Linotril™

℞

Clonazepam Tablets USP 0.5/1mg

COMPOSITION:
Linotril ™ 0.5
Each Uncoated T ablet Contains:
Clonazepam USP 0.5 mg
Ex cipients q.s

Linotril ™ 1
Each Uncoated T ablet Contains:
Clonazepam USP 1 mg
Ex cipients q.s
Colour : Sunset Y ellow Supra

DES CRIPTION:
LINOTRIL ™ contains Clonazepam for the treatment of All clinical forms of epileptic disease and seizures in infants, children and adults.
PHARMA COD YNAMICS:
Pharmacotherapeutic group: Antiepileptics, benzodiazepine derivate.
ATC code: N03AE01
Mechanism of action
Clonazepam e xhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic e ffects. Animal data and electroencephalographic investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spik e and wave dischar ge in absence seizures (petit mal), slow spik e wave, generalised spik e wave, spik es with temporal or other locations as well as irregular spik es and waves. Generalised EEG abnormalities are more readily suppressed by clonazepam than are focal EEG abnormalities such as focal spik es. Clonazepam has beneficial e ffects in generalised and focal epilepsies

PHARMA COKINETICS:
Absorption
Clonazepam is quickly and completely absorbed after oral administration. P eak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. Bioavailability is 90% after oral administration.
R outine monitoring of plasma concentrations of clonazepam is of unproven value since this does not appear to correlate well with either therapeutic response or side-e ffects.
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 o xidative hydro xylation and reduction of the 7-nitro group by the liver with formation of 7-amino or 7-acetylamino compounds, with trace amounts of 3-hydro xy 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 e xcreted 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.

THER APEUTIC INDICA TIONS:
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 comple x symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

POS OL OG Y AND METHOD OF ADMINISTR ATION:
Posology
A dults
Initial dosage should not e xceed 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 e ffects of centrally depressant drugs and may e xperience confusion. It is recommended that the initial dose should not e xceed 0.5 mg/day .
These are total daily dosages which should be divided into 3 or 4 doses tak en at intervals throughout the day . If necessary , lar ger 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 e xceed 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
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 lar gest 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 undertak en 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 e xisting anticonvulsant regimen, it should be considered that the use of multiple anticonvulsants may result in an increase of undesired effects.

CONTR AINDICA TION:
Known hypersensitivity to benzodiazepines
Hypersensitivity to the active substance or to any of the e xcipients
A cute pulmonary insuf fciency
Severe respiratory insuf fciency
Sleep apnoea syndrome
Myasthenia gravis
Severe hepatic insuf fciency
Clonazepam must not be used in patients in a coma, or in patients known to be abusing pharmaceuticals, drugs or alcohol.

SPECIAL W ARNING AND PRECA UTION FOR USE:
Clonazepam should be used with caution in patients with chronic pulmonary insuf fciency , or with impairment of renal or hepatic function, and in the elderly or debilitated. In these cases dosage should generally be reduced.
The dosage of clonazepam must be carefully adjusted to individual requirements in patients with pre-e xisting disease of the respiratory system (e.g. chronic obstructive pulmonary disease) or liver and in patients under going treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents.
Effects on the respiratory system may be aggravated by pre-e xisting 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 may be used only with particular caution in patients with spinal or cerebellar ataxia, in the event of acute into xication with alcohol or drugs and in patients with severe liver damage (e.g. cirrhosis of the liver).
Do not interrupt treatment abruptly . As with all other antiepileptic drugs, treatment with clonazepam even if of short duration, must be withdrawn by gradually reducing the dose in view of the risk of precipitating status epilepticus. This precaution must also be tak en when withdrawing another drug while the patient is still receiving clonazepam therapy .
Prolonged use of benzodiazepines may result in dependence with withdrawal symptoms on cessation of use.
In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.
Suicidal behaviour:
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 e xclude 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. P atients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emer ge.
Patients with a history of depression and/or suicide attempts should be k ept under close supervision.
Lactose intolerance
Clonazepam contain lactose. P atients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not tak e this medicine.
Porphyria
Clonazepam is considered to be probably nonporphyrinogenic, although there is some conflicting evidence. Therefore in patients with porphyria, clonazepam should be used with care.
Paediatric population
In infants and small children clonazepam may cause increased production of saliva and bronchial secretion. Therefore special attention must be paid to maintaining patency of the airways.

