Information for Health Professionals

Valium®

Diazepam

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Tranquilizer and anxiolytic.
ATC code: N05BA01.

1.2 Type of Dosage Form

Ampoules.

1.3 Route of Administration

- Intravenous injection
- Intramuscular injection

1.4 Sterile/Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

Active ingredient: diazepam.
Ampoules 10 mg in 2 mL.
Valium ampoules contain benzyl alcohol. For warning related to benzyl alcohol (see *2.4.1 Warnings and Precautions, General*).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

The injection form of Valium is indicated for basal sedation before proceeding with major therapeutic interventions, such as cardioversion, cardiac catheterization, endoscopy, radiological procedures, minor surgical interventions, in order to relieve apprehension, anxiety, acute stress and to diminish recollections of such procedures.

The injection form is also suitable for premedication of patients suffering from anxiety and stress.

Excitation: In psychiatry, Valium is used in the treatment of excitation states associated with acute anxiety and panic, as well as in motor unrest and delirium tremens.

Valium is indicated to treat status epilepticus and other convulsive states (including tetanus).

Valium is useful for the relief of reflex muscle spasm due to local trauma (injury, inflammation). It can also be used to combat spasticity arising from damage to spinal and supraspinal interneurons e.g. cerebral palsy and paraplegia, as well as in athetosis and “stiff-man” syndrome.

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2.2 Dosage and Administration

General

For optimal effect, the dosage should be carefully individualized. While the usual daily dosages given below will meet the needs of most patients, there will be some who may require higher doses.

For adults and adolescents, a parenteral dose of 2-20 mg injected i.m. or i.v. is generally recommended, depending on body weight, indication and severity of symptoms. In some indications (e.g. tetanus) higher doses may occasionally be required.

Intravenous injection of Valium should always be slow (approximately 0.5-1 mL per minute), as excessively rapid administration can lead to apnea; resuscitation apparatus must be kept ready at all times.

Special Dosage Instructions

Anesthesiology

Premedication: 10-20 mg intra-muscular; children 0.1-0.2 mg/kg body weight, 1 hour before the induction of anesthesia.

Induction of anesthesia: 0.2-0.5 mg/kg body weight given intravenously.

Basal sedation prior to the actual interventions: 10–30 mg intravenous, children: 0.1–0.2 mg/kg body weight. The best method of finding the right dosage for patients is by giving the initial injection of 5 mg (1 mL) or 0.1 mg/kg body weight, which is then repeated every 30 seconds by 2.5 mg (0.05 mg/kg body weight) until eyelids close.

Tetanus

0.1-0.3 mg/kg body weight should be given intravenously in intervals at 1-4 hours, or by infusion (3-4 mg/kg body weight in 24 hours); same dosage.

Status Epilepticus

0.15-0.25 mg/kg body weight should be given intravenously repeated as necessary after 10-15 minutes.

Maximum dose: 3 mg/kg body weight in 24 hours.

Excitation States (Acute Anxiety States, Motor Unrest or Delirium Tremens)

Initially 0.1-0.2 mg/kg body weight given intravenously, repeated at 8-hourly intervals until acute symptoms subside, then continue with oral treatment.

Muscle spasm

For muscle spasm due to local pathology, cerebral paralysis, athetosis, stiff-man syndrome, the initial dose is 5 mg – 10 mg i.m. or i.v. and then 5 mg–10 mg within 3–4 hours, if necessary.

Cardioversion

Relieve anxiety and apprehension and to diminish recollection of such procedures: 5 mg–15 mg i.v. within 5–10 minutes prior to procedures.

Intramuscular: Valium ampoules is injected into the muscle.

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2.3 Contraindications

Valium is contraindicated in patients with a known history of hypersensitivity to benzodiazepine or dependence on other drugs including alcohol. Acute withdrawal reactions occurs in patients which are dependent on other drugs and alcohol.

