SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diazepam 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg diazepam.

Excipient:

Each diazepam 5 mg tablet contains 122 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

5 mg: Pale yellow mottled, round, approximately 8.0 mm in diameter, flat, bevel edged tablets, debossed with ‘CY’ on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult

- Short-term (2-4 weeks) symptomatic treatment of anxiety that is severe, disabling or subjecting the individual to extreme distress
- Symptomatic treatment of acute alcohol withdrawal.

4.2 Posology and method of administration

Standard dosage

For optimal effect, the dosage should be carefully individualised. Treatment should begin at the lowest effective dose appropriate to the particular condition.

In order to obtain suitable doses of less than 5mg diazepam alternative products have to be used.

Duration of treatment

The duration of treatment should be as short as possible. In general, treatment should not last longer than 4 weeks including tapering off process. Extension beyond this period should not take place without re-evaluation of the patient's status.

The patient must be re-evaluated after a period of no more than 4 weeks and then regularly thereafter in order to assess the need for continued treatment.

- Long-term chronic use is not recommended. In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise.

Tapering off

Treatment should always be tapered off gradually. Patients who have taken benzodiazepines for a prolonged time may require a longer period during which doses are reduced.

Adults:

Anxiety

- Usual dose: 2 mg to 5 mg diazepam two to three times daily.
- Maximum dose: In severe cases the dose may be incrementally increased up to 30 mg diazepam daily in 2 to 4 divided doses. Adjusted on an individual basis.

Alcohol withdrawal symptoms

- 5 mg to 20 mg diazepam repeated once within 2 to 4 hours if necessary.

Special populations:

Individuals in the following patient groups should be checked regularly at the start of treatment. Monitoring during treatment is essential in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation, such as in children and adolescents, elderly patients and patients with impaired liver function.

In order to obtain suitable doses of less than 5mg diazepam alternative products have to be used.

Elderly patients

Distribution, elimination and clearance are changed in elderly patients, resulting in an extended half-life. The dose level should therefore be reduced to 50 % of the normal recommended dose.

These patients should be checked regularly at the start of treatment in order to minimise the dosage and/or the frequency of administration to prevent overdose due to accumulation.

- Initial dose: 2 mg to 2.5 mg once or twice daily. Increased gradually as necessary and tolerated.

Impaired renal function

Dose adjustment is usually not necessary. However, caution should be exercised when treating renally impaired patients with diazepam.

Impaired liver function

The dose must be reduced for individuals with cirrhosis and impaired liver function. Patients with severe hepatic impairment must not be treated with diazepam due to risk of hepatic encephalopathy (see section 4.3).

Paediatric population

Diazepam is not recommended for treatment of anxiety and acute alcohol withdrawal in children and adolescents (see section 4.1) as safety and efficacy have not been established. No data are available.

Method of Administration

For oral administration.

4.3 Contraindications

Diazepam Tablet is contra-indicated for patients with:

- Hypersensitivity to benzodiazepines or to any of the excipients listed in section 6.1.
- Myasthenia gravis.
- Sleep apnoea syndrome.
- Severe hepatic insufficiency.
- Severe respiratory insufficiency.
- Acute intoxication with other CNS active substances (e.g. hypnotics, analgesics, antidepressants, antipsychotics).

4.4 Special warnings and precautions for use

Concomitant use of alcohol/CNS depressants

The concomitant use of diazepam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of diazepam possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5).

Risk from concomitant use of opioids:

Concomitant use of diazepam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks concomitant prescribing of benzodiazepines and opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe benzodiazepines concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

Medical history of alcohol or drug abuse

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

Tolerance

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence

Treatment with diazepam can result in mental or physical dependency. The risk increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Withdrawal

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

Rebound insomnia and anxiety

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Sudden discontinuation of treatment with diazepam in patients with epilepsy or other patients who have had a history of seizures can result in convulsions or epileptic

status. Convulsions can also be seen following sudden discontinuation in individuals with alcohol or drug abuse.

Discontinuation should be gradual in order to minimise the risk of withdrawal symptoms.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia

Anterograde amnesia may occur even if benzodiazepines are used within the normal dose range, though this is seen in particular at high dose levels. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours (see also section 4.8). Amnestic effects may be associated with inappropriate behaviour.

Psychiatric and 'paradoxical' reactions

Paradoxical reactions (such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects) have been reported from the use of benzodiazepines. Such reactions are possibly seen more often in the treatment of children and elderly patients and should result in the discontinuation of treatment.

Specific patient groups

Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.

Elderly and debilitated patients should be given a reduced dose (see section 4.2). Due to the myorelaxant effect there is a risk of falls and consequently hip fractures in the elderly.

