For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

CLONOTRIL

(Clonazepam Dispersible Tablets)

COMPOSITION

CLONOTRIL 0.25

Each uncoated dispersible tablets contains:
Clonazepam I.P……. 0.25mg
Excipients…….. Q.S.
Colour…… Lake of tartrazine

CLONOTRIL 0.5

Each uncoated dispersible tablets contains:
Clonazepam I.P……. 0.5mg
Excipients…….. Q.S.
Colour…… Lake of tartrazine

CLONOTRIL 1

Each uncoated dispersible tablets contains:
Clonazepam I.P……. 1 mg
Excipients…….. Q.S.
Colour…… Lake of tartrazine

CLONOTRIL 2

Each uncoated dispersible tablets contains:
Clonazepam I.P……. 2 mg
Excipients…….. Q.S.
Colour…… Lake of tartrazine

INDICATIONS

Acute and chronic anxiety states and as an adjunctive therapy in patients with refractory epilepsy.

DOSAGES AND ADMINISTRATION

Method of administration: Oral use.

Mode of 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 cross-scored tablets facilitate the administration of lower daily doses in the initial stages of treatment.

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 doses throughout the day. 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.

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 2-4 weeks of treatment.

Adults
Initial dose not to exceed 1 mg/day.
The maintenance dosage for adults normally falls with the range 4 – 8 mg.

Elderly
Initial dose should not exceed 0.5 mg/day. The elderly are particularly sensitive to the effects of centrally depressant drugs and may experience confusion.

Children and Infants
Children should receive the 0.5 mg tablets to ensure optimum dosage adjustment.
Initial dose should not exceed 0.25 mg/day for infants and small children (1-5 yrs).
Initial dose should not exceed 0.5 mg/day for older children.

The maintenance dosage normally falls within the ranges:

Infants (0 - 1 year) 0.5 – 1 mg/day
Small children (1 – 5 years) 1 – 3 mg/day
School children (5-12 years) 3 – 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
In patients with mild to moderate hepatic impairment the dose should be adjusted to individual requirements and will probably be lower.

CONTRAINDICATIONS

Clonotril is contraindicated in patients with known sensitivity to benzodiazepines; or hypersensitivity to the active substance or to any of the excipients

- acute pulmonary insufficiency
- severe respiratory insufficiency
- sleep apnoea syndrome

- myasthenia gravis
- severe hepatic insufficiency.

Clonazepam must not be used in patients in a coma, or in patients known to be abusing pharmaceuticals, drugs or alcohol

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

Clonazepam should be used with caution in patients with chronic pulmonary insufficiency or with impairment of renal or hepatic function, and in the elderly or the debilitated. In these cases, dosage should generally be reduced.

As with all other antiepileptic drugs, treatment with clonazepam even if of short duration, must not be abruptly interrupted, but must be withdrawn by gradually reducing the dose in view of the risk of precipitating status epilepticus. In such cases a combination with other anti-epileptics is indicated. This precaution must also be taken when withdrawing another drug while the patient is still receiving clonazepam therapy.

Prolonged use of benzodiazepines may result in dependence development with withdrawal symptoms on cessation of use.

Clonazepam may be used only with particular caution in patients with spinal or cerebellar ataxia, in the event of acute intoxication with alcohol or drugs and in patients with severe liver damage (e.g. cirrhosis of the liver).

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

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

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

Clonazepam is considered to be probably nonporphyrinogenic, although there is some conflicting evidence. Therefore, in patients with porphyria, clonazepam should be used with care.

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

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.

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Dependence

Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products. In particular, long-term or high-dose treatment, may lead to reversible disorders such as dysarthria, reduced coordination of movements and gait disorder (ataxia), nystagmus and vision (diplopia). Furthermore, the risk of anterograde amnesia, which may occur using benzodiazepines at therapeutic dosages, increases 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.

The risk of dependence increases with dose and duration of treatment and is particularly pronounced in predisposed patients with a history of alcoholism and/or drug abuse.

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

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

DRUG 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.

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.

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 induce the metabolism of clonazepam causing higher clearance and lower 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.