Injection Valium is contraindicated in patients with acute pulmonary insufficiency, respiratory depression, phobia or obsession, and chronic psychoses, acute narrow angle glaucoma and open angle glaucoma, except for patients receiving the appropriate therapy.

2.4 Warnings and Precautions

2.4.1 General

Concomitant use of alcohol/CNS depressants
The concomitant use of Valium with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Valium possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardio-vascular depression (see *2.8 Interactions with other Medicinal Products and other Forms of Interactions* and *2.7 Overdose*).

However, the sedative effect can, on the contrary, benefit some patients by reducing respiratory effort. In severe chronic hypercapnia, any use of Valium is permitted only whenever the benefit is greater than the risks.

Medical history of alcohol or drug abuse
Valium should be used with extreme caution in patients with a history of alcohol or drug abuse (see *2.4.2 Drug Abuse and Dependence*).

Valium should be avoided in patients with dependence on CNS depressants including alcohol.

An exception to the latter is the management of acute withdrawal reactions.

Hepatic impairment
Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment. Special caution should be exercised when administering Valium to patients with mild to moderate hepatic impairment.

For effect on driving see *2.4.3 Ability to Drive and Use Machines*.

For warnings related to dependence, withdrawal and rebound anxiety see *2.4.2 Drug Abuse and Dependence*.

If Valium is to be administered concomitantly with a narcotic analgesics, the dosage of narcotic must be reduced at least a third and administered with low increments. In some cases, use of narcotic is unnecessary.

Valium injection is not to be given to patients while in shock, coma or during acute alcohol intoxication with signs of vital depressions.

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Monitoring must be maintained for an extended therapy and any prolonged use of this drug must have considered both the benefit and negative effect of the use of this drug.

Psychiatric and 'paradoxical' reactions
Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, the use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

Amnesia
It should be borne in mind that benzodiazepines may induce anterograde amnesia. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Tolerance
Some loss of response to the effects of benzodiazepines may develop after repeated use of Valium for a prolonged time.

Pediatric use
Since the safety and effectiveness in pediatric patients below the age of 6 months have not been established, Valium should be used in this age group with extreme caution and only when other therapeutic alternatives are not available.

Geriatric use
Lower doses should be used for elderly and debilitated patients.

Respiratory Insufficiency
A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering Valium to a patient with myasthenia gravis owing to pre-existing muscle weakness.

Care must be used in administering injectable Valium, particularly by the i.v. route, to the elderly, to very ill patients and to those with limited pulmonary reserve because of the possibility that apnea and/or cardiac arrest may occur.

The benzyl alcohol contained in Valium ampoules may lead to irreversible damage in the newborn, especially in the premature. Therefore, for these patients the ampoules should only be used if no therapeutic alternative is available.

Very small veins should not be selected for injection. In particular, intra-arterial injection or extravasation must be strictly avoided because venous thrombosis, phlebitis, local irritation, swelling or - less frequently - vascular changes may occur, particularly after rapid i.v. injection.

Valium ampoules should be used with caution in patients with sleep apnea due to possible additive effects on respiratory depression.

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2.4.2 Drug Abuse and Dependence

Dependence

Use of benzodiazepines and benzodiazepine-like agents may lead to the development of physical and psychological dependence (see *2.6 Undesirable Effects*). The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse. Abuse has been reported in poly-drug abusers. Valium should be used with extreme caution in patients with a history of alcohol or drug abuse.

In order to reduce the risk of dependency, benzodiazepines shall be used only after careful consideration of the indication and shall be used in shortest duration possible.

Withdrawal

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms These may consist of headache, diarrhea, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or convulsions.

When benzodiazepines are used, withdrawal symptoms may develop when switching to a benzodiazepine with a considerably shorter elimination half-life.

Rebound anxiety

A transient syndrome whereby the symptoms that led to treatment with Valium recurs in an enhanced form. This may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety, sleep disturbances, and restlessness.

