NEW ZEALAND DATA SHEET

PAXAM

1. Product Name

Paxam, 0.5 mg, 2 mg, tablets.

2. Qualitative and Quantitative Composition

Each Paxam tablet contains 0.5 mg or 2 mg of clonazepam.

Excipients with known effect: lactose, microcrystalline cellulose, maize starch and sunset yellow FCF (0.5 mg).

Allergen declaration: sulfites and sugars as lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Paxam 0.5 mg: peach, flat bevelled edged, 8 mm in diameter, debossed “CN” over “0.5” on one side and cross scored on the other.

Paxam 2 mg: white, flat bevelled edged, 8 mm in diameter, debossed “CN” over “2” on one side and cross scored on the other.

Paxam tablets may be halved and quartered.

4. Clinical Particulars

4.1 Therapeutic indications

Most clinical forms of epilepsy in infants and children, in particular typical and atypical absences (Lennox-Gastaut syndrome), nodding spasms, primary or secondary generalised tonic-clonic seizures.

Clonazepam may also be used in epilepsy of adults and in focal seizures.

4.2 Dose and method of administration

Dose

Standard dosage

The dosage of clonazepam must be individually adjusted according to the patient's clinical response, tolerance of the medicine and the patient's age. To ensure optimum dosage adjustment, infants and children up to the age of 10 years should be given the 0.5 mg tablets. The cross-scored 0.5 mg tablets facilitate the administration of lower daily doses to adults in the initial stages of treatment.

As a general rule, clonazepam is given as low-dose, single-agent therapy in new, non-therapy-resistant cases.

A single oral dose of clonazepam begins to take effect within 30-60 minutes and remains effective for 6-8 hours in children and 8-12 hours in adults.

Oral treatment

To avoid adverse reactions at the beginning of therapy, it is essential to start treatment with clonazepam at a low dose and increase the daily dose progressively until the maintenance dose suited to the individual patient has been reached.

The initial dose for infants and children up to the age of 10 years (or up to 30 kg bodyweight) is 0.01-0.03 mg/kg daily given in 2-3 divided doses. The dose should be increased by no more than 0.25-0.5 mg every third day until either a daily maintenance dose of approximately 0.1 mg/kg of bodyweight daily has been reached or seizures are controlled or undesired effects preclude further increase. The daily maximum dose in children is 0.2 mg/kg of bodyweight and should not be exceeded.

Based on established dosages for children up to 10 years (see above) and those for adults (see below) the following can be recommended for children between 10 and 16 years**:** The initial dose is 1-1.5 mg/day given in 2-3 divided doses. The dose may be increased by 0.25-0.5 mg every third day until the individual maintenance dose (usually 3-6 mg/day) is reached.

The initial dose for adults should not exceed 1.5 mg/day divided into 3 doses. The dose may be increased in increments of 0.5 mg every three days until either seizures are adequately controlled or undesirable effects preclude any further increase. The maintenance dose must be individualised for each patient depending upon response. Usually a maintenance dose of 3-6 mg per day is sufficient. The maximum therapeutic dose for adults is 20 mg daily and should not be exceeded.

The daily dose should be divided into 3 equal doses. If doses are not equally divided, the largest dose should be given in the evening. The maintenance dose level is best attained after 1-3 weeks of treatment. Once the maintenance dose level has been reached, the daily amount may be given in a single dose in the evening.

Before adding clonazepam to an existing anticonvulsant regimen, it should be considered that the use of multiple anticonvulsants may result in an increase of undesirable effects.

Average dosage range for maintenance therapy

Age	Daily dose	0.5 mg tablets	2 mg tablets
Infants and children up to 10 years (or 30 kg) (dose is weight dependant)	Up to 3 mg	Up to 6	-
Children (10 to 16 years)	3 to 6 mg	6 to 12	1½ to 3
Adults (17 years and older)	3 to 6 mg	6 to 12	1½ to 3

Special dosage instructions

Clonazepam can be administered concurrently with one or several other antiepileptic agents, in which case the dosage of each agent must be adjusted to achieve the optimum effect**.**

As with all antiepileptic agents, treatment with clonazepam must not be stopped abruptly, but must be reduced in a stepwise fashion (see section 4.8).

Special populations

Elderly

Particular care should be taken during up-titration in elderly patients.

