

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

COCLAM TABLETS 2 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg)

Each uncoated tablet contains:

Clonazepam USP.....2 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

All clinical forms of epileptic disease and seizures in infants, children and adults, especially absence seizures (petit mal), including atypical absence; primary or secondarily generalised tonic-clonic (grand mal), tonic or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

4.2 Posology and method of administration

Clonazepam is available as a tablet. The tablets should be administered with water by swallowing the tablet whole.

Seizure Disorders:

Adults:

Adults

Initial dosage should not exceed 1 mg/day.

The maintenance dosage for adults normally falls within the range 4 to 8 mg.

Elderly

The elderly are particularly sensitive to the effects of centrally depressant drugs and may experience confusion. It is recommended that the initial dose should not exceed 0.5 mg/day.

These are total daily dosages which should be divided into 3 or 4 doses taken at intervals throughout the day. If necessary, larger doses may be given at the discretion

of the physician, up to a maximum of 20 mg daily. The maintenance dose should be attained after 2 to 4 weeks of treatment.

Paediatric population

To ensure optimum dosage adjustment, children should be given the 0.5 mg tablets. Initial dosage should not exceed 0.25 mg/day for infants and small children (1 to 5 years) and 0.5 mg/day for older children.

The maintenance dosage normally falls within the ranges:

Infants (0 to 1 year)	0.5 to 1 mg/day
Small children (1 to 5 years)	1 to 3 mg/day
School children (5 to 12 years)	3 to 6 mg/day

In some forms of childhood epilepsy, certain patients may cease to be adequately controlled by clonazepam. Control may be re-established by increasing the dose or interrupting treatment with clonazepam for 2 or 3 weeks. During the interruption in therapy, careful observation and other drugs may be needed.

Hepatic Impairment

Patients with severe hepatic impairment should not be treated with clonazepam (see section 4.3).

Patients with mild to moderate hepatic impairment the dose should be adjusted to individual requirements and will probably be lower.

Method of administration

For oral administration

Treatment should be started with low doses. The dose may be increased progressively until the maintenance dose suited to the individual patient has been found.

The dosage of clonazepam must be adjusted to the needs of each individual and depends on the individual response to therapy. The maintenance dosage must be determined according to clinical response and tolerance.

The daily dose should be divided into 3 or 4 equal doses. If doses are not equally divided, the largest dose should be given before retiring. Once the maintenance dose level has been reached, the daily amount may be given in a single dose in the evening. Simultaneous administration of more than one antiepileptic drug is a common practice in the treatment of epilepsy and may be undertaken with clonazepam. The dosage of each drug may be required to be adjusted to obtain the optimum effect. If status epilepticus occurs in a patient receiving oral clonazepam, intravenous clonazepam may still control the status. Before adding clonazepam to an existing anticonvulsant regimen, it should be considered that the use of multiple anticonvulsants may result in an increase of undesired effects.

4.3 Contraindications

- Patients who are hypersensitive to other benzodiazepines, this drug or to any ingredient in the formulation or component of the container.
- Severe respiratory insufficiency
- Severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy.
- Sleep apnea syndrome
- Myasthenia gravis
- Narrow angle glaucoma

4.4 Special warnings and precautions for use

RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) and opioids may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

General

A paradoxical increase in seizure activity or the appearance of new seizure types has occurred in a very few patients during treatment with Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg). When used in patients in whom several different types of seizures coexist, Clonazepam Tablets USP 2 mg

(Coclam Tablets 2 mg) may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). These phenomena may require the addition of appropriate anticonvulsants or an increase in their dosage. The concomitant use of valproic acid and clonazepam may produce absence status.

The abrupt withdrawal of Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg), particularly in those patients on long-term, high dose therapy, may precipitate status epilepticus. Therefore, as with any other anticonvulsant, gradual withdrawal is essential when discontinuing Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg). While Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) is being gradually withdrawn, the simultaneous substitution of incremental doses of another anticonvulsant may be indicated.

Risks from concomitant use of opioids and benzodiazepines

Concomitant use of benzodiazepines, including Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg), and opioids may result in profound sedation, respiratory

depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs 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 opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.

If a decision is made to prescribe Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg), prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. 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 Tablets USP 2 mg (Coclam Tablets 2 mg) is used with opioids.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Some loss of effect may occur during the course of clonazepam treatment.