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

2.4.3 Ability to Drive and Use Machines

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or operate machinery. Prior to receiving Valium, the patient should be warned not to drive a vehicle or operate a machine until completely recovered. The physician should decide when these activities may be resumed.

If sleep duration is insufficient or alcohol is consumed, the likelihood of impaired alertness may be increased (see *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

If the product is prescribed to a woman of childbearing potential, she should contact her physician regarding discontinuation of the product if she intends to become or suspects that she is pregnant.

2.5.2 Pregnancy

The safety of Valium for use in human pregnancy has not been established. An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested.

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Review of spontaneously reported adverse drug events shows no greater incidence than would be anticipated from a similar untreated population. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Before administering Valium during pregnancy, especially during the first trimester, possible risks for the fetus should - as with any other drug - be weighed against the expected therapeutic benefit for the mother.

Continuous administration of benzodiazepines during pregnancy may give rise to hypotension, reduced respiratory function and hypothermia in the newborn child (see *3.2.5 Pharmacokinetics in Special Populations*). Withdrawal symptoms in newborn infants have occasionally been reported with this class of drugs.

Labour and Delivery
Special care must be taken when Valium is used during labour and delivery, as high single doses may produce irregularities in the fetal heart rate and hypotonia, poor sucking, hypothermia and moderate respiratory depression in the neonate. With newborn infants it must be remembered that the enzyme system involved in the breakdown of the drug is not yet fully developed (especially in premature infants).

2.5.3 Lactation
Since diazepam passes into breast milk, Valium should not be administered to breast-feeding mothers.

2.5.4 Pediatric Use
For uses on children, the efficacy and safety of parenteral Valium has not been proven in neonates (age 30 days or less).

For pediatric use, in order to achieve the maximum clinical effect with minimum amount of drug and thus reducing severe side effects such as apnea or prolong drowsiness, it is recommended that the drug is administered slowly at period of more than 3 minutes at dosage no greater than 0.25 mg/kg, after an interval of 15-30 minutes, the initial dose may be repeated safely. If the symptoms did not subside after three administration, appropriate use of additional drug may be recommended for the condition being treated.

See also section *3.2.5 Pharmacokinetics in Special Populations.*

2.5.5 Geriatric Use
Benzodiazepine pharmacologic effects appear to be greater in elderly patients than in younger patients even at similar plasma benzodiazepine concentrations, possibly because of age-related changes in drug–receptor interactions, post-receptor mechanisms and organ function.

See also section *3.2.5 Pharmacokinetics in Special Populations.*

2.5.6 Renal Impairment
In treating patients with kidney failure, precautions must be taken (see *3.2.5 Pharmacokinetics in Special Populations*).

2.5.7 Hepatic Impairment
In treating patients with liver failure, precautions must be taken (see *2.4.1 Warnings and Precautions, General, 3.2.5 Pharmacokinetics in Special Populations*).

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2.6 Undesirable Effects

2.6.1 Clinical Trials
No text.

2.6.2 Postmarketing Experience
The most commonly reported undesirable effects are fatigue, drowsiness, and muscle weakness; they are usually dose- related. These phenomena occur predominantly at the start of therapy and usually disappear with prolonged administration.

Nervous System Disorders: Ataxia, dysarthria, slurred speech, headache, tremor, dizziness, decreased alertness. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

Psychiatric Disorders: Paradoxical reactions such as restlessness, agitation, irritability, disorientation, aggressiveness, nervousness, hostility, anxiety, delusion, anger, nightmares, abnormal dreams, hallucinations, psychoses, hyperactivity, inappropriate behaviour and other adverse behavioural effects are known to occur. Should this occur, the use of the drug should be discontinued. They are more likely to occur in children and in the elderly. Confusional state, emotional and mood disturbances, depression, changes in libido have also been reported.

Chronic use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see *2.4.2 Drug Abuse and Dependence*).

Abuse of benzodiazepines has been reported in poly-drug abusers (see *2.4.2 Drug Abuse and Dependence*).

