1 NAME OF THE MEDICINAL PRODUCT

Clonazepam XGX Pharma 1 mg/ml, concentrate for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution (one ampoule) contains 1 mg of clonazepam.

Excipients with known effect

Anhydrous ethanol (158 mg/ml), benzyl alcohol (31 mg/ml), propylene glycol (805 mg/ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection/infusion

A colourless or slightly yellowish-greenish solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Administered intravenously, Clonazepam 1 mg/ml is indicated for the treatment of status epilepticus in all clinical forms.

4.2 Posology and method of administration

Posology

Dosage in epilepsy

The dosage is individual and is adapted to the patient's age, clinical effect and tolerance. For further information on intravenous administration, see section 4.4.

Adults and adolescents (12-18 years):

Slow intravenous injection (for about 5 minutes) of 1 ampoule of clonazepam (1 mg) diluted with 1.0 ml water for injections. For adults and adolescents, this dose can be repeated as needed. The maximum recommended dose in adults and adolescents is 20 mg daily.

The dose may be given as an intramuscular injection or slow intravenous infusion (see section 6.6).

Only in exceptional cases, where intravenous administration is not possible, intramuscular (IM) route of administration should be used, due to the slow absorption rate following IM administration (after IM administration, the T_{max} is 3 hours, see section 5.2).

Elderly

The lowest possible dose should be used in elderly patients and caution should be exercised when titrating the dose (see section 4.4).

Paediatric population:

Due to the presence of ethanol, benzyl alcohol and propylene glycol in the formulation, this product is not indicated for use in infants and in children under 12 years (see section 4.3).

Renal impairment

The safety and efficacy of clonazepam in patients with renal impairment have not been studied. However, with regard to pharmacokinetics (see section 5.2) no dose adjustment is required in these patients.

Hepatic impairment

Patients with severe hepatic impairment should not be treated with clonazepam (see section 4.3). Patients with mild to moderate hepatic impairment should be given the lowest possible dose.

Withdrawal

Clonazepam should not be discontinued abruptly. Discontinuation should be done by slow dose reduction to avoid provoking tonic clonic seizures. Withdrawal symptoms are highly variable and can range from a few hours up to a week or more. In less severe cases withdrawal symptoms may be limited to tremor, restlessness, insomnia, anxiety, headache, and difficulty concentrating. However, withdrawal symptoms such as sweating, muscle and abdominal spasms and altered consciousness may occur. In rare cases delirium and convulsions may occur.

In the event of withdrawal symptoms careful medical monitoring and patient support are necessary.

Method of administration

The product can be administered by slow intravenous injection, intravenous infusion or as an intramuscular injection.

Slow intravenous injection

Slow intravenous injection shoud be used for acute treatment, not for long term treatment. The solution of one ampoule of the product containing 1 mg of the active substance can be used only after dilution with 1.0 ml water for injections to prevent local irritation at the injection site. The solution for injection should be prepared immediately before administration.

Intravenous infusion

The solution for infusion should be used for long term treatment and prepared immediately before administration.

All intravenous treatment should be administered slowly, with constant monitoring of EEG, respiration and blood pressure.

Intramuscular injection

Only in exceptional cases, where intravenous administration is not possible, intramuscular (IM) route of administration should be used, due to the slow absorption rate following IM administration. For intramuscular injection product should not be diluted since administration will be more painful.

There is evidence that clonazepam can be adsorbed by the plastic infusion bags and infusion sets containing PVC. This can lead to a reduction in clonazepam concentration by up to 50%, especially where prepared bags containing clonazepam are stored for 24 hours or more, in warm ambient conditions, or where long tubing sets or slow rates of infusion are used. PVC-containing bags and infusion sets should be avoided when infusing clonazepam. When infusing clonazepam caution should be exercised when switching between PVC and non-PVC-containing bags and infusion sets.

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to other medicines of the benzodiazepine group.
- Severe respiratory failure.

- Severe hepatic impairment.
- Patients who are in coma.
- Patients known to be abusing pharmaceuticals, drugs or alcohol.
- Children under 12 years of age.

