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

Clonotril P

(Paroxetine Controlled Release and Clonazepam Capsules)

COMPOSITION

Clonotril P 12.5

Each hard gelatine capsule contains:
Paroxetine Hydrochloride (As Hemihydrate) I.P. equivalent to Paroxetine 12.5 mg
(As enteric coated controlled release tablet)
colours: Red Oxide of Iron and Titanium Dioxide I.P.
Clonazepam I.P. 0.5 mg
(As immediate release tablet)
Approved colours used in hard gelatine capsule shells

Clonotril P 25

Each hard gelatine capsule contains:
Paroxetine Hydrochloride (As Hemihydrate) I.P. equivalent to Paroxetine 25 mg
(As enteric coated controlled release tablet)
colours: Red Oxide of Iron, Yellow Oxide of Iron and Titanium Dioxide I.P.
Clonazepam I.P. 0.5 mg
(As immediate release tablet)
Approved colours used in hard gelatine capsule shells

INDICATIONS

For the treatment of patients with co-morbid depression and anxiety.

DOSAGES AND ADMINISTRATION

The recommended dose is once daily in the morning with food.
The tablet should be swallowed rather than chewed.

CONTRAINDICATIONS

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

CLONAZEPAM

- 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

PAROXETINE

• Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs). In exceptional circumstances, linezolid (an antibiotic which is a reversible non-selective MAOI) can be given in combination with paroxetine provided that there are facilities for close observation of symptoms of serotonin syndrome and monitoring of blood pressure.

Treatment with paroxetine can be initiated:
- two weeks after discontinuation of an irreversible MAOI, or
- at least 24 hours after discontinuation of a reversible MAOI (e.g. moclobemide, linezolid, methylthioninium chloride (methylene blue; a preoperative visualising agent which is a reversible non-selective MAOI)). At least one week should elapse between discontinuation of paroxetine and initiation of therapy with any MAOI.

• Paroxetine should not be used in combination with thioridazine, because, as with other medicinal products which inhibit the hepatic enzyme CYP450 2D6, paroxetine can elevate plasma levels of thioridazine. Administration of thioridazine alone can lead to QTc interval prolongation with associated serious ventricular arrhythmia such as torsades de pointes, and sudden death.

• Paroxetine should not be used in combination with pimozide.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

CLONAZEPAM

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).

<u>PAROXETINE</u>

Paediatric population

Paroxetine should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Monoamine oxidase inhibitors (MAOIs)

Treatment with paroxetine should be initiated cautiously two weeks after terminating treatment with an irreversible MAOI or 24 hours after terminating treatment with a

reversible MAO inhibitor. Dosage of paroxetine should be increased gradually until an optimal response is reached

Suicide/ suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which paroxetine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Akathisia/psychomotor restlessness

The use of paroxetine has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Serotonin syndrome/Neuroleptic malignant syndrome

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment of paroxetine, particularly when given in combination with other serotonergic and/or neuroleptic medicinal products. As these syndromes may result in potentially life-threatening conditions, treatment with paroxetine should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme

agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Paroxetine should not be used in combination with serotonin-precursors (such as L-tryptophan, oxitriptan) due to the risk of serotonergic syndrome.

Mania
As with all antidepressants, paroxetine should be used with caution in patients with a history of mania. Paroxetine should be discontinued in any patient entering a manic phase.

Renal/hepatic impairment
Caution is recommended in patients with severe renal impairment or in those with hepatic impairment.

Diabetes
In patients with diabetes, treatment with an Selective Serotonin Reuptake Inhibitor (SSRI) may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted. Additionally, there have been studies suggesting that an increase in blood glucose levels may occur when paroxetine and pravastatin are coadministered.

Epilepsy
As with other antidepressants, paroxetine should be used with caution in patients with epilepsy.

Seizures
Overall the incidence of seizures is less than 0.1% in patients treated with paroxetine. The medicinal product should be discontinued in any patient who develops seizures.

Electro Convulsive Therapy (ECT)
There is little clinical experience of the concurrent administration of paroxetine with ECT.

Glaucoma
As with other SSRI's, , paroxetine can cause mydriasis and should be used with caution in patients with narrow angle glaucoma or history of glaucoma.

Cardiac conditions
The usual precautions should be observed in patients with cardiac conditions.

Hyponatraemia
Hyponatraemia has been reported rarely, predominantly in the elderly. Caution should also be exercised in those patients at risk of hyponatraemia e.g. from concomitant medications and cirrhosis. The hyponatraemia generally reverses on discontinuation of paroxetine.