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

Gastrointestinal Disorders: Nausea, dry mouth or hypersalivation, constipation and other gastrointestinal disturbances.

Eye Disorders: Diplopia, vision blurred.

Vascular Disorders: Hypotension, circulatory depression.

Investigations: Irregular heart rate, very rarely increased transaminases, increased blood alkaline phosphatase.

Renal and Urinary Disorders: Incontinence, urinary retention.

Skin and Subcutaneous Tissue Disorders: Skin reactions.

Ear and Labyrinth Disorders: Vertigo.

Cardiac Disorders: Cardiac failure including cardiac arrest.

Respiratory Disorders: Respiratory depression including respiratory failure.

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Hepatobiliary Disorders: Very rarely jaundice.

General Disorders and Administration Site Conditions:
Venous thrombosis, phlebitis, local irritation, swelling or - less frequently - vascular changes may occur, particularly after rapid i.v. injection.

Very small veins should not be selected for injection. In particular, intra-arterial injection or extravasation must be strictly avoided.

Intramuscular injection can result in local pain, in some cases accompanied by injection site erythema. Tenderness is relatively common.

Respiratory, Thoracic and Mediastinal Disorders: Cardiorespiratory depression may occur if the Valium is administered rectally.

Laboratory Abnormalities
See undesirable effects listed above (section *2.6.2 Post Marketing*).

2.7 Overdose

Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Valium is seldom life-threatening, but may lead to areflexia, apnea, hypotension, cardiorespiratory depression, coma (rarely), and death (very rarely). Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Overdose of benzodiazepines in combination with other CNS depressants (including alcohol) may be fatal and should be closely monitored. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

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

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

Further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe consider the use of flumazenil (Anexate®), a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil (Anexate®), for further information on the correct use of this drug.

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2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

Pharmacokinetic Drug-Drug Interaction (DDI)
The metabolism of diazepam and its main metabolite, DMDZ depends on the cytochrome P450 isozymes CYP3A4 and CYP2C19. Modulators of these enzymes may lead to changes in diazepam disposition and effects. Strong interactions are seen with compounds which affect both of diazepam's oxidative metabolic pathways simultaneously; moderate effects only occur even with strong inhibitors if they affect only one of diazepam's metabolic pathways. Inhibitors of CYP3A4 and CYP2C19 decrease metabolic rate and may led to higher than normal concentrations of diazepam and the desmethyl metabolite and consequently to increased/ prolonged sedation and anxiolytic effects. Such changes may exacerbate diazepam's effects in patients with increased sensitivity, e.g. due to their age, reduced liver function or treatment with other drugs that impair oxidation. Inducers of CYP3A4 and CYP2C19 may lead to lower than expected concentrations and hence to a lack of desired efficacy.

Effect of other drugs on the pharmacokinetics of diazepam
Enzyme inhibitors
Grapefruit juice contains strong inhibitors of CYP3A4. Diazepam exposure was strongly increased (AUC 3.2-fold; C_{max} 1.5-fold) and time to reach maximum concentration was delayed when diazepam was given with grapefruit juice instead of water.

Antimycotic azole derivatives inhibit CYP3A4 and CYP2C19 pathways and lead to increased exposure to diazepam (diazepam AUC ratio fluconazole 2.5; voriconazole 2.2) and prolonged elimination half-life of diazepam (with fluconazole from 31 h to 73 h; with voriconazole from 31 h to 61 h). The influence of the antimycotics on diazepam levels was only seen at 4 hours after administration and beyond. Itraconazole has a more moderate effect with no clinically significant interaction with diazepam as determined by psychomotor performance tests.

The serotonin reuptake inhibitor fluvoxamine is also an inhibitor of both of diazepam's degradation pathways and increased not only exposure to diazepam by 180% and prolonged its elimination half-life from 51 h to 118 h, but also increased exposure and time to reach steady state of the desmethyl metabolite. Fluoxetine showed a more moderate effect on diazepam AUC (approximately 50% increase) and did not affect psychomotor response because combined concentrations of diazepam and desmethyldiazepam were similar with and without fluoxetine.