4.4 Special warnings and precautions for use

Suicidal ideation, suicidal behaviour and depression

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents for various indications. A meta-analysis of randomised placebo controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of action regarding this risk is not known and the available data do not exclude the possibility of an increased risk for clonazepam.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should seek medical advice if signs of suicidal ideation or behaviour emerge. Patients with a history of depression and/or suicide attempts should be kept under close supervision.

CNS

Clonazepam may be used only with particular caution in patients with spinal or cerebellar ataxia.

Concomitant use with alcohol/CNS depressants

The concomitant use of clonazepam with alcoholic beverages and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of clonazepam, including severe sedation, clinically relevant respiratory and/or cardiovascular depression (see section 4.5).

Amnesia

Anterograde amnesia may occur with the use of benzodiazepines at therapeutic doses and the risk increases with higher doses.

Myasthenia gravis

Particular caution should be exercised when administering clonazepam to patients with myasthenia gravis due to the additional risk for muscle weakness and respiratory depression.

Psychiatric and "paradoxical" reactions

During treatment with benzodiazepines, paradoxical reactions such as restlessness, agitation, irritability, aggression, anxiety, delusions, anger, nightmares, hallucinations, psychosis, inappropriate behavior, and other behavioral disorders have been reported (see section 4.8). Paradoxical reactions may be a class effect of benzoidazepines. If this occurs during treatment with Clonazepam, gradual discontinuation of treatment should be considered (see *Discontinuation of treatment or dose reduction*). Paradoxical reactions are more common in children and the elderly.

Paediatric population

Due to the presence of ethanol, benzyl alcohol and propylene glycol in the formulation, this medicinal product is not indicated for use in infants and in children under 12 years (see section 4.3).

Respiratory disorders

The dosage of clonazepam must be carefully adjusted to individual requirements in patients with pre-existing disease of the respiratory system (e.g. chronic obstructive pulmonary disease). Effects on the respiratory system may be aggravated by pre-existing airways obstruction or brain damage or if other medications which depress respiration have been given. As a rule, this effect can be avoided by careful adjustment of the dose to individual requirements.

Responsiveness

Like all drugs of this type, Clonazepam may, depending on dosage, method of administration and individual susceptibility, modify the patient's reactions (e.g. driving ability, behaviour in traffic) (see section 4.7).

As a general rule, epileptic patients are not allowed to drive. Even when the condition is adequately controlled on clonazepam, it should be remembered that any increase in dosage or alteration in timing of administration may modify the patient's reactions, depending on individual susceptibility. See also section 4.7.

Concomitant anti-epileptic treatment

The dosage of clonazepam must be carefully adjusted to individual requirements in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents (see section 4.5).

Interruption of treatment or dose reduction

Administration of anticonvulsants, including clonazepam, must not be abruptly interrupted because of the risk of precipitating status epilepticus. If the attending physician decides for the need for dose reduction or discontinuation, this has to be done gradually. In such cases a combination with other antiepileptics is recommended.

Intravenous administration

A vein of acceptable diameter should be selected for intravenous administration. The injection must be administered very slowly, under constant monitoring of EEG, respiration and blood pressure. Rapid injection or insufficient diameter of the vein are associated with the risk of thrombophlebitis that can lead to thrombosis. Respiratory depression may occur, particularly following intravenous administration of clonazepam.

In adults and adolescents, the injection rate should not exceed 0.25-0.5 mg (0.5-1 ml of prepared solution) per minute (see section 4.2). Adverse effects involving the nervous and muscular system including fatigue, are quite frequent and usually transient. They generally disappear spontaneously in the course of treatment or with dose reduction. These effects can be partially prevented by increasing the dose slowly at the start of treatment (see section 4.8).

Porphyria

Clonazepam may trigger attacks of porphyria. Therefore in patients with porphyria, clonazepam should be used with care.

History of drug abuse and dependence

Use of benzodiazepines may lead to the development of physical and psychological dependence (see section 4.8). In particular long-term or high-dose treatment may lead to reversible disorders such as dysarthria, reduced coordination of movements and gait disorder (ataxia), nystagmus and vision disorders (diplopia). Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increases at higher dosages. Amnestic effects may be associated with inappropriate behaviour. With certain forms of epilepsy, an increase in the frequency of seizures (see section 4.8) during long-term treatment is possible.