Hepatic impairment

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

CNS, psychosis and depression

Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) should be used with particular caution in patients with ataxia.

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

Patients with a history of depression and/or suicide attempts should be kept under close supervision.

Concomitant use of alcohol/CNS depressants

The concomitant use of Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of RIVOTRIL possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression.

Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) should be used only with particular caution in patients with ataxia, and in the event of acute intoxication with alcohol or drugs.

Patients should be advised against the concurrent use of alcohol and other CNS depressant drugs.

Psychiatric and 'paradoxical' reactions

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

Psychiatric

Suicidal Ideation and Behaviour:

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

Patients with a history of depression and/or suicide attempts should be kept under close supervision.

All patients treated with antiepileptic drugs (AEDs), irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which AEDs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known. There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (AED or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total

number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (AED or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more AEDs). Therefore, the small increased risk of suicidal ideation and behavior reported from the meta-analysis (0.43% for patients on AEDs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (AED or placebo) for nonepilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking AEDs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct AED treatment in both arms.

Amnesia

Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increasing at higher dosages.

Lactose intolerance

Lactose is a non-medicinal ingredient in Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg). Therefore, 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 has to be used with care because it may have a porphyrogenic effect.

Medical history of alcohol or drug abuse

Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) should be used with extreme caution in patients with a history of alcohol or drug abuse.

Benzodiazepines have produced habituation, dependence and withdrawal symptoms similar to those noted with barbiturates and alcohol. The risk of dependence increases with dose and duration, and is greater in patients with a medical history of alcohol and drug abuse.

Dependence and Tolerance

With long-term Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) treatment at the therapeutic doses, development of physical and psychological dependence may occur. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse. Abuse has been reported in poly-drug abusers.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. The possibility that such effects may also occur following short-term use, especially at high doses, or if the daily dose is reduced rapidly or abruptly discontinued, should be considered. Symptoms of withdrawal include tremor, sweating, agitation, sleep disturbances and anxiety, headaches, diarrhea, muscle pain, extreme anxiety, tension, restlessness, mood changes, confusion, and irritability. In severe cases the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact or hallucinations. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, abrupt withdrawal of the drug should be avoided and treatment - even if only of short duration - should be terminated by gradually reducing the daily dose.

Renal

The safety and efficacy of clonazepam in patients with renal impairment has not been studied.

Clonazepam metabolites are excreted by the kidneys; to avoid excessive accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

Respiratory

Respiratory depression may occur following administration of Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg). This effect may be aggravated by pre-existing airway 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.

Treatment with Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) should be instituted with caution in patients with chronic respiratory diseases.

Hypersecretion in the upper respiratory passages has at times been a troublesome adverse reaction during Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) therapy, especially in small mentally retarded children who ordinarily have difficulty handling secretions. Therefore special attention must be paid to maintaining patency of the airways.

Falls and fractures

There have been reports of falls and fractures among benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Hypersalivation

Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of respiratory depression, Clonazepam Tablets USP 2 mg (Coclam Tablets 2 mg) should be used with caution in patients with chronic respiratory diseases.

4.5 Interaction with other medicinal products and other forms of interaction

Since alcohol can provoke epileptic seizures, irrespective of therapy, patients must under no circumstances drink alcohol while under treatment with antiepileptic drugs. In combination with clonazepam, alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects

See *section 4.9* for warnings concerning other central nervous system depressants, including alcohol.

Enhanced effects on sedation, respiration and haemodynamics may occur when clonazepam is co-administered with any centrally acting depressants e.g. alcohol, and other anticonvulsant (antiepileptic) agents, anaesthetics, hypnotics, psychoactive drugs and some analgesics as well as muscle relaxants and may result in mutual potentiation of drug effects.

In combination therapy with centrally-acting medications, the dosage of each drug must be adjusted to achieve the optimum effect.

There is an increased sedative effect when clonazepam is given with tricyclic and tricyclic-related antidepressants, antihistamines (less so for non-sedating antihistamines and not usually for topically applied antihistamines), antipsychotics, baclofen, lofexidine, mirtazapine, nabilone, tizanidine.