Combined hormonal contraceptives appear to reduce the clearance (by 40%) and prolong elimination half-life (by 47%) of diazepam. Diazepam-induced psychomotor impairment in women on contraceptives may be higher during the 7-day menstrual pause when off the hormone preparation than when taking the contraceptive. There is some limited evidence that benzodiazepines can increase the incidence of break-through bleeding in women with hormonal contraceptives. A drug interaction causing pregnancy was not observed.

The proton pump inhibitor omeprazole, a CYP2C19 and CYP3A4 inhibitor, administered at a dose of 20 mg o.d. increased the diazepam AUC by 40% and the half-life by 36%, at a dose of 40 mg o.d. omeprazole increased the diazepam AUC by 122% and the half-life by 130%. The elimination of desmethyldiazepam was reduced as well. The effect of omeprazole was only seen in extensive but not slow metabolizers of CYP2C19. Esomeprazole (but not lansoprazole or pantoprazole) has the potential to inhibit the metabolism of diazepam to a similar degree as omeprazole.

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The histamine H_2-receptor antagonist cimetidine, an inhibitor of multiple CYP isozymes, including CYP3A4 and CYP2C19, reduces the clearance of diazepam by 40 to 50% and of desmethyldiazepam by approximately 30%. The effect is no different after one day or after chronic treatment with cimetidine and results in higher exposure to and a prolonged elimination half-life of diazepam and its main metabolite after single dosing and to higher steady-state concentrations after multiple dosing of diazepam. Enhanced sedation was seen with co-administration of cimetidine. No such pharmacokinetic interaction was seen with the H_2-antagonists ranitidine and famotidine.

Disulfiram inhibits the metabolism of diazepam (median decrease in clearance 41%, increase in half-life 37%) and probably the further metabolism of diazepam's active metabolites. Enhanced sedative effects may result.

Antituberculosis therapy may change the disposition of diazepam. In presence of isoniazid diazepam mean exposure (AUC) and half-life were increased (on average 33-35%) with the largest changes seen in subjects with slow-acetylator phenotype.

The calcium channel blocker diltiazem, a substrate for the same CYP isozymes as diazepam and an inhibitor of CYP3A4, increased AUC (by approximately 25%) and prolonged half-life (by 43% in extensive CYP2C19 metabolizers) of diazepam with little differences between subjects with different CYP2C19 phenotypes. In the presence of diltiazem exposure to desmethyldiazepam also tended to increase.

The primary metabolite of idelalisib is a strong CYP3A4 inhibitor and increases the serum concentrations of diazepam so that dose reduction may have to be considered.

The psychostimulants modafinil and armodafinil induce CYP3A4 and inhibit CYP2C19; they may prolong the elimination of diazepam and cause excessive sedation.

Enzyme inducers
Rifampicin very potently induces CYP3A4 and has also a significant accelerating effect on the CYP2C19 pathway. When dosed at 600 mg daily for 7 days, diazepam clearance was increased 4.3-fold and AUC decreased by -77%. A significant reduction in exposure to all diazepam metabolites was also observed. Doubling the daily rifampicin dose did not further increase its effect.

Carbamazepine is a known inducer of CYP3A4 and accelerated elimination (increased clearance, reduced half-life) of diazepam 3-fold while increasing concentrations of desmethyl-diazepam.

Effect of diazepam on the pharmacokinetics of other drugs
Diazepam has not been found to induce or inhibit metabolizing enzymes. Nevertheless some interactions with other drugs occur where diazepam is the precipitant.

Phenytoin therapy was associated with higher concentrations and increased phenytoin intoxication when combined with diazepam. However, some authors have found no interaction or even lowered plasma concentrations of phenytoin when co-administered with diazepam.

