decreased.

Dependence

Use of Dormicum may lead to physical dependence. This risk increases with prolonged use, high doses and in predisposed patients with a known history of alcohol and/or prescription drug abuse.

Depending on the substance's duration of action, withdrawal symptoms occur a few hours to one week, or even longer, after discontinuation of treatment.

To minimise the risk of dependence, benzodiazepines should be prescribed only after thorough consideration of the indication and taken for as short a period as possible (as a hypnotic, for example, generally for no longer than two weeks). The need for continued treatment must be periodically reviewed. Prolonged treatment is indicated only in certain patients (for example, with panic states) and its benefit, given the risks, is less clear.

To avoid withdrawal symptoms, it is recommended that treatment be discontinued in all cases by gradual dose reduction. If such symptoms occur nonetheless, they require very close medical surveillance and patient management.

Withdrawal symptoms
Withdrawal symptoms may comprise headaches, muscle pains, extreme anxiety, tension, nervousness, confusion and irritability. Severe cases may also include episodes of derealisation and depersonalisation, hyperacusis, tingling and numbness of the extremities, sensitivity to light, noise and touch, hallucinations and convulsions.
Since the risk of withdrawal symptoms and rebound sleep disturbance is increased after abrupt withdrawal, it is recommended that the dose be decreased slowly.

Even after short-term use, discontinuation of the product may be followed by recurrence of the sleep disturbance for a few nights. This phenomenon can generally be avoided by stepwise dose reduction.

Lactose intolerance
Film-coated Dormicum tablets contain lactose. Patients with rare hereditary problems due to galactose intolerance (Lapp lactase deficiency or glucose-galactose malabsorption) should not take the tablets.

Interactions

Pharmacokinetic drug-drug interaction (DDI)
Because midazolam is almost exclusively metabolised by the CYP3A4 isoenzyme of cytochrome P450, modulators of CYP3A4 may alter the plasma concentrations of midazolam and hence its clinical effects.

When coadministered with a CYP3A4 inhibitor, the clinical effects of orally administered midazolam may be enhanced and prolonged, making the use of a lower dose necessary. Conversely, the effect of midazolam may be diminished and short-lived when coadministered with a CYP3A4 inducer, making the use of a higher dose necessary.

In the case of CYP3A4 induction and irreversible inhibition (so-called mechanism-based inhibition), the effect on the pharmacokinetics of midazolam may persist for several days, or even a few weeks, after administration of the CYP3A4 modulator. Notable examples include clarithromycin, erythromycin, HIV protease inhibitors, verapamil and diltiazem.

In the case of coadministration with ethinylestradiol/norgestrel oral contraceptives (mechanism-based inhibitors), exposure to midazolam is not significantly modified.

Classification of CYP3A4 inhibitors

CYP3A4 inhibitors can be classified by the strength of their inhibitory effect and the degree to which their clinical effects are altered by coadministration with oral midazolam:

- Very strong inhibitors: increase in the midazolam AUC by a factor greater than ten and in C_{max} by a factor greater than three.

The following medicines fall into this category: ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, including protease inhibitor combinations containing ritonavir.

The combination of oral midazolam with very strong CYP3A4 inhibitors is contraindicated (see Contraindications*).*

- Strong inhibitors: increase in the midazolam AUC by a factor of between five and ten and increase in C_{max} by a factor greater than three and

- moderately strong inhibitors:

Increase in the midazolam AUC by a factor of between two and five and increase in C_{max} by a factor of between two and three. The following medicines are identified as moderately strong inhibitors: fluconazole, clarithromycin, telithromycin, saquinavir, erythromycin, diltiazem, verapamil, nefazodone, aprepitant, tabimoreline.

If administration of Dormicum film-coated tablets cannot be avoided in patients treated with a strong inhibitor, the dose of midazolam should be decreased by 50-75%.

Combination of midazolam with strong and moderately strong CYP3A4 inhibitors requires careful evaluation of the individual patient's condition, with particular regard to an increased sensitivity to the potential adverse effects of midazolam (see Warnings and Precautions*).*

- Weak inhibitors: increase in the midazolam AUC by a factor of between 1.25 and less than two and increase in C_{max} by a factor of between 1.25 and less than two.

The following medicines and herbals belong to this category: posaconazole, roxithromycin, cimetidine, ranitidine, fluvoxamine, bicalutamide, propiverine, grapefruit juice, *Echinacea purpurea*, and *Curcuma* rhizome.
Coadministration of midazolam with weak CYP3A4 inhibitors does not normally lead to marked changes in the clinical effect of midazolam.