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

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy. In patients with chronic hepatic disease dosage may need to be reduced.

The usual precautions in treating patients with impaired renal function should be observed. In renal failure, the half-life of diazepam is not clinically significantly changed, and dose adjustment is usually not necessary.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Potentially suicidal individuals should not have access to large amounts of diazepam due to the risk of overdosing.

Diazepam Tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

If diazepam is used with other centrally acting agents, careful consideration has to be given to the pharmacology of the agents employed, particularly with compounds that may potentiate or be potentiated by the action of diazepam, such as neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, anaesthetics for general anaesthesia and narcotic analgesics. Such concomitant use may increase sedative effects and cause depression of respiratory and cardiovascular functions. Concomitant use of narcotic analgesics may promote psychic dependency due to enhancement of euphorigenic effects.

Concomitant use not recommended

Alcohol

Alcohol should not be consumed while undergoing treatment with diazepam due to additive CNS inhibition and enhanced sedation (see section 4.4).

Opioids

The concomitant use of benzodiazepines and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Phenobarbital

Mechanism: Additive CNS inhibition.

Effect: Increased risk of sedation and respiratory depression.

Clozapine

Mechanism: Pharmacodynamic synergism.

Effect: Severe hypotension, respiratory depression, unconsciousness and potentially fatal respiratory and/or cardiac arrest. Therefore, concomitant use is not recommended and should be avoided.

Special caution with concomitant use

Theophylline

Mechanism: A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain.

Effect: Counteraction of the pharmacodynamic effects of diazepam, for example, reduction of sedation and psychomotor effects.

Muscle relaxants (suxamethonium, tubocurarin)

Mechanism: Possible pharmacodynamic antagonism.

Effect: Modified intensity of neuromuscular blockage.

Pharmacokinetic interactions

Diazepam is mainly metabolised to the pharmacologically active metabolites N-desmethyldiazepam, temazepam and oxazepam. The oxidative metabolism of diazepam is mediated by CYP3A4 and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to glucuronic acid. Inhibitors of CYP3A4 and/or CYP2C19 can give rise to increased concentrations of diazepam while enzyme inducing drugs such as rifampicin, hypericum perforatum and certain antiepileptics can result in substantially decreased plasma concentrations of diazepam.

Concomitant use not recommended

Inducers

Rifamycins (rifampicin)

Mechanism: Rifampicin is a potent inducer of CYP3A4 and substantially increases the hepatic metabolism and clearance of diazepam. In a study with healthy subjects administered 600 mg or 1.2 g rifampicin daily for 7 days, the clearance of diazepam was increased by about fourfold. Co-administration with rifampicin gives rise to substantially decreased concentrations of diazepam.

Effect: Reduced effect of diazepam. The concomitant use of rifampicin and diazepam should be avoided.

Carbamazepine

Mechanism: Carbamazepine is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. This can result in up to three-fold greater plasma clearance and a shorter half-life of diazepam.

Effect: Reduced effect of diazepam.

Phenytoin

Mechanism - effect on diazepam: Phenytoin is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam.

Mechanism - effect on phenytoin: The metabolism of phenytoin may be increased or decreased or remain unaltered by diazepam in an unpredictable way.

Effect on diazepam: Reduced effect of diazepam.

Effect on phenytoin: Increased or decreased serum concentration of phenytoin. Phenytoin concentrations should be monitored more closely when diazepam is added or discontinued.

Phenobarbital

Mechanism: Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam.

Effect: Reduced effect of diazepam.

Inhibitors

Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)

Mechanism: Antiviral agents may inhibit the CYP3A4 metabolic pathway for diazepam.

Effect: Increased risk of sedation and respiratory depression. Therefore, concomitant use should be avoided.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)

Mechanism: Increased plasma concentration of benzodiazepines, due to inhibition of the CYP3A4 and/or CYP2C19 metabolic pathway.

Fluconazole: Co-administration with 400 mg fluconazole on the first day and 200 mg on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.5-fold and prolonged the half-life from 31 hours to 73 hours.

Voriconazole: A study with healthy subjects found that 400 mg voriconazole twice daily on the first day and 200 mg twice daily on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.2-fold and prolonged the half-life from 31 hours to 61 hours.

Effect: Increased risk of undesired effects and toxicity of benzodiazepine. Concomitant use should be avoided or the dose of diazepam reduced.

Fluvoxamine

Mechanism: Fluvoxamine inhibits both CYP3A4 and CYP2C19 which leads to inhibition of the oxidative metabolism of diazepam. Co-administration with fluvoxamine results in an increased half-life and an approximately 190 % increased plasma concentrations (AUC) of diazepam.