There have also been reports that the metabolic elimination of phenytoin is affected by diazepam. In addition, there is no known interference with commonly used antidiabetic, anticoagulant or diuretic drugs.

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Pharmacodynamic Drug-Drug Interaction (DDI)
Alcohol should be avoided in patients receiving Valium (see *2.4.1 Warnings and Precautions, General*).

See section *2.7 Overdose* for warning of other central nervous system depressants including alcohol.

Enhanced side effects such as sedation and cardio-respiratory depression, may also occur when Valium co-administered with any centrally acting depressants including alcohol.

There are several reports of severe hypotension, respiratory depression or loss of consciousness in patients under combined treatment with clozapine and benzodiazepines, including diazepam.

Additive CNS depressant effects can be expected when combining phenothiazines and benzodiazepines; sedation, respiratory depression and airway obstruction has been reported with the combined use of levopromazine and diazepam.

Additive effects of olanzapine and diazepam on sedation and hypotension occur in the absence of a pharmacokinetic interaction. Concomitant parenteral use is not recommended.

Diazepam boosts the subjective opioid effects of methadone. It increases methadone effects on pupil diameter and sedation and also causes significantly greater deterioration in reaction time when compared to methadone alone. No pharmacokinetic interaction occurs between the two drugs.

Reversible loss of control of Parkinson's disease has been seen in some patients treated with combined levodopa and diazepam. This might be caused by decreased striatal dopamine levels.

The xanthines theophylline and caffeine oppose the sedative and possibly anxiolytic effects of diazepam partially through blocking of adenosine receptors.

Diazepam pretreatment changes the pharmacodynamics and pharmacokinetics of the anaesthetic ketamine. Ketamine N-demethylation was inhibited leading to a prolonged half-life and prolonged ketamine-induced sleeping time. In the presence of diazepam, a reduced ketamine concentration is required to achieve adequate anaesthesia.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action
Diazepam is a member of the group of benzodiazepine tranquilizers which exert anxiolytic, sedative, muscle-relaxant, anticonvulsant and amnesic effects. Its action is enhanced by generation of active metabolites (mainly desmethydiazepam). The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines, the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.

3.1.2 Clinical/Efficacy Studies
No text.

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3.1.3 Immunogenicity
Not applicable.

3.2 Pharmacokinetic Properties

3.2.1 Absorption
On i.m. injection the extent of absorption is complete. The rate of absorption is variable and depends on site and depth of the injection.

Following daily dosing, diazepam levels reach a steady state within approximately 5 days; it takes about twice as long before desmethyldiazepam levels reach a steady-state. Average steady-state levels of diazepam after once daily administration are approximately twice as high as the peak levels of the drug after the first dose.

During treatment, the elimination half-life of diazepam may increase by 50% due to a reduction in hepatic clearance. Reports on the evolution of plasma levels during long-term treatment are conflicting. A strong decrease of diazepam levels during long-term treatment, possibly due to metabolic auto-induction, has been found, but in other studies plasma concentrations of both diazepam and its desmethyl metabolite were independent of duration of therapy.

3.2.2 Distribution
Diazepam is widely distributed into tissues despite high binding to plasma proteins (98%-99%, mainly albumin and to lesser extent α1-acid glycoprotein). After intravenous administration, a pronounced distribution phase is seen in plasma concentrations with a half-life of distribution of up to 3 hours. The volume of distribution at steady state averages between 0.88 and 1.1 l/kg when derived from plasma or serum concentration measurements. Both protein binding and volume of distribution of desmethyldiazepam are similar to those of diazepam. The high protein binding limits the extent of diazepam uptake into the cerebrospinal fluid (CSF). CSF levels in man following single and multiple doses approximate closely the free drug concentration in plasma. Upon multiple dosing desmethyl diazepam, but not diazepam, may significantly accumulate in CSF. Diazepam has very rapid uptake into and equilibration with brain tissue, with equilibrium concentrations in brain exceeding those in plasma. The overall time-course of receptor occupancy was consistent with the time-course of the sum of brain concentrations of diazepam plus metabolites