CYP3A4 inducers
Patients cotreated with midazolam and CYP3A4 inducers may require higher doses, in particular in combination with a strong inducer of CYP3A4. The well-known strong inducers of CYP3A4 are rifampicin, carbamazepine and phenytoin. Patients receiving these medicines require higher doses of midazolam. The moderately strong inducers of CYP3A4 are efavirenz and St John's wort.

Pharmacodynamic drug-drug interactions (DDI)

As can be expected, coadministration of midazolam with other sedatives/hypnotics potentiates the sedative and hypnotic effect. Such sedatives/hypnotics include: alcohol, opiates/opioids (used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; also sedative antidepressants, antihistamines, antiepileptics and centrally acting antihypertensive drugs. This potentiation of effect may, as appropriate, be put to therapeutic use. This accentuation of effect should be particularly taken into account in high-risk patients. In isolated cases, the mutual potentiation of alcohol and Dormicum may produce unpredictable reactions.

Midazolam decreases the minimum alveolar concentration (MAC) of inhalational anesthetics.

Enhanced side effects such as sedation and cardiovascular depression may also occur when midazolam is coadministered with any centrally acting depressant, including alcohol. The combined ingestion of alcohol and midazolam should be avoided

Refer to the *Overdosage* section for warnings regarding other central nervous system depressants, including alcohol.

Drugs increasing alertness and memory, such as the AchE inhibitor physostigmine, may abolish the hypnotic effects of midazolam. Similarly, administration of caffeine partly abolished the sedative effect of midazolam at a dose of 250 mg.

Pregnancy and lactation

Pregnancy

Clear evidence exists of risks to the human fetus associated with benzodiazepine use during pregnancy.

Benzodiazepines should not be used in pregnancy unless absolutely necessary.

Caution is mandatory when benzodiazepines are taken in the last trimester of pregnancy or at high doses during delivery since an irregular heart rate and hypotension may occur in the fetus, together with poor sucking, respiratory depression, decreased activity, decreased muscle tone (floppy infant syndrome), withdrawal symptoms and hypothermia in the neonate.

The risk of malformations in humans appears to be low after therapeutic doses of benzodiazepines are taken at the start of pregnancy, although some epidemiological studies have suggested the existence of an increased risk of cleft palate. Cases of malformation and mental retardation in children exposed during the prenatal period have

been reported after benzodiazepine overdosage and intoxication. Children whose mothers have taken benzodiazepines for a prolonged period during pregnancy may develop physical dependence. Such children exhibit withdrawal symptoms in the post-partum period.

Lactation

Given that midazolam is excreted in breast milk, it should not be used in nursing mothers.

Effects on ability to drive and operate machinery

Dormicum has a marked effect on the ability to drive or operate machinery.

Patients should be instructed not to drive or operate machinery until they have fully recovered their normal alertness and reactions. Such activities should be avoided for the first seven to eight hours after taking the drug.

Undesirable effects

Fatigue should generally be expected during treatment with midazolam: this symptom occurs predominantly at the start of therapy and normally disappears with repeated administration.

Because of these adverse effects, elderly users are at increased risk of falls and fractures.

The following undesirable effects have been reported very rarely after administration of Dormicum tablets.

Immune system

Hypersensitivity reactions.

Psychiatric disorders

Confusional state, emotional disorder. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration.

Occasional libido disorders.

Pre-existing depression may be unmasked during benzodiazepine therapy.
Paradoxical reactions such as nervousness, agitation, confusion, apathy, aggression, rages, delusional ideas, sullenness, nightmares, hallucinations, euphoria, psychosis, inappropriate behaviour or other behavioural disturbances. The drug should be withdrawn if such paradoxical reactions occur. The probability of such reactions is higher in elderly patients.

Dependence: use of midazolam – even at therapeutic doses – may lead to the development of physical dependence after prolonged administration. Abrupt drug withdrawal may be associated with withdrawal symptoms or rebound phenomena, such as rebound insomnia, mood changes, anxiety, and nervousness that may even include

withdrawal convulsions. Psychological dependence may occur. Abuse may be found among poly-drug abusers.

Nervous system

Prolonged sedation, convulsions (more frequently in premature infants or neonates whose mothers have taken midazolam in pregnancy), daytime drowsiness, headaches, dizziness, decreased attention, ataxia, tremor, stupor, psychomotor hyperactivity. These phenomena occur predominantly at the start of therapy and generally disappear with repeated administration.

When used as premedication, midazolam may contribute to postoperative sedation.