Renal impairment

The safety and efficacy of clonazepam in patients with renal impairment has not been studied, however based on pharmacokinetic considerations no dose adjustment is required in these patients (see section 5.2).

Hepatic impairment

The safety and efficacy of clonazepam in patients with hepatic impairment has not been studied. No data are available on the influence of hepatic disease on clonazepam pharmacokinetics (see section 4.4).

4.3 Contraindications

Clonazepam is contraindicated in patients with a known hypersensitivity to benzodiazepines or any of the excipients (see section 6.1).

Clonazepam is contraindicated in patients with

- chronic obstructive airways disease with incipient respiratory failure
- severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy
- dependence on drugs of abuse and CNS depressants including alcohol

4.4 Special warnings and precautions for use

General

Some loss of effect may occur during the course of clonazepam treatment.

Following the prolonged use of clonazepam at therapeutic doses, withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from 4 weeks to 4 months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur after use of clonazepam (see dependence below).

Only a small minority of patients with the common seizure types achieves a lasting remission with clonazepam. Tolerance to the anticonvulsant effect of clonazepam may occur after 4 weeks to 6 months of continuous treatment in the majority of patients leading to increased seizure frequency. Increasing the dose in this situation is rarely worthwhile. If seizures are no longer being adequately controlled, the medicine should be discontinued and alternative treatment implemented.

Hepatic impairment

Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment (see section 4.3). Special caution should be exercised when administering clonazepam to patients with mild to moderate hepatic impairment. In patients in whom benzodiazepine therapy for periods longer than 4 weeks is deemed necessary, periodic liver function tests are recommended.

Lactose intolerance

Since Paxam contains lactose, patients with rare hereditary problems of galactose intolerance (the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine.

Porphyria

In patients with porphyria, clonazepam should be used with care because it may have a porphyrogenic effect.

Concomitant use of alcohol and/or CNS depressants

The concomitant use of clonazepam with alcohol and/or CNS depressants has the potential to increase the clinical effects of clonazepam; possibly including severe sedation, that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression (see section 4.5).

Since alcohol can provoke epileptic seizures irrespective of therapy and may potentiate the CNS depressant effects of clonazepam, it is imperative that patients should abstain from drinking alcohol while under treatment with clonazepam. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of clonazepam.

Clonazepam should be used with particular care in patients with ataxia, in the event of acute intoxication with alcohol or drugs, other anti-epileptic medicines, hypnotics, analgesics, neuroleptic agents, antidepressants or lithium, or if the patient suffers from sleep apnoea.

As up to 70% of clonazepam metabolites are excreted via the kidneys, the pharmacodynamics of clonazepam and its metabolites might be altered.

Concomitant use with opioids

Concomitant use of benzodiazepines, including clonazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe clonazepam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when clonazepam is used with opioids (see section 4.5).

Hypotension

Although hypotension has occurred rarely, clonazepam should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Amnesia

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines. The risk increases at higher doses.

Sleep apnoea

Benzodiazepines are not recommended for use in patients with sleep apnoea due to possible additive effects on respiratory depression. Sleep apnoea appears to be more common in patients with epilepsy and the relationship between sleep apnoea, seizure occurrence and post-ictal hypoxia needs to be considered in light of benzodiazepine-induced sedation and respiratory depression. Therefore, clonazepam should only be used in epileptic patients with sleep apnoea when the expected benefit exceeds the potential risk.

Myasthenia gravis

As with any substance with CNS depressant and/or muscle relaxant properties, clonazepam could increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

Acute narrow-angle glaucoma

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

Impaired renal function and blood dyscrasias

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances patients on benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. In patients in whom benzodiazepine therapy for periods longer than 4 weeks is deemed necessary, periodic blood counts and liver function tests are recommended.

Psychiatric and paradoxical reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, nervousness, hostility, anxiety, delusion, sleep disturbances, nightmares, hallucinations, psychoses, vivid dreams, acute rage, stimulation or excitement, inappropriate behaviour and other adverse behaviour effects may occur. Should such reactions occur, clonazepam should be discontinued.

Impaired respiratory function

Caution in the use of clonazepam is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease (COPD), benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension. The dosage of clonazepam must be carefully adjusted to individual requirements in patients with pre-existing disease of the respiratory system.

Depression, psychosis and schizophrenia

Clonazepam is not recommended as primary therapy in patients with depression and/or psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required. Patients with a history of depression and/or suicide attempts should be kept under close supervision.