3.2.3 Metabolism
Diazepam is mainly metabolized to pharmacologically active metabolites such as desmethyldiazepam, a pathway accounting for 50-60% of total diazepam; 3-hydroxylation (27% of total diazepam clearance is slow, leading to only low plasma levels of the oxidation products temazepam and oxazepam. Oxazepam and temazepam are further conjugated to glucuronides.
After multiple doses of diazepam plasma concentration ratios of desmethyldiazepam/diazepam were 1.1 ± 0.2, temazepam/diazepam 0.11 ± 0.05, and oxazepam/diazepam 0.09 ± 0.03.

Oxidation of diazepam is mediated by cytochrome P450 isozymes; formation of desmethyldiazepam mainly by CYP2C19 and CYP3A and 3-hydroxy-diazepam (temazepam) and oxazepam by CYP3A. Because CYP2C19 is polymorphic, extensive metabolizers (EMs), and poor metabolizers (PMs) of diazepam can be distinguished. PMs of diazepam showed significantly lower clearance (12 vs 26 mL/min) and longer elimination half-life (88 vs 41 h) of diazepam than EMs after a single oral dose. Also, PMs had lower clearance, higher AUC and longer elimination half-life of desmethyldiazepam. There appear to be inter-ethnic differences in this polymorphism.

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3.2.4 Elimination

The plasma concentration-time decline of diazepam after administration is biphasic, an initial rapid and extensive distribution phase being followed by a prolonged terminal elimination phase. Thypical elimination half-life values are in the range of 24-48 hours for diazepam and 40-100 hours for the active metabolite desmethyldiazepam. The clearance of diazepam is 20-40 mL/min.

Only insignificant amounts of unchanged diazepam are eliminated indicating that the drug is almost completely metabolized before leaving the body; Oxazepam-glucuronide is the main drug-related product in urine.

3.2.5 Pharmacokinetics in Special Populations

Geriatric Population

The unbound fraction of diazepam correlates positively with age and was higher in elderly than in young subjects. Age decreases the capacity of the liver for N-demethylation and 3-hydroxylation of diazepam. An age-dependent decrease in clearance of unbound drug occurs and is responsible for the observed 2-4 fold increase in elimination half-life in the elderly, with a stronger effect seen in males than females. Hence the extent of accumulation of unbound pharmacologically active diazepam in elderly persons during multiple dosing will be greater than in younger adults.

The elimination of desmethyldiazepam is slower in elderly males, but not in females.

Hepatic Impairment

Disposition of both diazepam and desmethyldiazepam is altered in liver disease. In acute viral hepatitis, the half-life of diazepam is increased by about 2-fold but returns slowly to normal on recovery. A more marked (2- to 5-fold) increase in the elimination half-life is seen in patients with alcoholic cirrhosis. These changes are primarily due to impaired hepatic metabolism; altered distribution due to changes in protein binding may be contributory. The reduced clearance of diazepam and desmethyldiazepam leads to their increased accumulation during long-term dosing. This in turn is associated with increased sedation.

Renal Impairment

In chronic renal failure elimination of diazepam, as indicated by clearance of unbound drug, was similar to that in healthy volunteers; thus steady-state concentrations of unbound diazepam at any given daily dose on the average should not be different between patients with renal insufficiency and healthy individuals. Due to changes in plasma protein binding and tissue distribution of diazepam its elimination half-life was shortened in the renal patients from (mean +/- S.E.) 92 +/- 23 h in control to 37 +/-7 h in renal failure subjects.

Pregnancy

Diazepam and desmethyldiazepam readily cross the placental barrier. The fetus can also carry out N-demethylation of diazepam. Long-term treatment leads to accumulation of both compounds in the fetus with high levels in the fetal heart, lungs and brain.