The risk of dependence and/or abuse increases with dose and duration of treatment. It is also higher in patients with a prior history of alcohol and/or drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. During long-term treatment, withdrawal symptoms may develop after a lengthy period of use, especially with high doses or if the daily dose is reduced rapidly or abruptly discontinued. The symptoms include tremor, sweating, agitation, sleep disturbances and anxiety, headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability and epileptic seizures which may be associated with the underlying disease.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact or hallucinations. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, abrupt withdrawal of the drug should therefore be avoided and treatment - even if only of short duration - should be terminated by gradually reducing the daily dose. The risk of withdrawal symptoms is increased when benzodiazepines are administered together with day-time sedatives (crossed tolerance).

Elderly

Special caution should be exercised in elderly patients in the titration phase of treatment with clonazepam. Benzodiazepine pharmacologic effects appear to be greater in elderly patients. This could give rise to increased musclerelaxant effects (which could result in falls and fractures), increased cardiorespiratory effects and stronger adverse cognitive and sedative effects as compared to younger patients.

Hepatic impairment

Benzodiazepines can induce hepatic encephalopathy in patients with severe hepatic impairment. Therefore, caution and lowest possible dose should be used in treatment of patients with mild to moderate hepatic impairment (see section 4.2). Clonazepam is contraindicated in patients with severe hepatic impairment (see section 4.3).

History of alcohol or drug abuse

This medicine should be used with extreme caution in patients with a history of alcohol or drug abuse or in the event of acute intoxication with alcohol or drugs.

This medicinal product contains benzyl alcohol, ethanol and propylene glycol

Benzyl alcohol

This medicine contains 31 mg benzyl alcohol in each ampoule which is equivalent to 31 mg/ml.

Benzyl alcohol may cause allergic reactions.

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known.

Increased risk due to accumulation in young children.

High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment, pregnant or breast-feeding women because of the risk of accumulation and toxicity (metabolic acidosis).

Ethanol

This medicine contains 80 % V/V ethanol (alcohol), ie up to 158 mg ethanol per dose, equivalent to 4 ml beer or 2 ml wine per dose.

A dose of 20 mg of this medicine administered to an adult weighing 70 kg would result in exposure to 45 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 7.5 mg/100 ml (see Appendix 1 of report EMA/CHMP/43486/2018).

For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.

The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents.

The alcohol in this medicine may alter the effects of other medicines. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects in particular in young children with low or immature metabolic capacity.

If this medicine is given slowly over 2 hours, the effects of alcohol may be reduced.

Propylene glycol

This medicine contains 805 mg propylene glycol in each ampoule which is equivalent to 805 mg/ml.

Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

4.5 Interaction with other medicinal products and other forms of interaction

Clonazepam can be administered concurrently with one or more antiepileptic agents. But adding an extra medicinal product to the patient’s regimen should involve a careful evaluation of the response to the treatment, because unwanted effects such as sedation and apathy are more likely to occur. In such cases, the dosage of each medicine must be adjusted to achieve the optimum desired effect.

Concurrent treatment with phenytoin or primidone may change (usually increase) the serum concentration of these two substances.

Pharmacokinetic drug interactions

The antiepileptic drugs phenytoin, phenobarbital, carbamazepine, lamotrigine and valproate may increase the clearance of clonazepam thereby decreasing the plasma concentrations of the latter during combined treatment.

Clonazepam itself does not induce the enzymes responsible for its own metabolism.

In vitro data indicate that CYP3A4 catalyzes clonazepam metabolism, but the degree of CYP3A4 contribution to clonazepam elimination has not been quantified *in vivo*. Caution is advised when inserting and discontinuing, and during treatment with drugs that are potent inhibitors or inducers of CYP3A4 as a dose adjustment may be required. Such drugs include certain herbal remedies, e.g. St. John's wort. Clonazepam itself does not induce the enzymes responsible for its metabolism.

The selective serotonin reuptake inhibitors sertraline, fluoxetine and the antiepileptic drug felbamate do not significantly affect the pharmacokinetics of clonazepam when administered concomitantly.