Antiepileptic drugs

When clonazepam is used in conjunction with other antiepileptic drugs, side-effects such as sedation and apathy, and toxicity may be more evident, particularly with hydantoins or phenobarbital and combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment. The combination of clonazepam and sodium valproate has, rarely, been associated with the development of absence status epilepticus. Although some patients tolerate and benefit from this combination of drugs, this potential hazard should be borne in mind when its use is considered.

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

In concurrent treatment with phenytoin or primidone, a change, usually a rise, in the serum concentration of these two substances has occasionally been observed.

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

Opioids

The concomitant use of sedative medicines 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*).

Hepatic enzyme inhibitors and inducers

Known inhibitors of hepatic enzymes, e.g. cimetidine, have been shown to reduce the clearance of benzodiazepines and may potentiate their action. Metabolism of clonazepam is inhibited (i.e. plasma concentration is increased) by disulfiram, fluvoxamine and ritonavir.

Known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines.

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

Special Precautions

The plasma concentration of clonazepam is possibly reduced by theophylline.

Clonazepam may possibly antagonise effects of levodopa.

There are enhanced hypotensive and sedative effects when clonazepam is given with alpha-blockers or with moxonidine.

There is an enhanced hypotensive effect when clonazepam is given with ACE inhibitors, adrenergic neurone blockers, angiotensin-II receptor antagonists, beta-blockers, calcium channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyl dopa, minoxidil, nitrates or nitroprusside.

4.6 Pregnancy and lactation

Teratogenic Effects:

Pregnancy Category D.

Nursing Mothers:

Mothers receiving clonazepam should not breastfeed their infants.

Pediatric Use:

Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of clonazepam is important in pediatric patients being treated for seizure disorder.

Safety and effectiveness in pediatric patients with panic disorder below the age of 18 have not been established.

4.7 Effects on ability to drive and use machines

As a general rule, epileptic patients are not allowed to drive. Even when adequately controlled on clonazepam, it should be remembered that any increase in dosage or alteration in timings of dosage may modify patients' reactions, depending on individual susceptibility. Even if taken as directed, clonazepam can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is impaired.

This effect is aggravated by consumption of alcohol. Driving, operating machinery and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment.

The decision for allowing the patient to drive rests with their doctor and should be based on the patient's response to treatment and the dosage involved.

This medicine can impair cognitive function and can affect a patient's ability to drive safely.

4.8 Undesirable effects

The following have been observed.

Frequencies are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Immune system disorders

Allergic reactions and very rare cases of anaphylaxis have been reported to occur with benzodiazepines. Angioedema may occur in rare cases.

Endocrine disorders

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

Psychiatric disorders

Impaired concentration, restlessness, 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: excitability, irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares, vivid dreams and psychotic disorders and activation of new types of seizures may be precipitated. If these occur, the benefit of continuing the drug should be weighed against the adverse effect. The addition to the regimen of another suitable drug may be necessary or, in some cases, it may be advisable to discontinue clonazepam therapy.

Dependence

In rare cases loss of libido may occur.

Nervous system disorders

Somnolence, slowed reaction, muscular hypotonia, dizziness and ataxia. These undesirable effects occur relatively frequently and 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.

Headache was observed in rare cases. Causing of generalised fits was observed very rarely.

Particularly in long-term or high-dose treatment, reversible disorders such as a slowing or slurring of speech (dysarthria), reduced coordination of movements and gait disorder (ataxia) and nystagmus may occur. Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increasing at higher dosages. Amnestic 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.

Although clonazepam has been given uneventfully to patients with porphyria, rarely it may induce convulsions in these patients.

Eye disorders

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

Common: nystagmus

Cardiac Disorders

Cardiac failure including cardiac arrest has been reported.

Respiratory, thoracic and mediastinal disorders

Rarely respiratory depression may occur, particularly on intravenous administration of clonazepam. This effect 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.

In infants and small children, and particularly those with a degree of mental impairment, clonazepam may give rise to salivary or bronchial hypersecretion with drooling. Supervision of the airway may be required.

Gastrointestinal disorders

The following effects have been reported in rare cases: nausea, gastrointestinal and epigastric symptoms

Skin and subcutaneous tissue disorders

The following effects may occur in rare cases: urticaria, pruritus, rash, transient hair loss and pigmentation changes.

Musculoskeletal and connective tissue disorders

Muscle weakness, this undesirable effect occurs relatively frequently and 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 the treatment.

