AUSTRALIAN PRODUCT INFORMATION

PAXAM®

(clonazepam) tablets

1 NAME OF THE MEDICINE

Clonazepam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg or 2 mg of clonazepam as the active ingredient.

Excipients of known effect: sugars as lactose and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

PAXAM 0.5: 8 mm, flat bevel edged, peach tablet, debossed "CN" over "0.5" on one side and cross scored on the other.

PAXAM 2: 8 mm, flat bevel edged, white tablet, debossed "CN" over "2" on one side and cross scored on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Most types of epilepsy in children, especially absences (petit mal), myoclonic seizures and tonic-clonic fits, whether due to primary generalised epilepsy, or to secondary generalisation of partial epilepsy.

In adults, all varieties of generalised epilepsy (including myoclonic, akinetic, tonic and tonic-clonic seizures), and in partial epilepsy (including psychomotor seizures).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage of clonazepam is essentially individualised and depends in the first instance on the age of the patient. It will be determined in each patient according to clinical response and tolerance. In order to minimise initial adverse effects, it is essential to commence with low doses and increase the daily dose progressively until a maintenance dose suited to the individual patient has been reached. Some degree of tolerance may be observed to both the adverse and therapeutic effects. If epilepsy is not adequately controlled at the maximum recommended dosage level, alternative or combination therapy should be considered (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

As with all antiepileptic agents, treatment with clonazepam must not be stopped abruptly, but must be reduced in a stepwise fashion (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dosage for Initiation of Therapy:

Children: 2 to 5 years: 0.5 mg/day (half a 0.5 mg tablet morning and evening); 6 to 12 years: 0.75 mg/day (half a 0.5 mg tablet in the morning, one 0.5 mg tablet in the evening).

Adults: 1 mg/day (one 0.5 mg tablet morning and evening).

Table 1: Average Dosage Range for Maintenance Therapy

Age	Daily dose (mg)	Tablets 0.5 mg	Tablets 2 mg
Small children (2-5 years)	1.5 – 3	3 – 6	¾ – 1½
School children (6-12 years)	3 – 6 mg	6 – 12	1½ – 3
Adults	4 – 8 mg	8 – 16	2 – 4

* Maximum daily dose for adults is 20 mg/day

The daily quota should, if possible, be divided into three or four doses spread over the day.

The maintenance dose should be attained after 2 to 4 weeks of treatment. To obtain optimum adjustment of the dose in children, the 0.5 mg tablets should be used.

Use in the Elderly

Elderly patients are usually more sensitive to the effects of benzodiazepines. Particular care should be taken during up-titration in elderly patients. The lowest possible dose should be used in the elderly. The maintenance dose will usually be in the lower range of adult dosage (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Impaired Hepatic Function

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

Impaired Renal Function

The safety and efficacy of clonazepam in patients with renal impairment has not been studied. Based on pharmacokinetic considerations no dose adjustment is required in these patients, however the pharmacodynamics of the probable accumulated clonazepam metabolites may necessitate dosage review in these patients (see Section 5.2 PHARMACOKINETIC PROPERTIES – Pharmacokinetics in Special Populations).

4.3 CONTRAINDICATIONS

Clonazepam is contraindicated in patients with

- known hypersensitivity to clonazepam
- known hypersensitivity to benzodiazepines
- known hypersensitivity to any of the excipients in PAXAM
- chronic obstructive airways disease with incipient respiratory failure
- dependence on drugs of abuse and CNS depressants including alcohol
- severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Lactose Intolerance

Since PAXAM contains lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Porphyria

Clonazepam should be used with care in patients with porphyria because it may have a porphyrogenic effect.

Concomitant Use of Alcohol and 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.9 OVERDOSE).

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.

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 with 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).

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 behavioural 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

Caution must be exercised in administering clonazepam to individuals 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.

Dependence

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. 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 sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. 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. 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 the occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

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.

Use in Hepatic Impairment

Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment (see Section 4.3 CONTRAINDICATIONS). 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.

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 the use of clonazepam (see Dependence below).

Only a small minority of patients with the common seizure types achieve 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.

Use in Renal Impairment and Blood Dyscrasias

Patients with impaired renal 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 are recommended.

Use in the 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.

Paediatric Use

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.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Clonazepam can be administered concurrently with one or more other anti-epileptic medicines, 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 anti-epileptic 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 concentration 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 earlier Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 earlier Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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).

Use in Pregnancy

Pregnancy category: B3

The risk of a mother with epilepsy and taking anticonvulsants 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 fetus of uncontrolled convulsions. It is therefore recommended that:

- women on anticonvulsant medicines receive pre-pregnancy counselling with regard to the risk of fetal abnormalities;
- anticonvulsants should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose;
- folic acid supplement (5 mg daily) 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. These medicines cross the placenta and appear in the fetus and may after continuous administration during a large part of pregnancy, give rise to irregularities in the heartbeat of the unborn child, hypotonia, reduced respiratory function, poor feeding and hypothermia in the newborn child. Withdrawal symptoms in newborn infants have occasionally been reported with this class of medicines.