Epilepsy

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)

When clonazepam is administered to persons with convulsive disorders, an increase in the frequency and/or severity of grand mal seizures may occur, necessitating increased anticonvulsant medication. Abrupt withdrawal of benzodiazepines in persons with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures. When in the judgement of the clinician, the need for dosage reduction or discontinuation arises, this should be done gradually.

Abuse

Abuse of benzodiazepines has been reported. Benzodiazepines should be used with caution in patients with a history of alcohol or drug abuse, dependence on CNS depressants, those known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Before prescribing and throughout treatment, assess each patient’s risk for abuse, misuse and addiction. Use of benzodiazepines, particularly patients at elevated risk, necessitates counselling about the risks and proper use.

Dependence, tolerance and withdrawal

The use of benzodiazepines may lead to development of physical and psychological dependence, as defined by the presence of a withdrawal syndrome on discontinuation of the medicine. 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, or in patients with marked personality disorders. Regular monitoring in such patients is essential. Abuse has been reported in poly-drug users.

Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to benzodiazepines may develop from continued therapy. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Abrupt discontinuation or rapid dosage reduction of benzodiazepines after continued use may precipitate acute withdrawal reactions. Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency. These symptoms range from insomnia, anxiety, agitation, sleep disturbances, headaches, diarrhoea, irritability, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feeling of motion, metallic taste), depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional state, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones, are more common in patients who have received excessive doses over a prolonged period, or in patients who have been dependent on alcohol or other narcotic drugs in the past. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, clonazepam should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication. An individual withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected.

A sudden discontinuation of benzodiazepines may result in convulsion. Particular care should be taken in patients with epilepsy, and in other patients who have had a history of seizures, alcohol or drug dependence.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 - 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

In some cases, patients taking benzodiazepines have developed protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months.

Special populations

Paediatric

Salivary and bronchial hypersecretion can occur in infants and small children and supervision is required to ensure that airways remain free, especially on commencing therapy or in the event of respiratory infection.

Elderly

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.

Elderly or debilitated patients may be particularly susceptible to the pharmacologic effects of benzodiazepines such as giddiness, ataxia and confusion, which may increase the risk of a fall. Literature suggests that such 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.

Elderly patients, patients with pre-existing disease of the respiratory system (e.g. chronic obstructive lung disease), liver or kidney disease, or those who are receiving treatment with other centrally acting medications or anticonvulsant agents, require very careful dosage adjustment.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicines and other forms of interaction

Clonazepam can be administered concurrently with one or more antiepileptic agents, in which case the dosage of each medicine must be adjusted to achieve the optimum effect. Interactions have been reported between some benzodiazepines and other anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together and that serum level monitoring of the other anticonvulsant is performed more frequently.

Pharmacokinetic interactions

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

Phenytoin - the effect of clonazepam on phenytoin plasma levels is not clear as the latter may increase or decrease according to study reports depending on dosing and patient factors.

Carbamazepine - levels may be lowered by clonazepam.

Clonazepam itself does not appear to induce the enzymes responsible for its own metabolism. The enzymes involved in the metabolism of clonazepam have not been clearly identified but include CYP3A4. Inhibitors of CYP3A4 (e.g. fluconazole) may impair the metabolism of clonazepam and lead to exaggerated concentrations and effects.

The selective serotonin reuptake inhibitors (SSRIs) sertraline and fluoxetine do not significantly affect the pharmacokinetics of clonazepam when administered concomitantly.

Pharmacodynamic interactions

Benzodiazepines, including clonazepam, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression e.g. other anticonvulsant (anti-epileptic) agents, lithium, barbiturates, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anaesthetics. This is especially true in the presence of alcohol (see section 4.4).

Clonazepam undergoes oxidative metabolism and, consequently, may interact with disulfiram or cimetidine resulting in increased plasma levels of clonazepam. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with either disulfiram or cimetidine; some patients may require a reduction in benzodiazepine dosage.

The anticholinergic effects of atropine and similar medicines, antihistamines and antidepressants may be potentiated

Minor EEG changes, usually low voltage fast activity, of no known clinical significance, has been reported with benzodiazepine administration.