Pharmacodynamic drug interactions

The combination of clonazepam with valproic acid may occasionally cause absences.

Enhanced effects on sedation, respiration and haemodynamics may occur when clonazepam is coadministered with any centrally acting depressants including alcohol. See section 4.9 Overdosage for warnings of other CNS depressants, including alcohol.

In combination therapy with CNS depressants, the dosage of each medicine must be adjusted to achieve the optimum effect.

Opioids

The concomitant use of sedative medicinal products such as benzodiazepines or related drugs such as clonazepam with 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general

For all anti-epileptic drugs, it has been shown that in the offspring of treated women with epilepsy, the prevalence of malformations is two to three times greater than the

rate of approximately 3 % in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the underlying condition is responsible has not been elucidated. Discontinuation of anti-epileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

Risks related to clonazepam

From animal studies it cannot be excluded that clonazepam possesses the possibility of producing congenital malformations (see section 5.3).

Clonazepam crosses the placenta in humans. Administration of high doses in the last trimester of pregnancy or during labour can cause irregular heart rhythm of the unborn child and hypothermia, hypotonia, mild respiratory depression and poor feeding in the neonate. In isolated cases, withdrawal symptoms in the child have also been reported. It is important to note that both the pregnancy itself and abrupt discontinuation of the medication can cause exacerbation of epilepsy.

Clonazepam contains benzyl alcohol. As this preservative may cross the placenta and may cause accumulation in toxicity (metabolic acidosis), Clonazepam should be used with caution during pregnancy.

Clonazepam contains propylene glycol. While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case-by-case basis.

Breast-feeding

Clonazepam is excreted in human milk to such an extent that that there is a risk of affecting the breastfed newborns/infants even with therapeutic doses.

Breast-feeding should be discontinued during treatment with Clonazepam.

4.7 Effects on ability to drive and use machines

Even if taken as directed, clonazepam can show reactions to such an extent that the ability to drive a vehicle or operate machinery is impaired. This undesirable effect is aggravated by consumption of alcoholic beverages.

Driving, operating machinery and other activities requiring increased attention should therefore be avoided altogether or at least during the first few days of treatment.

4.8 Undesirable effects

The frequency categories are as follows:

Very common (1/10)

Common (1/100 to < 1/10)

Uncommon (1/1 000 to < 1/100)

Rare (1/10 000 to < 1/1 000)

Very rare (< 1/10 000)

Not known (cannot be estimated from the available data)

System organ class/frequency	Undesirable effects
Immune system disorders	
Very rare	Anaphylactic reactions
Not known	Hypersensitivity
Psychiatric disorders	
Rare	Libido disorders
Not known	Emotional disorders, affective disorders, confusion, disorientation, depression, restlessness, irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disorders, delusions, anger, nightmares and abnormal dreams, hallucinations, psychomotor hyperactivity, psychoses, inappropriate behaviour, other undesirable effects on behaviour, dependence, and withdrawal syndrome (see section 4.4)
Nervous system disorders	
Common	Impaired concentration, somnolence, delayed response, hypotonia, dizziness, ataxia (see section 4.4), nystagmus
Rare	Headache
Not known	Reversible disorders (dysarthria, reduced coordination of movements and gait disturbance (ataxia)), anterograde amnesia and amnesia which may be associated with inappropriate behavior (see section 4.4), epilepsy
Eye disorders	
Not known	Diplopia (see section 4.4)
Cardiac disorders	

Not known	Heart failure (including cardiac arrest)
Respiratory, thoracic and mediastinal disorders	
Not known	Respiratory depression (see section 4.4)
Gastrointestinal disorders	
Rare	Nausea, upper abdominal pain
Skin and subcutaneous tissue disorders	
Rare	Urticaria, pruritus, rash, transient hair loss, pigmentation changes
Musculoskeletal and connective tissue disorders	
Common	Muscle weakness (see section 4.4)
Renal and urinary disorders	
Rare	Urinary incontinence
Reproductive system and breast disorders	
Rare	Erectile dysfunction
General disorders and administration site conditions	
Common	Fatigue (tiredness, apathy) (see section 4.4)
Not known	Paradoxical reactions, including irritability, thrombophlebitis/thrombosis
Injury, poisoning and procedural complications	
Not known	Risk of falls and fracture
Investigations	
Rare	Thrombocytopenia

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Symptoms

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Clonazepam is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and

cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory diseases.