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

Known inhibitors of hepatic enzymes, e.g. cimetidine, have been shown to reduce the clearance of benzodiazepines and may potentiate their action and known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines.

FERTILITY, PREGNANCY AND LACTATION

Fertility

Preclinical studies in animals have shown reproductive toxicity and from preclinical studies it cannot be excluded that clonazepam possesses the possibility of producing congenital malformations. From epidemiological evaluations there is evidence that anticonvulsant drugs act as teratogens. However, it is difficult to determine from published epidemiological reports which drug or combination of drugs is responsible for defects in the new born. The possibility also exists that other factors e.g. genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. Clonazepam should only be administered to pregnant women if the potential benefits outweigh the risk to the foetus.

Pregnancy

During pregnancy, Clonazepam may be administered only if there is a compelling indication. Clonazepam has harmful pharmacological effects on pregnancy and the foetus/new born child. Administration of high doses in the last trimester of pregnancy or during labour can cause irregularities in the heart beat of the unborn child and hypothermia, hypotonia, mild respiratory depression and poor feeding in the neonate. Infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the post-natal period. It should be borne in mind that both pregnancy itself and abrupt discontinuation of the medication can cause exacerbation of epilepsy. Therefore, clonazepam should not be used in pregnancy unless clearly necessary.

Breast-feeding

Although, clonazepam has been found to pass into the maternal milk in small amounts only, mothers undergoing treatment with this drug should not breastfeed. If there is a compelling indication for clonazepam, breastfeeding should be discontinued.

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 on this question rests with the patient's physician 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. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• Clonazepam is likely to affect your ability to drive and use machines
• Do not drive until you know how the medicine affects you
• It is an offence to drive while under the influence of this medicine
• However, you would not be committing an offence (called 'statutory defence') if:
- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely

UNDESIRABLE EFFECTS

- *Immune System Disorders*

Allergic reactions and very few cases of anaphylaxis and angioedema have been reported to occur with benzodiazepines.

- *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. In rare cases loss of libido may occur. Clonazepam generally has a beneficial effect on behaviour disturbances in epileptic patients.

- *Nervous System Disorders*

Somnolence, slowed reaction, muscular hypotonia, dizziness, ataxia, light-headedness, co-ordination disturbances, fatigue and muscle weakness. These undesirable effects occur relatively frequently and are usually transient and generally disappear spontaneously in the course of the treatment or on reductions 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 generalized 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 co-ordination of movements and gait (ataxia) and nystagmus may occur. Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risks increasing at higher dosages. Amnestic effects may be associated with inappropriate behavior. With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible.

- *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 System Disorders*

Rarely respiratory depression may occur with intravenous clonazepam, particularly if pre-existing airways obstruction or brain damage or if other depressant drugs have been administered. As a rule, this effect can be avoided by careful adjustment of the dose in 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, pigmentation changes and angioedema.

- *Musculoskeletal and Connecting 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, decrease in sexual drive (loss of libido) and impotence 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. Paradoxical reactions including irritability have been observed (see also psychiatric disorders).

- *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 case decreased platelet count may occur. Isolated cases of blood dyscrasias and abnormal liver function tests have been reported.

- *Dependence and withdrawal*

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

OVERDOSE

As with other benzodiazepine drugs, overdosage should not present undue problems of management or threat to life. Patients have recovered from overdoses in excess of 60mg without special treatment. Severe somnolence with muscle hypotonia will be present.

Symptoms:

The symptoms of over dosage 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 in elderly people it may be more protracted and cyclical. 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 1-2 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'.
7. The benefit of gastric decontamination is uncertain. Consider activated charcoal (50g for an adult, 10-15g for a child) in adults or children who have taken more than 0.4mg/kg within 1 hour, provided they are not too drowsy.

Warning
The use of flumazenil is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, Benzodiazepine derivatives
ATC Code: N03 AE01

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.

Pharmacokinetic properties

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 sulphate 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 radiolabeled 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.

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.

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

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store below 30℃. Protect from sunlight and moisture. Keep out of reach of children.

PRESENTATION
CLONOTRIL is available in pack of 10 tablets.

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
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IN/CLONOTRIL 0.25,0.5,1mg,2mg /Sep-17/03/PI