Renal and urinary disorders

In rare cases urinary incontinence may occur.

Reproductive System and breast disorders

In rare cases erectile dysfunction or loss of libido may occur.

General disorders and administration site conditions

Fatigue (tiredness, lassitude), this undesirable effect occurs relatively frequently and 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.

Withdrawal reactions (*see section 4.4*)

Investigations

In rare cases decreased platelet count may occur. As with other benzodiazepines, isolated cases of blood dyscrasias and abnormal liver function tests have been reported.

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.

Paediatric population

For paediatric specific events please refer to the information listed under headings: Endocrine Disorders and Respiratory, Thoracic and Mediastinal System Disorders in section 4.8.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

Symptoms

The symptoms of overdose or intoxication vary greatly from person to person depending on age, bodyweight and individual response. 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 coma, areflexia, apnoea, hypotension and cardiorespiratory depression. Coma, if it occurs, usually lasts only 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 severe chronic obstructive airways disease.

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

Management

1. Maintain a clear airway and adequate ventilation if indicated.
2. Supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.
3. Further absorption should be prevented using an appropriate method e.g. treatment within 1 to 2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients.
4. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.
5. Patients who are asymptomatic at 4 hours are unlikely to develop symptoms.
6. Flumazenil, a benzodiazepine antagonist is available but should rarely be required. If CNS depression is severe consider the use of flumazenil. 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 the effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug. Flumazenil is NOT TO BE USED IN MIXED OVERDOSE OR AS A 'DIAGNOSTIC TEST'.

Warning

The use of flumazenil is not indicated in epileptic patients who have been treated with benzodiazepines. Although flumazenil exerts a slight intrinsic anticonvulsant effect, its abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

If excitation occurs, barbiturates should not be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, benzodiazepine derivate.

ATC code: N03AE01

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. Animal data and electroencephalographic investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spike and wave discharge in absence seizures (petit mal), slow spike wave, generalised spike wave, spikes with temporal or other locations as well as irregular spikes and waves.

Generalised EEG abnormalities are more readily suppressed by clonazepam than are focal EEG abnormalities such as focal spikes. Clonazepam has beneficial effects in generalised and focal epilepsies

5.2 Pharmacokinetic properties

Clonazepam is rapidly and completely absorbed after oral administration. The **Absorption**

Clonazepam is quickly and completely absorbed after oral administration. Peak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. Bioavailability is 90% after oral administration.

Routine monitoring of plasma concentrations of clonazepam is of unproven value since this does not appear to correlate well with either therapeutic response or side-effects.

Distribution

The mean volume of distribution of clonazepam is estimated at about 3 L/kg. Clonazepam must be assumed to cross the placental barrier and has been detected in maternal milk.

Metabolism

The biotransformation of clonazepam involves oxidative hydroxylation and reduction of the 7-nitro group by the liver with formation of 7-amino or 7-acetylamino compounds, with trace amounts of 3-hydroxy derivatives of all three compounds, and their glucuronide and sulfate conjugates. The nitro compounds are pharmacologically active, whereas the amino compounds are not.

Elimination

The elimination half-life is between 20 and 60 hours (mean 30 hours).

Within 4 - 10 days 50 - 70% of the total radioactivity of a radiolabelled oral dose 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 0.5% appears as unchanged clonazepam in the urine.

Pharmacokinetics in special clinical situations

Based on kinetic criteria no dose adjustment is required in patients with renal failure.

5.3 Preclinical safety data

Carcinogenicity:

No 2-year carcinogenicity studies have been conducted with clonazepam. However, in an 18-month chronic 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-fetal effects were observed in either mice or rats following administration of oral clonazepam during organogenesis, at doses of up to 20 or 40 mg/kg/day, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Microcrystalline cellulose
Pregelatinised starch
Magnesium Stearate
Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

10 Tablets are packed in Alu-PVDC Amber blister. Such 3 blisters are then packed in well printed carton alongwith a pack insert

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Centaur Pharmaceuticals Pvt. Ltd.
Plant: I, Plot No 3, 5B,2C,
Tivim Industrial Estate, Karaswada,
Mapusa, Goa-403526,
India

8. MARKETING AUTHORISATION NUMBER(S)

H2022/CTD8401/18441

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/06/2022

10. DATE OF REVISION OF THE TEXT

21/06/2022