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

Treatment

It is necessary to monitor the patient's vital signs and take necessary measures depending on the patient's clinical status. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If CNS depression is severe, the use of flumazenil, a benzodiazepine antagonist, may be considered, but under closely monitored conditions. Flumazenil 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). Further information on the correct use of flumazenil (Anexate) are provided in its Summary of Product Characteristics.

Warning

The benzodiazepine antagonist flumazenil is not indicated in patients with epilepsy receiving benzodiazepines. Treatment with benzodiazepine antagonists in these patients may provoke seizures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptic drugs, benzodiazepine derivatives

ATC code: N03AE01

The central mechanism of action of benzodiazepines is via enhancement of GABA-mediated inhibition. Clonazepam binds to the benzodiazepine receptors and thereby produces a potentiation of the GABA system.

5.2 Pharmacokinetic properties

Absorption

After IM administration, the T_{max} is approximately 3 hours and the bioavailability is 93 %. Irregularities in the absorption profiles of clonazepam after IM administration are occasionally observed. The plasma concentrations of clonazepam, at which the optimum effects are observed, are between 20 and 70 ng/ml (average 55 ng/ml).

The threshold plasma concentration of clonazepam in patients with panic disorder is approximately 17 ng/ml.

Distribution

Clonazepam distributes very rapidly to various organs and body tissues, with preferential uptake by brain structures. The distribution half-life is approximately 0.5-3.5 hours. The mean volume of distribution of clonazepam is estimated at about 3 l/kg. The plasma protein binding of clonazepam is 82-86 %.

Biotransformation

The biotransformation of clonazepam involves oxidative hydroxylation at the C3 position and reduction of the 7-nitro group with formation via 7-amino to 7-acetylamino compounds. Hepatic cytochrome P-450 3A4 is implicated in the nitroreduction of clonazepam to pharmacologically inactive metabolites. The major metabolite is 7-amino-clonazepam, which showed only little anticonvulsant activity in experiments. Four additional secondary metabolites have been identified.

Elimination

The mean elimination half-life is 30-40 hours. The clearance is 55 ml/min. The elimination kinetics in children is similar to those observed in adults.

From the total radioactivity of the radiolabelled oral dose 50-70 % of clonazepam is excreted in the urine and 10-30 % in the faeces, almost exclusively in the form of free or conjugated metabolites. Less than 2 % of unchanged clonazepam appears in urine. The metabolites are present in urine both as free and conjugated (glucuronide and sulphate) compounds.

Special Populations

Patients with renal failure

Renal disease does not affect the pharmacokinetics of clonazepam. Based on kinetic criteria, no dose adjustment is required in patients with renal failure.

Patients with hepatic failure

The influence of hepatic impairment on clonazepam pharmacokinetics has not been investigated.

Elderly

The pharmacokinetics of clonazepam in the elderly has not been established.

Paediatric population

In general, the elimination kinetics in children are similar to those observed in adults. Following therapeutic doses in children (0.03-0.11 mg/kg), serum concentrations were within the same range (13-72 ng/ml) as the effective concentrations in adults.

In neonates, doses of 0.10 mg/kg resulted in concentrations between 28-117 ng/ml at the end of a short infusion and decreased to 18-60 ng/ml 30 minutes later. In neonates, the clearance values were dependent on the postnatal age. Limited data indicate that the elimination half-life per kilogram of body weight in premature and full-term infants (gestational age 28-42 weeks, postnatal age 0.5-44 days) is comparable to those reported in adults.

In children, clearance values of 0.42 +/- 0.32 ml/min/kg (age 2-18 years) and 0.88 +/- 0.4 ml/min/kg (age 7-12 years) were reported. These values decreased with increasing body weight. Ketogenic diet in children does not affect clonazepam concentrations.

5.3 Preclinical safety data

Carcinogenicity

No 2-year carcinogenicity studies have been conducted with clonazepam. However, in an 18-month clinical study in rats no treatment-related histopathological changes were seen up to the highest tested dose of 300 mg/kg/day.