Anterograde amnesia may occur, even at therapeutic doses. Risk increases dose proportionately. The amnesic effect may be associated with inappropriate behaviour.
Anterograde amnesia may still be present at the end of the procedure and in isolated cases has been reported to last even longer.

Eye disorders

Diplopia. This phenomenon occurs predominantly at the start of therapy and generally disappears with repeated administration.

Cardiac disorders

Heart failure, including cardiac arrest, increased heart rate.

Vascular disorders

Hypotension.

Respiratory organs

Respiratory depression, respiratory distress, respiratory arrest, laryngospasm.

Life-threatening events are more likely to occur in adults over 60 years of age and in patients with pre-existing respiratory or cardiac insufficiency, above all if injection is too rapid or the dose high (see *Warnings and precautions*).

Gastrointestinal disorders

Gastrointestinal disorders, nausea, vomiting, constipation, dry mouth, hiccough.

Skin disorders

Skin reactions such as urticaria, skin rash, pruritus.

Musculoskeletal disorders

Muscle weakness. This phenomenon occurs predominantly at the start of therapy and usually disappears with repeated administration.

Overdosage

Symptoms
The symptoms of Dormicum overdosage essentially comprise an intensification of the therapeutic effect (clouding of consciousness, ataxia, dysarthria, nystagmus). Dormicum overdosage is seldom life-threatening when the drug is taken alone, but may lead to areflexia, apnea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, generally lasts only a few hours but it may also be more protracted and cyclical, above all in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory or central nervous system effects.

After oral ingestion, further absorption should be prevented using appropriate methods, e.g. by administering activated charcoal within the following one or two hours. In drowsy patients, airway protection is imperative when using activated charcoal. In cases of mixed ingestion, gastric lavage may be considered, but not as a routine measure.
If CNS depression is severe, the use of flumazenil (Anexate®), a benzodiazepine antagonist, should be considered. However, it should be administered under closely monitored conditions. The drug has a short half-life (about one hour), meaning that patients administered flumazenil must be monitored once its effects have worn off. Flumazenil should be used with great caution after the ingestion of medicines that lower the seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil (Anexate®) for further information on the correct use of this medicine.

Properties and effects

ATC code: N05CD08

Mechanism of action

Dormicum is a sleep-inducing agent characterised by a rapid onset of action and a short residence time in the body.

Sleep onset generally occurs less than 20 minutes after Dormicum ingestion, with sleep duration returning to normal for the patient's age. Dormicum also exerts anxiolytic, hypnotic, anticonvulsant and muscle-relaxant effects. It impairs psychomotor function after single and/or repeated administration but only causes minimal hemodynamic changes.

In patients treated with a suitable dose producing an appropriate sleep duration, no impairment of performance or reaction times has been observed.

Pharmacodynamics

Midazolam, the active ingredient of Dormicum, is a benzodiazepine derivative. The free base is a lipophilic substance with low solubility in water.

Thanks to the basic nitrogen in position 2 of the imidazobenzodiazepine ring system, the active ingredient of Dormicum is able to form water-soluble salts with acids.

From the pharmacological viewpoint, Dormicum is characterised by a rapid onset of action and, thanks to rapid metabolic transformation, by a short duration of action. Dormicum displays low toxicity and hence possesses a wide therapeutic safety margin.

As for other benzodiazepines, it is presumed that agonistic binding to gamma-aminobutyric acid ($GABA_A$) receptors in the central nervous system is responsible for the clinical effect. The hypothesis supposes that benzodiazepines do not directly activate $GABA_A$ receptors but require the endogenous ligand, i.e. GABA, to exert their effects.

Dormicum exerts a very rapid sedative and sleep-inducing effect. It also exerts anxiolytic, anticonvulsant and muscle-relaxant effects.

Clinical efficacy

Several controlled clinical trials as well as various sleep laboratory studies have shown that Dormicum shortens sleep onset and prolongs sleep duration without quantitatively impairing REM sleep. Waking phases are reduced and sleep has a more marked restorative effect.

Pharmacokinetics

Absorption

After oral administration of Dormicum, midazolam is absorbed rapidly and completely.

The absolute bioavailability of the tablets ranges between 30 and 50%. The pharmacokinetics of midazolam are linear in the 7.5-20 mg oral dose range.

Peak plasma concentrations of 70-120 ng/ml are reached within one hour after ingesting a single 15 mg dose of midazolam tablets. Concomitant food ingestion delays the time to peak plasma concentration by one hour (fed t_{max} = 1.7 h; fasted t_{max} = 1 h), indicating a reduced absorption rate of midazolam. The absorption half-life is 5-20 minutes.