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.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Use in Lactation

Clonazepam must not be given to breastfeeding 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 of clonazepam, breast feeding should be discontinued.

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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects to clonazepam occur in about 50% of patients, depending on dose and they 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.

More common adverse effects. Drowsiness or somnolence (50%), ataxia (30%), behaviour problems (25%), hypersalivation (10%), fatigue (8%), muscle weakness (5%), vertigo (5%) and light-headedness, tiredness, sleepiness, lassitude and dizziness.

These effects are generally temporary and usually disappear during treatment either spontaneously or by dose reduction.

Less common adverse effects. Agitation (1.5%), excitability (0.7%), irritability (1.5%), aggressive behaviour (1.4%), disturbances of concentration, depression (1%), confusion (1.9%), bronchial hypersecretion (1.4%), slowed reactions and antero-grade amnesia, restlessness and disorientation have been observed.

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

Even if taken as directed, clonazepam can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is seriously impaired. The effect is increased if the patient has also taken alcohol (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

Table 2: Adverse Effects

Cardiac Disorders	Palpitations;
Endocrine Disorders	Increased libido, hirsutism;
Gastrointestinal Disorders	Anorexia, vomiting, dyspepsia, increased appetite, constipation, dysphagia, hyperphagia, hepatomegaly;
General Disorders and Administration Site Conditions	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 Disorder	Dysuria, enuresis, nocturia, urinary retention;
Respiratory Thoracic and Mediastinal System Disorders	Chest congestion, mucus obstruction of nasopharynx, rhinorrhoea, shortness of breath.

Table 3: 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. In rare cases, loss and/or changes in libido may occur.
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 and Administration Site Conditions	Fatigue (tiredness, lassitude) occurs relatively frequently and is usually transient and generally disappears spontaneously during 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 during 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, ataxia. These undesirable effects occur relatively frequently, are usually transient and generally disappear spontaneously during 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 coordination of gait and movements (ataxia) or nystagmus may occur. Anterograde amnesia may occur with the 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 disturbances, 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, excitability, irritability, aggressiveness, agitation, nervousness, hostility, anxiety, sleep disturbances, delusion, anger, nightmares and abnormal dreams, hallucinations, psychoses, hyperactivity, inappropriate behaviour and other

	adverse behavioural effects are known to occur. Should this occur, the use of the drug should be discontinued. Dependence and withdrawal (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Dependence).
Renal and Urinary Disorder	In rare cases urinary incontinence may occur.
Reproductive System and Breast Disorder	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 and 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, pruritis, 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 Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability

Clonazepam is rapidly and almost completely (82 – 98%) absorbed after oral administration, with peak serum levels being reached between 2 to 3 hours. The absorption half-life is 24 min. With continuous therapy, accumulation occurs, and although values differ in different reports, the therapeutic serum level appears to be between 10 and 80 ng/mL. In one study with increase in dosage to 5 mg/day, the average level of clonazepam after 15 days was 54 ng/mL. A steady state is usually reached within 2 to 3 weeks.

Plasma concentrations of clonazepam at steady states for once daily dosage regimens 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 ng/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 ng/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%.

Metabolism

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.

Excretion

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 intravenously.

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 sulfate) 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.

Pharmacokinetics in Special Populations

Renal Impairment

Renal Impairment does not affect the pharmacokinetics of clonazepam. Therefore, based on pharmacokinetic considerations, no dosage 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

Genotoxicity

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

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/m2/day (greater than 100-fold MRHD).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

PAXAM 0.5 tablets contain lactose monohydrate, microcrystalline cellulose, maize starch, magnesium stearate and sunset yellow FCF aluminium lake.

PAXAM 2 tablets contain lactose monohydrate, microcrystalline cellulose, maize starch and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: bottle (HDPE) with a child resistant closure.

Pack sizes: 100, 200 tablets

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 54846 – PAXAM 0.5 clonazepam 0.5 mg tablet bottle

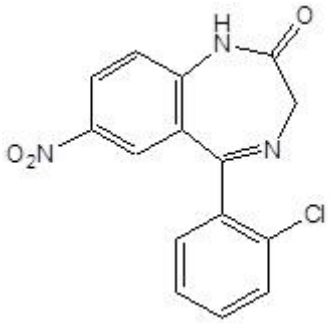
AUST R 54847 – PAXAM 2 clonazepam 2 mg tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Clonazepam is a light yellow powder which is practically insoluble in water.

Chemical name: 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one

Molecular formula: $C_{15}H_{10}ClN_3O_3$

Molecular weight: 315.7

CAS Number

1622-61-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

14/04/2010

10 DATE OF REVISION

28/05/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes.
4.3	Added hypersensitivity to clonazepam as a contraindication.
4.4	Added additional information in Use in Hepatic impairment for tolerance to the anticonvulsant effect of clonazepam in the majority of patients.
5.2	Added severe toxic effect statement on increased frequency of seizures.

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