Mutagenicity

Genotoxicity tests using bacterial systems with *in vitro* or host mediated metabolic activation did not indicate a genotoxic liability for clonazepam.

Impairment of fertility

Studies assessing fertility and general reproductive performance in rats showed a reduced pregnancy rate and impaired pup survival at doses of 10 and 100 mg/kg/day.

Teratogenicity

No adverse maternal or embryo-foetal effects were observed in either mice or rats following administration of oral clonazepam during organogenesis, at doses of 20 or 40 mg/kg/day, respectively.

In several rabbit studies following doses of clonazepam of up to 20 mg/kg/day, a low, non-dose-related incidence of a similar pattern of malformations (cleft palate, eyelid malformation, fused sternebrae and limb defects) was observed (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous ethanol

Benzyl alcohol

Glacial acetic acid

Propylene glycol

6.2 Incompatibilities

Do not prepare Clonazepam infusions using sodium bicarbonate solution.

Do not store the solution in PVC bags, the active substance clonazepam is absorbed by PVC (see section 4.2 and 6.6).

6.3 Shelf life

3 years

Stability for up to 2 hours at room temperature (25 ± 2°C) and refrigerator (2 – 8°C) is documented for diluted intravenous infusion in

- 0.9 % NaCl
- 0.45 % NaCl + 2.5 % glucose
- 5 % glucose
- 10 % glucose

From a microbiological point of view the product should be used immediately after dilution.

6.4 Special precautions for storage

Store below 25°C. Do not freeze. Keep the ampoules in the outer carton in order to protect from light.

Storage condition after reconstitution, see section 6.3.

6.5 Nature and contents of container

10 ampoules of amber transparent borosilicate glass with high hydrolytic resistance (type I).

Ampoules are packed in two plastic trays, before placement in the carton box.

Pack size:10 ampoules of 1 ml.

6.6 Special precautions for disposal

Slow intravenous injection

The solution of one ampoule of the product containing 1 mg of the active substance can be used only after dilution with 1.0 ml water for injections to prevent local irritation at the injection site. The solution for injection should be prepared immediately before administration. Intravenous injection should be administered slowly, with constant monitoring of EEG, respiration, and blood pressure.

Intravenous infusion

The solution for infusion should be prepared immediately before administration.

Mix at most 1 ml (= 1 mg) concentrate in 85 ml solution for infusion. For example, 3 mg clonazepam (3 ampoules) can be diluted in 250 ml of the following solutions: Sodium Chloride Intravenous Infusion 0.9 % w/v, Glucose Intravenous Infusion 5 % and 10 %, Sodium Chloride and Glucose Intravenous Infusion (0.45 % sodium chloride and 2.5 % glucose).

There is evidence that clonazepam can be adsorbed within plastic infusion bags and infusion sets containing PVC and leading to a reduction in clonazepam concentration by up to 50 %, especially where prepared bags are stored for 24 hours or more, in warm ambient conditions, or where long tubing sets or slow rates of infusion are used. PVC-containing bags and infusion sets should be avoided when infusing clonazepam. When infusing clonazepam caution should be exercised when switching between PVC and non-PVC-containing bags and infusion sets.

Any potential change of colour of the solutions for injection and intravenous infusions of the medicinal product has no impact on activity or properties of the product.

The use of packages for infusion fluid and infusion sets made of PVC for the preparation of solutions of the medicinal product is not recommended due to the considerable reduction in clonazepam content in the course of storage. Solutions of the medicinal product intended for infusion in 0.9 % NaCl solution, 0.45 % NaCl solution + 2.5 % glucose solution, 5 % glucose solution and 10% glucose solution, stored at room temperature (25 ± 2°C) in packages containing PVC should be used within 1 hour in relation to the loss of the active substance as a result of sorption on PVC.

Intramuscular injection

Only in exceptional cases, where intravenous administration is not possible, intramuscular (IM) route of administration should be used, due to the slow absorption rate following IM administration. For intramuscular injection product should not be diluted since administration will be more painful.

Unless inevitable, do not remove Clonazepam ampoules with the active substance from the package which protects the product from light.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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