Haemorrhage
There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRIs. Other haemorrhagic manifestations e.g. gastrointestinal haemorrhage have been reported. Elderly patients may be at an increased risk.

Caution is advised in patients taking SSRIs concomitantly with oral anticoagulants, medicinal products known to affect platelet function or other medicinal products that may increase risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

Interaction with tamoxifen
Paroxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, paroxetine should whenever possible be avoided during tamoxifen treatment.

Withdrawal symptoms seen on discontinuation of paroxetine treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt. In clinical trials adverse events seen on treatment discontinuation occurred in 30% of patients treated with paroxetine compared to 20% of patients treated with placebo. The occurrence of withdrawal symptoms is not the same as the medicinal product being addictive or dependence producing.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction.

Dizziness, sensory disturbances (including paraesthesia, electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability and visual disturbances have been reported following discontinuation of paroxetine. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that paroxetine should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs.

Paroxetine contains small amount of lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

DRUG INTERACTION
CLONAZEPAM

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.

PAROXETINE

Serotonergic medicinal products
As with other SSRIs, co-administration with serotonergic medicinal products may lead to an incidence of 5-HT associated effects.

Caution should be advised and a closer clinical monitoring is required when serotonergic drugs (such as L-tryptophan, triptans, tramadol, linezolid, methylthioninium chloride (methylene blue), SSRIs, lithium, pethidine and St. John's Wort – Hypericum perforatum

– preparations) are combined with paroxetine. Caution is also advised with fentanyl used in general anaesthesia or in the treatment of chronic pain. Concomitant use of paroxetine and MAOIs is contraindicated because of the risk of serotonin syndrome.

Pravastatin
An interaction between paroxetine and pravastatin has been observed in studies suggesting that co-administration of paroxetine and pravastatin may lead to an increase in blood glucose levels. Patients with diabetes mellitus receiving both paroxetine and pravastatin may require dosage adjustment of oral hypoglycaemic agents and/or insulin.

Pimozide
Increased pimozide levels of on average 2.5 times have been demonstrated in a study of a single low dose pimozide (2 mg) when co-administered with 60 mg paroxetine. This may be explained by the known CYP2D6 inhibitory properties of paroxetine,due to the narrow therapeutic index of pimozide and its known ability to prolong QT interval, concomitant use of pimozide and paroxetine is contraindicated.

Drug metabolizing enzymes
The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolizing enzymes.

When paroxetine is to be co-administered with a known drug metabolising enzyme inhibitor, consideration should be given to using paroxetine doses at the lower end of the range. No initial dosage adjustment is considered necessary when the drug is to be co-administered with known drug metabolising enzyme inducers (e.g. carbamazepine, rifampicin, phenobarbital, phenytoin)) or with fosamprenavir/ritonavir. Any paroxetine dosage adjustment (either after initiation or following discontinuation of an enzyme inducer) should be guided by clinical effect (tolerability and efficacy).

Fosamprenavir/ritonavir: Co-administration of fosamprenavir/ritonavir 700/100 mg twice daily with paroxetine 20 mg daily in healthy volunteers for 10 days significantly decreased plasma levels of paroxetine by approximately 55%. The plasma levels of fosamprenavir/ritonavir during co-administration of paroxetine were similar to reference values of other studies, indicating that paroxetine had no significant effect on metabolism of fosamprenavir/ritonavir. There are no data available about the effects of long-term co-administration of paroxetine and fosamprenavir/ritonavir exceeding 10 days.'

Procyclidine
Daily administration of paroxetine increases significantly the plasma levels of procyclidine. If anti-cholinergic effects are seen, the dose of procyclidine should be reduced.

Anticonvulsants
Carbamazepine, phenytoin, sodium valproate. Concomitant administration does not seem to show any effect on pharmacokinetic/dynamic profile in epileptic patients.

CYP2D6 inhibitory potency of paroxetine

As with other antidepressants, including other SSRIs, paroxetine inhibits the hepatic cytochrome P450 enzyme CYP2D6. Inhibition of CYP2D6 may lead to increased plasma concentrations of co-administered medicinal products metabolized by this enzyme. These include certain tricyclic antidepressants (e.g. clomipramine, nortriptyline and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine), risperidone, atomoxetine, certain Type 1c antiarrhythmics (e.g. propafenone and flecainide) and metoprolol. It is not recommended to use paroxetine in combination with metoprolol when given in cardiac insufficiency, because of the narrow therapeutic index of metoprolol in this indication.

Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75% reduction in plasma levels of one of the more active forms of tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including paroxetine) should whenever possible be avoided.

Alcohol
As with other psychotropic medicinal products patients should be advised to avoid alcohol use while taking paroxetine.

Oral anticoagulants
A pharmacodynamic interaction between paroxetine and oral anticoagulants may occur. Concomitant use of paroxetine and oral anticoagulants can lead to an increased anticoagulant activity and haemorrhagic risk. Therefore, paroxetine should be used with caution in patients who are treated with oral anticoagulants.

NSAIDs and acetylsalicylic acid, and other antiplatelet agents
A pharmacodynamic interaction between paroxetine and NSAIDs/acetylsalicylic acid may occur. Concomitant use of paroxetine and NSAIDs/acetylsalicylic acid can lead to an increased haemorrhagic risk.

Caution is advised in patients taking SSRIs, concomitantly with oral anticoagulants, medicinal products known to affect platelet function or increase risk of bleeding (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, acetylsalicylic acid, NSAIDs, COX-2 inhibitors) as well as in patients with a history of bleeding disorders or conditions which may predispose to bleeding.

FERTILITY, PREGNANCY AND LACTATION

CLONAZEPAM

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.

PAROXETINE

Fertility

Animal data have shown that paroxetine may affect sperm quality. In vitro data with human material may suggest some effect on sperm quality, however, human case reports with some SSRIs (including paroxetine) have shown that an effect on sperm quality appears to be reversible. Impact on human fertility has not been observed so far.

Pregnancy

Some epidemiological studies suggest an increased risk of congenital malformations, particularly cardiovascular (e.g. ventricular and atrial septum defects) associated with the use of paroxetine during the first trimester.The mechanism is unknown. The data suggests

that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is less than 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Paroxetine should only be used during pregnancy when strictly indicated. The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant.

Abrupt discontinuation should be avoided during pregnancy.

Neonates should be observed if maternal use of paroxetine continues into the later stages of pregnancy, particularly the third trimester.

The following symptoms may occur in the neonates after maternal paroxetine use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty in sleeping. These symptoms could be due to either serotonergic effects or withdrawal symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may have an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Animal studies showed reproductive toxicity, but did not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development

Breast-feeding

Small amounts of paroxetine are excreted into breast milk. In published studies, serum concentrations in breast-fed infants were undetectable (<2 ng/ml) or very low (<4 ng/ml) and no signs of medicinal product effects were observed in these infants. Since no effects are anticipated, breast-feeding can be considered.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

CLONAZEPAM

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

PAROXETINE

Paroxetine has no or negligible influence on the ability to drive and use machines.

Clinical experience has shown that therapy with paroxetine is not associated with impairment of cognitive or psychomotor function. However, as with all psychoactive medicinal products, patients should be cautioned about their ability to drive a car and operate machinery.

Although paroxetine does not increase the mental and motor skill impairments caused by alcohol, the concomitant use of paroxetine and alcohol is not advised.

UNDESIRABLE EFFECTS

CLONAZEPAM

- *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.

PAROXETINE

Some of the adverse drug reactions listed below may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy. Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as:
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)

Blood and lymphatic system disorders
Uncommon: abnormal bleeding, predominantly of the skin and mucous membranes (mostly ecchymosis).
Very rare: thrombocytopenia.

Immune system disorders
Very rare: severe and potentially fatal allergic reactions (including anaphylactoid reactions and angioedema).

Endocrine disorders
Very rare: syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Metabolism and nutrition disorders
Common: decreased appetite, increases in cholesterol levels.
Rare: hyponatraemia.

Hyponatraemia has been reported predominantly in elderly patients and is sometimes due to syndrome of inappropriate anti-diuretic hormone secretion (SIADH).
Uncommon: Altered glycaemic control has been reported in diabetic patients.

Psychiatric disorders
Common: somnolence, insomnia, agitation, abnormal dreams (including nightmares)
Uncommon: confusion, hallucinations.
Rare: manic reactions, anxiety, depersonalization, panic attacks, akathisia
Frequency not known: Suicidal ideation and suicidal behaviour*, aggression*

* Cases of suicidal ideation and suicidal behaviours have been reported during paroxetine therapy or early after treatment discontinuation.

* cases of aggression were observed in post marketing experience
These symptoms may also be due to the underlying disease.