Some specific interactions noted with clonazepam are:

Alcohol - epileptic patients should not under any circumstances consume alcohol while being treated with clonazepam, since alcohol may alter the effect of the medicine, reduce the efficacy of treatment or produce unexpected side effects (see section 4.4).

Sodium valproate - reports of sodium valproate causing petit mal status epilepticus with clonazepam exist.

Opioids – the concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy. When treating women of childbearing potential, the benefits of treatment should be weighed against the risks and the patient should be informed of the increased risk of miscarriage.

Pregnancy

Category B3

The risk of a mother with epilepsy giving birth to a baby with an abnormality is about THREE times that of the normal population. Some of this risk is due to the anticonvulsant medicines taken. Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine.

Overall the risk of having an abnormal child is far outweighed by the dangers to the mother and foetus of uncontrolled convulsions. It is therefore recommended that:

- Women on anticonvulsant medicines receive pre-pregnancy counselling with regard to the risk of foetal abnormalities;
- Anticonvulsant should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose;
- Folic acid supplement (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Clonazepam is a benzodiazepine. Data from observational studies suggest that there is an increased risk of miscarriage from benzodiazepine exposure during pregnancy. These medicines cross the placenta and appear in the foetus and may after continuous administration during a large part of pregnancy, give rise to hypotonia, reduced respiratory function and hypothermia in the newborn child.

Oral administration of clonazepam during the period of organogenesis has elicited a low, non-dose-related incidence of a similar pattern of malformations in rabbits (cleft palate, open eyelids, fused sternebrae, limb defects) and mice (exencephaly, central nervous system defects) at doses less than MRHD. These effects were not observed in rats at oral doses more than 20-fold MRHD. The clinical significance of these findings is unknown.

Withdrawal symptoms in newborn infants have been reported with benzodiazepines.

Breast-feeding

Clonazepam must not be given to nursing women. Clonazepam is excreted in human breast milk, and may cause drowsiness and feeding difficulties in the infant. If there is a compelling reason for use, breast feeding should be discontinued.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

As with all patients taking CNS-depressant medications, patients receiving clonazepam should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from clonazepam therapy. Abilities may be impaired on the day following use (see section 4.8).

4.8 Undesirable effects

Adverse effects to clonazepam occur in about 50% of patients, depending on dose and are usually referable to its sedative and muscle relaxant effects and are also usually transitory (however, they can continue in up to 10% of patients and may result in withdrawal of the medicine). Adverse effects can, to a certain extent, be avoided by a low initial dose, which is gradually increased in the absence of side effects.

Adverse events which have been reported and may be related to clonazepam administration are:

Cardiac disorders: palpitations.

Endocrine disorders: increased libido, hirsutism.

Gastrointestinal disorders: anorexia, vomiting, dyspepsia, increased appetite, constipation, dysphagia, hyperphagia, hepatomegaly.

General disorders: ankle and facial oedema, lethargy.

Haemic and lymphatic system disorders: leucopenia, eosinophilia, anaemia, lymphadenopathy.

Investigations: abnormal liver function test.

Metabolism and nutrition disorders: weight gain, weight loss, dehydration.

Nervous system disorders: apathy, aphonia, coma, dysdiadochokinesis (inability to perform rapid, alternating movements), hemiparesis, respiratory depression, tremor.

Psychiatric disorders: dysphoria, forgetfulness, hallucinations, hysteria, insomnia, psychosis, suicidal attempt (the behavioural effects are more likely to occur in patients with a history of psychiatric disturbances).

Renal and urinary disorders: dysuria, enuresis, nocturia, urinary retention.

Respiratory thoracic and mediastinal system disorders: chest congestion, mucus obstruction of nasopharynx, rhinorrhoea, shortness of breath.

Post-marketing experience

Cardiac disorders: Cardiac failure including cardiac arrest has been reported.

Endocrine disorders: Isolated cases of reversible development of premature secondary sex characteristics in children (incomplete precocious puberty) have been reported.

Eye disorders: Particularly in long-term or high-dose treatment, reversible disorders of vision (diplopia) may occur.

Gastrointestinal disorders: Hypersalivation occurs relatively commonly. The following effects have been reported in rare cases: nausea and epigastric symptoms (discomfort).

General disorders: Fatigue (tiredness, lassitude) occurs relatively frequently, is usually transient and generally disappears spontaneously in the course of the treatment or on reduction of the dosage. It can be partially prevented by increasing the dose slowly at the start of treatment.