Plasma protein binding of diazepam is decreased during pregnancy, particularly during the last trimester, partly due to the fall in serum albumin concentration. Increased pharmacological effects may result after acute dosing (see *2.5.2 Pregnancy*).

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Pediatric Population
During the first day of life, the free fractions of diazepam and desmethyldiazepam increased sharply to twice the values at birth and subsequently declined slowly to reach near control values at one week of age. These changes parallel those of free fatty acid concentrations.

Newborns and premature infants metabolize diazepam more slowly than older children and adults leading to a prolonged half-life (very pronounced in premature newborns) unless there was exposure to inducing agents before or immediately after birth. The newborn's capacity to carry out metabolic processes involved in the biotransformation of diazepam, including hydroxylation, demethylation, and glucuronide conjugation, remains limited before 5 months of age; after this time hepatic enzymes develop to or even exceed adult capacity.

Diazepam and its metabolites are excreted in breast milk. Concentrations of diazepam in milk are only 10% of those in maternal blood. Normalized for body weight, approximately 5% of the mother's dose reaches the baby. After multiple administrations of more than 10 mg daily doses the amounts transferred may be large enough to show effects in the baby (see *2.5.3 Nursing Mothers*).

3.3 Nonclinical Safety

3.3.1 Carcinogenicity
The carcinogenic potential of oral diazepam has been studied in several rodent species. An increase in the incidence of hepatocellular tumors occurred in male mice. No significant increase in the incidence of tumors was observed in female mice, rats, hamsters or gerbils.

3.3.2 Genotoxicity
A number of studies have provided weak evidence of a mutagenic potential at high concentrations which are, however, far above therapeutic doses in humans.

3.3.3 Impairment of Fertility
Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of oral doses of 100 mg/kg/day prior to and during mating and throughout gestation and lactation.

3.3.4 Reproductive toxicity
Diazepam was found to be teratogenic in mice at dose levels of 45-50 mg/kg, 100 mg/kg, and 140 mg/kg/day as well as in hamsters at 280 mg/kg. In contrast, this drug was shown to be non teratogenic at 80 and 300 mg/kg/day in rats and at 20 and 50 mg/kg/day in rabbits (see *2.5.1 Pregnancy*).

3.3.5 Other
No text.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage and Stability
Following incorrect storage, the contents may become turbid or phase-separated. In this event the ampoule must no longer be used.

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This medicine should not be used after the expiry date (EXP) shown on the pack. Improper storage may cause content of the ampoule to become murky or separated. If this happens, the drug should not be used. Keep drug at room temperature, protected from the light.

4.2 Special Instructions for Use, Handling and Disposal

Incompatibilities

Valium ampoules can be diluted with the following infusion solutions: sodium chloride (NaCl) 0.9%, dextrose 5% or dextrose 10% (1-2 ampoules of Valium per 250 mL of infusion solutions). Solutions must be fresh (r.p.) and shall be used within 24 hours. Valium ampoule solutions may not be mixed or diluted with other drugs or solutions in syringes or infusion bottle.

Chemically and physically in use stability has been demonstrated for 24 hours at room temperature.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Use of PVC-containing infusion sets

When diluted inside the infusion bag, diazepam may be absorbed into the infusion bag as well as equipments which are made of PVC. Amount absorbed will be dependent among others on solution concentration and infusion speed. If it is not possible to administer Valium i.v. directly, the Valium absorption may be decreased by use of infusion bottle which is made from PP (polypropylene) glass as well as infusion equipments which are made from PE (polyethylene) or teflon.

Use of PVC-containing containers and infusion sets may result in decreased concentrations of diazepam.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

Medicine: keep out of reach and sight of children
Obat: jauhkan dari jangkauan anak-anak
On medical prescription only
Harus dengan resep dokter

Packs

Box, 5 ampoules @ 2 mL Reg. No.: DPI1079000643A1

Made by:
Cenexi SAS
Fontenay-sous-Bois, France
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(This PI draft has been reviewed and approved for submission by Novita on 18-Feb-2021)

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