Distribution

The tissue distribution of midazolam is rapid: the distribution phase is complete within 1-2 hours after oral administration. The volume of distribution at steady state is 0.7-1.2 l/kg after intravenous administration. Midazolam is 96-98% bound to plasma proteins. Protein binding is due essentially to albumin. There is slow and insignificant passage into the cerebrospinal fluid.

In humans, midazolam has been shown to cross the placental barrier slowly and enter the fetal circulation. Half to one hour after administration of a 15 mg oral dose, the ratio of fetal (cord blood) to maternal serum concentration was 0.6-1.0. The elimination half-life of midazolam in newborn infants is approximately 6.3 hours. Small amounts of midazolam have also been detected in human breast milk.

Metabolism

Midazolam is almost entirely eliminated by biotransformation. Less than 1% of the dose is recovered in urine as the unchanged substance. Midazolam is hydroxylated by the cytochrome P450 CYP3A4 isoenzyme. The two isoenzymes, CYP3A4 and CYP3A5, are actively involved in the hepatic oxidative metabolism of midazolam. The two main oxidised metabolites are 1'-hydroxymidazolam (also named α-hydroxymidazolam) and 4'-hydroxymidazolam. The major urinary and plasma metabolite is 1'-hydroxymidazolam. 60-80% of the dose is glucuronidated and excreted in the urine in the form of the 1'-hydroxymidazolam conjugate. Plasma concentrations of 1'-hydroxymidazolam may reach 30-50% those of the parent compound. 1'-hydroxymidazolam is pharmacologically active and contributes significantly (about 34%) to the effect of oral midazolam. Studies have not shown clinically relevant genetic polymorphism in the oxidative metabolism of midazolam (see *Interactions*).

Elimination

In young healthy volunteers, the elimination half-life of midazolam ranges between one and half hours and two and half hours.

No accumulation occurs when midazolam is taken once daily in the evening. Repeated administration of midazolam does not induce specific metabolic enzymes. The elimination half-life of 1'-hydroxymidazolam is less than one hour.

Pharmacokinetics in special patient groups

Elderly patients

In male volunteers over 60 years of age the elimination half-life of midazolam was significantly longer (by a factor of 2.5) than in young male volunteers. In elderly male volunteers, total midazolam clearance was markedly reduced and the bioavailability of the oral tablet was significantly increased.

However, no significant difference was observed in elderly female volunteers compared to young female volunteers.

Patients with hepatic impairment

The pharmacokinetics of midazolam were significantly modified in patients with chronic liver disease, including advanced liver cirrhosis. In particular, in cirrhotic patients, the elimination half-life was prolonged and the total bioavailability of oral midazolam significantly increased compared to the control group as a consequence of decreased liver clearance.

Patients with renal impairment

The pharmacokinetics of midazolam are not altered in patients with chronic renal failure. However the major midazolam metabolite, 1'-hydroxymidazolam glucuronide, which is excreted through the kidney, accumulates in severe renal failure. This accumulation produces a prolonged sedation. Oral midazolam should therefore be administered with great caution in patients with renal impairment.

Obese patients

In obese patients the volume of distribution of midazolam is increased. As a consequence, the elimination half-life of midazolam is longer in obese than in normal-weight patients (5.9 hours versus 2.3 hours). The oral bioavailability of midazolam tablets was identical in obese and normal-weight patients. This may require longer patient monitoring after surgery. Patients should be alerted to the fact that the effect of midazolam may be prolonged.

Preclinical data

Mutagenic and carcinogenic potential

Liver and thyroid tumours were observed in long-term studies in mice and rats. According to prevailing opinion, these data cannot be extrapolated to humans.

The results of *in vitro* and *in vivo* genotoxicity studies show that no mutagenic, clastogenic or aneugenic effects are to be expected during the intended clinical use of midazolam.

Reproductive toxicology

Like all benzodiazepines, midazolam crosses the placental barrier.

Teratogenicity

In studies in rats and mice, midazolam showed no evidence of teratogenic properties.

However, signs of behavioural disturbances were observed in the offspring of dams exposed to benzodiazepines.

Additional information

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the packaging.

Special precautions for storage

Dormicum film-coated tablets 7.5 mg: do not store above 30°C.

Dormicum film-coated tablets 15 mg: protect from light and do not store above 30°C.

Packs

7.5 mg (scored) tablets	10
15 mg (scored) tablets	10, 30, 100

This is a medicament
A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
The doctor and the pharmacist are experts in medicine, its benefits and risks.
Do not by yourself interrupt the period of treatment prescribed for you.
Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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