Fever may occur.

In rare cases chest pain or headache may occur.

Paradoxical reactions including irritability have been observed (see also psychiatric disorders).

Haemic and lymphatic system disorders: In rare cases thrombocytopenia may occur.

Immune system disorders: Allergic reactions and very few cases of anaphylaxis have been reported to occur with benzodiazepines.

Musculoskeletal and connective tissue disorders: Muscle weakness occurs relatively frequently, is usually transient and generally disappears spontaneously in the course of the treatment or on reduction of the dosage. It can be partially prevented by increasing the dose slowly at the start of treatment.

Nervous system disorders: Impaired concentration, drowsiness, somnolence, slowed reaction, muscular hypotonia, dizziness, and ataxia. These undesirable effects occur relatively frequently, are usually transient and generally disappear spontaneously in the course of the treatment or on reduction of the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment. Vertigo occurs relatively commonly.

Particularly when treatment is over prolonged periods or at high doses, reversible disorders such as a slowing or slurring of speech (dysarthria), reduced co-ordination of gait and movements (ataxia) and nystagmus may occur.

Anterograde amnesia may occur with use of benzodiazepines at therapeutic dosages; the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour.

With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible.

Psychiatric disorders: Emotional and mood disturbance, confusional state and disorientation have been observed.

Depression may occur in patients treated with clonazepam, but it may be also associated with the underlying disease.

The following paradoxical reactions have been observed: restlessness, irritability, aggressiveness, agitation, nervousness, hostility, anxiety, sleep disturbances, delusion, anger, nightmares, abnormal dreams, hallucinations, psychoses, hyper activity, inappropriate behaviour and other adverse behaviour effects are known to occur. Should this occur, the use of the medicine should be discontinued.

In rare cases loss and/or change in libido may occur.

Dependence and withdrawal (see section 4.4).

Renal and urinary disorders: In rare cases urinary incontinence may occur.

Reproductive system and breast disorders: In rare cases erectile dysfunction may occur.

Respiratory thoracic and mediastinal system disorders: Bronchial hypersecretion occurs relatively commonly. Pharyngeal oedema has been reported in rare cases. Respiratory depression is possible. Depression of respiration may be increased if there is obstruction of the airways or pre-existing brain damage, or if other medications, which depress respiration, have been given. This effect can be avoided by careful adjustment of the final dose.

In infants and young children, clonazepam may cause increased production of saliva and bronchial secretions; therefore, special attention must be paid to maintaining patency of the airways.

Skin and subcutaneous tissue disorders: The following effects may occur in rare cases: urticaria, pruritus, skin rash, transient hair loss (alopecia), angioneurotic oedema, pigmentation disorder.

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.

Investigations: In rare cases decreased platelet count may occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Symptoms

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, dysarthria, nystagmus, hypotonia, hypotension, respiratory depression, coma and very rarely death. Coma may be more protracted and cyclical, particularly in elderly patients. Increased frequency of seizures may occur in patients at supratherapeutic plasma concentrations (see section 5.2). Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other CNS depressants, including alcohol. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment

Treatment of overdose is symptomatic; institute supportive measures as indicated by the patient's clinical state. If the overdosage is known to be small, observation of the patient and monitoring of their vital signs only may be appropriate. In adults or children who have taken an overdose of benzodiazepines within 1-2 hours, consider activated charcoal with airway protection if indicated.

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

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, ATC code: N03AE01

Mechanism of action

Clonazepam is an anticonvulsant which exhibits several pharmacological properties characteristic of the benzodiazepine class of medicines.

The exact site and mode of action of the anticonvulsant action of clonazepam is unknown.

Benzodiazepines enhance the polysynaptic inhibitory processes at all levels of the central nervous system. Clonazepam is more effective in blocking spread of electrical activity in the lesion itself.

5.2 Pharmacokinetic properties

Absorption

Clonazepam is rapidly and almost completely (82 - 98%) absorbed after oral administration of tablets with peak serum levels being reached between 2 - 3 hours. The absorption half-life is 24 minutes.

With continuous therapy, accumulation occurs and although values differ in different reports, the therapeutic serum level appears to be between 10 and 80 nanogram/ml. In one study with increase in dosage to 5 mg/day the average level of clonazepam after 15 days was 54 nanogram/ml. A steady state is usually reached within 2 - 3 weeks.