Effect: Drowsiness, reduced psychomotor performance and memory. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Special caution with concomitant use

Inducers

Corticosteroids

Mechanism: Chronic use of corticosteroids may cause increased metabolism of diazepam due to induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation.

Effect: Reduced effects of diazepam.

Inhibitors

Cimetidine

Mechanism: Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. In one study where 300 mg cimetidine was administered four times daily for 2 weeks, the combined plasma level of diazepam and its active metabolite, desmethyldiazepam, was found to be increased by 57 %, but reaction times and other motor and intellectual tests remained unaffected.

Effects: Increased action of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Omeprazole

Mechanism: Omeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Omeprazole prolongs the elimination half-life of diazepam and increases the plasma concentrations (AUC) of diazepam approximately between 30 to 120 %. The effect is seen in CYP2C19 extensive metabolisers but not in slow metabolisers, with a low clearance of diazepam.

Effects: Increased action of diazepam. Reduction of the diazepam dose may be necessary.

Esomeprazole

Mechanism: Esomeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Co-administration with ezomeprazole results in an extended half-life and an increase in plasma concentrations (AUC) of diazepam by approximately 80 %.

Effect: Increased effect of diazepam. Reduction of the diazepam dose may be necessary.

Isoniazid

Mechanism: Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathway for diazepam. Co-administration with 90 mg isoniazid twice daily for 3 days resulted in a prolonged elimination half-life of diazepam and in a 35 % increased plasma concentration (AUC) of diazepam.

Effect: Increased effect of diazepam.

Itraconazole

Mechanism: Increased plasma concentration of diazepam due to inhibition of the CYP3A4 metabolic pathway. In a study with healthy subject given 200 mg itraconazole daily for 4 days increased the AUC of a single 5 mg oral dose of diazepam by about 15 %, but there was no clinically significant interaction as determined by psychomotor performance tests.

Effect: Possible increased effect of diazepam.

Fluoxetine

Mechanism: Fluoxetine inhibits the metabolism of diazepam via CYP2C19 and other pathways, resulting in elevated plasma concentrations and decreased clearance of diazepam.

Effect: Increased effect of diazepam. Concomitant use should be monitored closely.

Disulfiram

Mechanism: Reduced metabolism of diazepam leading to prolonged half-life and increased plasma concentration of diazepam. The elimination of the N-desmethyl metabolites of diazepam is slowed down which can give rise to marked sedative effects.

Effect: Increased risk of CNS inhibition such as sedation.

Oral contraceptives

Mechanism - effect on diazepam: Inhibition of oxidative metabolism of diazepam.

Mechanism - effect on oral contraceptives: Co-administration of diazepam and combined oral contraceptives has been known to cause breakthrough bleeding. The mechanism of this reaction is unknown.

Effect on diazepam: Increased effects of diazepam.

Effect on oral contraceptives: Breakthrough bleeding, but no contraceptive failures have been reported.

Grapefruit juice

Mechanism: Grapefruit juice is believed to inhibit CYP3A4 and increases the plasma concentration of diazepam. Cmax is increased by 1.5 times and AUC by 3.2 times.

Effect: Possible increased effect of diazepam.

Other

Cisapride

Mechanism: Accelerated absorption of diazepam.

Effect: Temporary increase of the sedative effects of orally administered diazepam.

Levodopa

Mechanism: Unknown.

Effect: Concomitant use with diazepam resulted in reduced effects of levodopa in a small number of case reports.

Valproic acid

Mechanism: Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism.

Effect: Increased serum concentrations of diazepam.

Ketamine

Mechanism: Due to similar oxidative processes, diazepam competitively inhibits ketamine metabolism. Pre-medication with diazepam leads to prolonged half-life of ketamine with enhanced effect as a result.

Effect: Increased sedation.

4.6 Fertility, Pregnancy and lactation

Women of childbearing potential

Any woman wishing to become or suspects that she is pregnant should be urged to contact her doctor concerning stopping the treatment.

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3).

There are limited amount of data from the use of diazepam in pregnant women.

The risk of malformations in humans following administration of therapeutic doses of benzodiazepines during early pregnancy appears low, although some epidemiological studies indicated an increased risk for cleft palate. There have been case reports of malformations and mental retardation in children exposed prenatally to overdoses or intoxication with benzodiazepines.

If, for compelling medical reasons, diazepam is administered during the last trimester of pregnancy, or at high dose levels around the time of birth, effects can be expected in the neonate, such as hypothermia, hypotonia (“Floppy Infant Syndrome”), irregularities in the heart rate, poor suckling and respiratory depression, due to the substance's pharmacological effect.