Nervous system disorders
Common: concentration impaired, dizziness, tremor, headache
Uncommon: extrapyramidal disorders.
Rare: convulsions, restless legs syndrome (RLS)
Very rare: serotonin syndrome (symptoms may include agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor).

Reports of extrapyramidal disorder including oro-facial dystonia have been received in patients sometimes with underlying movement disorders or who were using neuroleptic medicinal products.

Eye disorders
Common: blurred vision.
Uncommon: mydriasis
Very rare: acute glaucoma.

Ear and labyrinth disorders
Frequency not known: tinnitus.

Cardiac disorders
Uncommon: sinus tachycardia.
Rare: bradycardia.

Vascular disorders
Uncommon: transient increases or decreases in blood pressure, postural hypotension
Transient increases or decreases of blood pressure have been reported following treatment with paroxetine, usually with pre-existing hypertension or anxiety.

Respiratory, thoracic and mediastinal disorders
Common: yawning.

Gastrointestinal disorders
Very common: nausea.
Common: constipation, diarrhoea, vomiting, dry mouth.
Very rare: gastrointestinal bleeding.

Hepato-biliary disorders
Rare: elevation of hepatic enzymes.
Very rare: hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure).

Elevation of hepatic enzymes has been reported. Post-marketing reports of hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure) have also been received very rarely. Discontinuation of paroxetine should be considered if there is prolonged elevation of liver function test results.

Skin and subcutaneous tissue disorders
Common: sweating.
Uncommon: skin rashes, pruritus.
Very rare: severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), urticaria, photosensitivity reactions.

Musculoskeletal and connective tissue disorders
Rare: arthralgia, myalgia.
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Renal and urinary disorders
Uncommon: urinary retention, urinary incontinence.

Reproductive system and breast disorders
Very common: sexual dysfunction.
Rare: hyperprolactinaemia/galactorrhoea.
Very rare: priapism.

General disorders and administration site conditions
Common: asthenia, body weight gain.
Very rare: peripheral oedema.

Withdrawal symptoms seen on discontinuation of paroxetine treatment
Common: dizziness, sensory disturbances, sleep disturbances, anxiety, headache
Uncommon: agitation, nausea, tremor, confusion, sweating, emotional instability, visual disturbances, palpitations, diarrhoea, irritability.

Discontinuation of paroxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia electric shock sensations and tinnitus), sleep disturbances (including intense dreams), agitation or anxiety, nausea, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances have been reported.

Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out

Adverse events from paediatric clinical trials
The following adverse events were observed:
Increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder. Increased hostility occurred particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age.

Additional events that were seen are: decreased appetite, tremor, sweating, hyperkinesia, agitation, emotional lability (including crying and mood fluctuations), bleeding related adverse events, predominantly of the skin and mucous membranes.Events seen after discontinuation/tapering of paroxetine are: emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide), nervousness, dizziness, nausea and abdominal pain.

OVERDOSE

CLONAZEPAM

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.

PAROXETINE

Symptoms and signs
A wide margin of safety is evident from available overdose information on paroxetine. Experience of paroxetine in overdose has indicated that, in addition to, vomiting, dilated pupils, fever, blood pressure changes, headache, involuntary muscle contractions, agitation, anxiety and tachycardia have been reported. Patients have generally recovered without serious sequalae even when doses of up to 2000 mg have been taken alone. Events such as coma or ECG changes have occasionally been reported and, very rarely with a fatal outcome, but generally when paroxetine was taken in conjunction with other psychotropic medicinal products, with or without alcohol.

Treatment
No specific antidote is known.
The treatment should consist of those general measures employed in the management of overdose with any antidepressant. Administration of 20-30 g activated charcoal may be considered if possible within a few hours after overdose intake to decrease absorption of paroxetine. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Patient management should be as clinically indicated.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

CLONAZEPAM

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.

PAROXETINE

Pharmacotherapeutic group: Antidepressants – selective serotonin reuptake inhibitors, ATC code: N06A B05

Mechanism of action
Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) uptake and its antidepressant action and effectiveness in the treatment of OCD, Social anxiety disorders/social phobia, Generalised anxiety disorder, Post-traumatic stress disorder and Panic disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurones.

Paroxetine is chemically unrelated to the tricyclic, tetracyclic and other available antidepressants.

Paroxetine has low affinity for muscarinic cholinergic receptors and animal studies have indicated only weak anticholinergic properties.