Plasma concentrations of clonazepam at steady state for a once-daily dosage regimen are 3-fold higher than those after single oral doses. Following multiple oral doses of 2 mg three times daily steady-state pre-dose plasma concentrations of clonazepam ranged from 30 – 80 nanogram/ml. The plasma concentration-dose relationship of clonazepam is linear. Severe toxic effects, resulting in increased frequency of seizures for some patients, have been reported at steady state plasma concentrations above 100 nanogram/ml.

The absolute bioavailability is 90%.

Distribution

Clonazepam enters the cerebral tissues rapidly.

The distribution half-life is approximately between 0.5 – 1 hour. The apparent volume of distribution, 3 L/kg, suggests concentration in some tissues.

The plasma protein binding of clonazepam ranges from 82 - 86%.

Biotransformation

Clonazepam is metabolised in the liver. The metabolic pathways include hydroxylation, reduction of the nitro groups to an amine and addition of acetate to the amino grouping. Clonazepam is extensively metabolised by reduction to 7-amino-clonazepam and by N-acetylation to 7-acetamido-clonazepam. Hydroxylation at the C-3 position also occurs. Hepatic cytochrome P-450 3A4 is implicated in the nitroreduction of clonazepam to pharmacologically inactive metabolites.

Elimination

The mean elimination half-life is 39.0 ± 8.3 hours. The mean clearance ± SD is 55.1 ± 8.2 ml/min following a single dose of 2 mg clonazepam given IV.

50 - 70% of the dose is excreted in the urine and 10 - 30% in the faeces as metabolites. The urinary excretion of unchanged clonazepam is usually less than 2% of the administered dose. The metabolites are present in urine both as free and conjugated (glucuronide and sulphate) compounds.

Clinical significance of pharmacokinetics

With chronic dosing, accumulation occurs. However, there is a wide variation in therapeutic plasma levels and a correlation between adverse effects with plasma levels or the rate of increase in plasma concentration of clonazepam and its metabolites has not been established. Consequently, monitoring of plasma levels, as is often done with some anticonvulsants, would be valuable.

It should be emphasised that because of the effect of clonazepam on plasma levels of other anticonvulsants administered concomitantly (and vice versa) the patient should be monitored carefully in the initial stages for clinical response and occurrence of side effects.

Special Populations

Renal impairment

Renal impairment does not affect the pharmacokinetics of clonazepam. Therefore, based on pharmacokinetic consideration, no dose adjustment may be required in patients with renal impairment, the pharmacodynamics of probable accumulated clonazepam metabolites may necessitate dosage review in these patients.

Hepatic impairment

The influence of hepatic disease on clonazepam pharmacokinetics has not been investigated. However, due to the sole hepatic metabolism of clonazepam, the pharmacokinetics of clonazepam are expected to be affected on theoretical grounds.

Elderly patients

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

Neonates

Although the elimination half-life (41.9 ± 29.8 hours) and clearance values in neonates pre-treated with phenobarbital are the same order of magnitude as those reported in non-pretreated adults, post-natal age does however affect the clearance of clonazepam under normal conditions.

5.3 Preclinical safety data

Fertility

Dietary administration of clonazepam to male and female rats was associated with a reduced pregnancy rate and impaired pup survival at doses of 60 mg/m^2/day or greater (4-fold the maximal recommended human dose [MRHD]); the no-effect dose was 6 mg/m^2/day (less than clinical exposure).

Carcinogenicity

No 2-year carcinogenicity studies have been conducted with clonazepam. An 18-month chronic study in rats showed no treatment-related histopathological changes at dietary doses up to 1800 mg/m^2/day (greater than 100-fold MRHD).

Genotoxicity

Clonazepam and five of its metabolites were negative in bacterial gene mutation assays. Chromosomal damage assays have not been conducted with clonazepam.

6. Pharmaceutical Particulars

6.1 List of excipients

Paxam tablet also contains

- lactose
- microcrystalline cellulose
- maize starch
- magnesium stearate
- Sunset Yellow FCF (0.5 mg)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2.5 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

HDPE bottle with a child-resistant closure. Bottles of 100 tablets.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
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Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

9 September 1999

10. Date of Revision of the Text

22 November 2024

Summary table of changes

Section	Summary of new information
4.6	Added risk of miscarriage from benzodiazepine exposure during pregnancy.
4.8	Updated ADR reporting website.