In addition, infants born to mothers who have taken benzodiazepines regularly during the last stage of pregnancy may develop a physical dependence and be at risk of developing withdrawal symptoms following the birth.

Diazepam should only be used in pregnant women on compelling indication at the lowest possible dose for the minimum amount of time.

Breast-feeding

Diazepam is excreted in breast milk. Diazepam should not be used during breast-feeding.

Fertility

Studies in animals have shown a decrease in pregnancy rate and reduced number of surviving offspring in rats at high doses. There are no human data.

4.7 Effects on ability to drive and use machines

Diazepam significantly affects the ability to drive and to operate machines.

This is usually due to impaired motor skills, tremor, somnolence, amnesia, impaired concentration and tiredness (see section 4.8).

The effect can be observed immediately after the start of treatment and it can last for several days following discontinuation due to the long half-life of diazepam.

4.8 Undesirable effects

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision predominantly occur at the start of therapy but usually disappear with repeated administration. Among elderly patients there may be confusion conditions at high dose levels. There is an increased risk of falls and associated fractures in elderly patients using benzodiazepines.

Increased salivary and bronchial secretion has been reported, in particular in children.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

Dependence

Chronic use (even at therapeutic doses) may lead to the development of physical and psychic dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4). Abuse of benzodiazepines has been reported.

The frequencies of adverse events are ranked according to the following:

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).

System organ class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Rare	Blood dyscrasia
	Very rare	Leukopenia
Immune system disorders	Very rare	Anaphylaxis
Psychiatric disorders	Common	Confusion
	Rare	Psychiatric and paradoxical reactions such as excitation, restlessness, agitation, irritability, aggressiveness, delusion, rages, hallucinations, psychoses, memory loss, nightmares, inappropriate behaviour and other adverse behavioural effects.[1] Emotional poverty, decreased alertness and depression.[2]
Nervous system disorders	Very common	Drowsiness
	Common	Ataxia, impaired motor ability, tremor
	Uncommon	Anterograde amnesia.[3] Concentration difficulties, balance disorders, dizziness, headache, slurred speech.
	Rare	Unconsciousness, insomnia, dysarthria
Eye disorders	Not known	Reversible disorders of vision: blurred vision, diplopia, nystagmus
Cardiac disorders	Rare	Bradycardia, heart failure including cardiac arrest
Vascular disorders	Rare	Hypotension, syncope
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression
	Rare	Respiratory arrest, increased bronchial secretion
Gastrointestinal disorders	Uncommon	Gastrointestinal disorders (nausea, vomiting, constipation, diarrhoea), increased salivary secretion.
	Rare	Dry mouth, increased appetite
Hepatobiliary	Rare	Jaundice, changes of hepatic

disorders		parameters (elevation of ALT, AST, alkaline phosphatase)
Skin and subcutaneous tissue disorders	Uncommon	Allergic skin reactions (itching, erythema, rash)
Musculoskeletal and connective tissue disorders	Uncommon	Myasthenia
Renal and urinary disorders	Rare	Urinary retention, incontinence
Reproductive system and breast disorders	Rare	Gynaecomastia, impotence, increased or reduced libido
General disorders and administration site conditions	Common	Fatigue, withdrawal symptoms (anxiety, panic, palpitations, sweating, tremor, gastrointestinal disorders, irritability, aggression, disrupted sensory perception, muscle spasms, general malaise, loss of appetite, paranoid psychosis, delirium and epileptic attacks).[4]
Investigations	Very rare	Elevation of transaminases

[1] Known to occur when using benzodiazepines or benzodiazepine-like agents. These reactions may be quite severe. They are more likely to occur in children and the elderly. Diazepam should be discontinued if such symptoms occur (see section 4.4).

[2] Pre-existing depression may be unmasked during benzodiazepine use.

[3] May occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

[4] The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In every case of overdose it should be assessed whether multiple agents are involved, for example in an attempted suicide. Symptoms of overdose are more pronounced in the presence of alcohol or drugs causing a depression in central nervous system.

Symptoms

Symptoms of mild overdose include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, dysarthia, hypotension and hypotonia. Severe overdose can lead to central circulatory and respiratory depression (cyanosis, loss of consciousness leading to respiratory failure, cardiac arrest) and coma. Admission in the intensive care unit is required. In the recovery phase of an overdose, severe agitation has been reported.