INTER ACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTER ACTION:
Since alcohol can provok e epileptic seizures, irrespective of therapy , patients must under no circumstances drink alcohol while under treatment with antiepileptic drugs. In combination with clonazepam, alcohol may modif y the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects .
Enhanced eff ects 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 e ffects.
In combination therapy with centrally -acting medications, the dosage of each drug must be adjusted to achieve the optimum ef fect.
There is an increased sedative eff ect 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, lofe xidine, mirtazapine, nabilone, tizanidine.
Antiepileptic drugs
When clonazepam is used in conjunction with other antiepileptic drugs, side-effects such as sedation and apathy , and to xicity may be more evident, particularly with hydantoins or phenobarbital and combinations including them. This requires e xtra 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 .
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, fluvo xamine and ritonavir .
Known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines.
The selective serotonin reuptak e inhibitors sertraline and fluo xetine do not affect the pharmacokinetics of clonazepam when administered concomitantly .
Special P recautions
The plasma concentration of clonazepam is possibly reduced by theophylline.
Clonazepam may possibly antagonise e ffects of levodopa.
There are enhanced hypotensive and sedative eff ects when clonazepam is given with alpha-block ers or with mo xonidine.
There is an enhanced hypotensive eff ect when clonazepam is given with A CE inhibitors, adrener gic neurone block ers, angiotensin-II receptor antagonists, beta-block ers, calcium channel block ers, clonidine, diazo xide, diuretics, hydralazine, methyldopa, mino xidil, nitrates or nitroprusside.

PREGNA NCY AND LA CT ATION
Pregnancy
Preclinical studies in animals have shown reproductive to xicity and from preclinical studies it cannot be e xcluded that clonazepam possesses the possibility of producing congenital malformations .
Breast-feeding
Although clonazepam has been found to pass into the maternal milk in small amounts only , mothers under going 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 MA CHINES:
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 modif y patients' reactions, depending on individual susceptibility . Even if tak en as directed, clonazepam can slow reactions to such an e xtent that the ability to drive a vehicle or operate machinery is impaired. This e ffect 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.

UNDESIR ABLE EFFECTS:
The following have been observed.
Frequencies are defined according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune system disorders
Aller gic 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 se x 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 parado xical reactions have been observed: e xcitability , 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 e ffect. 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 ef fects 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 ef fects 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

R espiratory , thoracic and mediastinal disorders
Rarely respiratory depression may occur , particularly on intravenous administration of clonazepam. This ef fect may be aggravated by pre-e xisting 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 eff ects have been reported in rare cases: nausea, gastrointestinal and epigastric symptoms

Skin and subcutaneous tissue disorders
The following eff ects may occur in rare cases: urticaria, pruritus, rash, transient hair loss and pigmentation changes.

Musculosk eletal and connective tissue disorders
Muscle weakness, this undesirable eff ect 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.

R enal and urinary disorders
In rare cases urinary incontinence may occur .

R eproductive 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 eff ect 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.

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 R espiratory , Thoracic and Mediastinal System Disorders

INCOMP ATIBILITY :
Not applicable.

SHELF LIFE:
36 months

PACK AGING
10 T ablets are pack ed in Alu-PVC Blister & such 3 Blister are pack ed in printed carton along with pack insert.

STOR AGE CONDITION:
Stored at a temperature not e xceeding 30 °C. P rotect from light and moisture. Keep the medicine out of reach of children.

Marketed by:

LINUX Laboratories

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