Treatment

Following overdose with oral benzodiazepines, induction of vomiting can be considered (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. Activated charcoal can be given to reduce absorption in the early stages of intoxication. Further treatment is symptomatic and supportive. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

The use of flumazenil, a specific benzodiazepine-receptor antagonist, can be considered for the complete or partial reversal of the sedative effects of benzodiazepines. Flumazenil should only be administered under closely monitored conditions. Due to the short half-life of flumazenil, symptoms of benzodiazepine intoxication can recur after a short period of time. Therefore, monitoring of the patient's clinical state remains essential. For some patient groups treatment with flumazenil might be useful, especially with regard to preventing the need for artificial respiration. This applies for example to patients with pre-existing respiratory disorder or threatening respiratory insufficiency, elderly patients and children.

Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose.

Attention should be given to induction of withdrawal symptoms and convulsions, especially in the case of long-term benzodiazepine users and mixed intoxication with agents that lower the threshold for seizures (e.g. tricyclic antidepressants).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, benzodiazepine derivates, ATC code: N05BA01

Mechanism of action

Diazepam is an agonist that binds specifically to benzodiazepine receptors in the brain, thus enhancing the normal transmission of the signal substance GABA. GABA inhibits the transmission of important signal substance, by which means a neuronal inhibition is achieved. The muscle-relaxant effect is mediated via spinal synaptic reflexes.

Pharmacodynamic effects

Diazepam is an anxiolytic that acts by subduing the anxiety symptoms of agitation, restlessness and tension. Diazepam also has a sedative and muscle-relaxant effect with amnesic properties.

5.2 Pharmacokinetic properties

Absorption

Diazepam is rapidly and completely absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 30 to 90 minutes after oral ingestion. Absorption is delayed and decreased when administered with a moderate fat meal. In the presence of food mean lag times are approximately 45 minutes as compared with 15 minutes when fasting. There is also an increase in the average time to achieve peak concentrations to about 2.5 hours in the presence of food as compared with 1.25 hours when fasting. This results in an average decrease in C_{max} of 20 % in addition to a 27 % decrease in AUC (range 15 % to 50 %) when administered with food.

Distribution

Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98 %). Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk in concentrations approximately one tenth of those in maternal plasma (see section 4.6). The apparent volume of distribution is 1 to 2 L/kg.

Metabolism

Diazepam is mainly metabolised to the pharmacologically active metabolites N-desmethyldiazepam, temazepam and oxazepam.

The oxidative metabolism of diazepam is mediated by CYP3A4 and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to glucuronic acid.

The half-life for the metabolite N-desmethyldiazepam, which is biologically active, is 2 to 4 days.

Elimination

The decline in the plasma concentration-time profile after oral administration is biphasic, an initial rapid and extensive distribution phase being followed by a prolonged terminal elimination phase (half-life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly in their conjugated forms and approximately 10 % is excreted in the faeces. The clearance of diazepam is 20 to 30 mL/min.

Pharmacokinetics in special clinical situations

The elimination half-life may be prolonged in the newborn, in the elderly and in patients with liver disease. In renal failure, the half life of diazepam is not clinically significantly changed.

In elderly patients the half-life is approximately two fold greater than corresponding estimates in younger subjects

Overweight patients

Various studies have shown that the kinetics are changed in overweight patients, compared to those of a normal weight. In a study in which the test subjects were given 2 mg diazepam at night for 30 days, the accumulation was delayed and the half-life for the accumulated amount of diazepam in obese test subjects was extended compared to individuals of normal weight (7.8 days as against 3.1 days). The accumulated amount of the active metabolite desmethyl-diazepam was similarly significantly extended. The plasma elimination half-life for diazepam was extended to 82 hours in overweight test subjects. The altered pharmacokinetics in the case of long-term treatment of overweight patients are due presumably to the distribution volume.

These data indicate that overweight patients require significantly longer treatment times than patients of normal weight before the maximum effect of the drug occurs in long-term treatment. Similarly the therapeutic effect and undesirable effects, including withdrawal symptoms, can occur for longer periods following the discontinuation of more long-term treatment of overweight patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Impairment of fertility

Reproductive studies in rats showed decreases in the number of pregnancies and in the number of surviving offspring following administration of diazepam prior to and during mating and throughout gestation and lactation.

Teratogenicity

Exposure to diazepam in the first trimester produces an increased risk of cleft lip and palate (mice), CNS abnormalities and permanent functional disorder in the offspring (rats).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Sodium starch glycolate (Type A)
Talc
Magnesium stearate
Ferric oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC-Aluminium blisters and HDPE containers with child-resistant PP caps.

Pack sizes
PVC/PVdC -Aluminium blisters
10, 20, 25, 28, 30, 40, 50, 60, 90 or 100 tablets in a carton.

HDPE containers
25, 30 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited Sage House

319 Pinner Road

North Harrow, Middlesex, HA1 4HF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0432

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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