In accordance with this selective action, in vitro studies have indicated that, in contrast to tricyclic antidepressants, paroxetine has little affinity for alpha 1, alpha 2 and beta-adrenoceptors, dopamine (D2), 5-HT1 like, 5-HT2 and histamine (H1) receptors. This lack of interaction with post-synaptic receptors in vitro is substantiated by in vivo studies, which demonstrate lack of CNS depressant and hypotensive properties.

Pharmacodynamic effects
Paroxetine does not impair psychomotor function and does not potentiate the depressant effects of ethanol.

As with other selective 5-HT uptake inhibitors, paroxetine causes symptoms of excessive 5-HT receptor stimulation when administered to animals previously given monoamine oxidase (MAO) inhibitors or tryptophan.

Behavioural and EEG studies indicate that paroxetine is weakly activating at doses generally above those required to inhibit 5-HT uptake. The activating properties are not "amphetamine-like" in nature. Animal studies indicate that paroxetine is well tolerated by the cardiovascular system. Paroxetine produces no clinically significant changes in blood pressure, heart rate and ECG after administration to healthy subjects.
Studies indicate that, in contrast to antidepressants that inhibit the uptake of noradrenaline, paroxetine has a much-reduced propensity to inhibit the antihypertensive effects of

guanethidine. In the treatment of depressive disorders, paroxetine exhibits comparable efficacy to standard antidepressants.

There is also some evidence that paroxetine may be of therapeutic value in patients who have failed to respond to standard therapy.
Morning dosing with paroxetine does not have any detrimental effect on either the quality or duration of sleep. Moreover, patients are likely to experience improved sleep as they respond to paroxetine therapy.

Dose response
In the fixed dose studies there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, there are some clinical data suggesting that up titrating the dose might be beneficial for some patients.

Long-term efficacy
The long-term efficacy of paroxetine in depression has been demonstrated in a 52 weeks maintenance study with relapse prevention design: 12% of patients receiving paroxetine (20-40mg daily) relapsed, versus 28% of patients on placebo.

The long-term efficacy of paroxetine in treating obsessive-compulsive disorder has been examined in three 24 week maintenance studies with relapse prevention design. One of the three studies achieved a significant difference in the proportion of relapsers between paroxetine (38%) compared to placebo (59%).

The long-term efficacy of paroxetine in treating panic disorder has been demonstrated in a 24 week maintenance study with relapse prevention design: 5% of patients receiving paroxetine (10-40 mg daily) relapsed, versus 30% of patients on placebo. This was supported by a 36 weeks maintenance study.

The long-term efficacy of paroxetine in treating social anxiety disorder, generalized anxiety disorder and post-traumatic stress disorder has not been sufficiently demonstrated.

Adverse Events from Paediatric Clinical Trials
In short-term (up to 10-12 weeks) clinical trials in children and adolescents, the following adverse events were observed in paroxetine treated patients at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo were: increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder. Increased hostility occurred particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age. Additional events that were more often seen in the paroxetine compared to placebo group were: decreased appetite, tremor, sweating, hyperkinesia, agitation, emotional lability (including crying and mood fluctuations).

In studies that used a tapering regimen, symptoms reported during the taper phase or upon discontinuation of paroxetine at a frequency of at least 2% of patients and occurred at a rate at least twice that of placebo were: emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide), nervousness, dizziness, nausea and abdominal pain.

In five parallel group studies with a duration of eight weeks up to eight months of treatment, bleeding related adverse events, predominantly of the skin and mucous membranes, were observed in paroxetine treated patients at a frequency of 1.74% compared to 0.74% observed in placebo treated patients.

Adult suicidality analysis
A paroxetine-specific analysis of placebo controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behaviour in young adults (aged 18-24 years) treated with paroxetine compared with placebo (2.19% vs 0.92%). In the older age groups, no such increase was observed. In adults with major depressive disorder (all ages), there was an increase in the frequency of suicidal behaviour in patients treated with paroxetine compared with placebo (0.32% vs 0.05%); all of the events were suicide attempts. However, the majority of these attempts for paroxetine (8 of 11) were in younger adults.

Pharmacokinetic properties

CLONAZEPAM

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.

PAROXETINE

Absorption
Paroxetine is well absorbed after oral dosing and undergoes first-pass metabolism. Due to first-pass metabolism, the amount of paroxetine available to the systemic circulation is less than that absorbed from the gastrointestinal tract. Partial saturation of the first-pass effect and reduced plasma clearance occur as the body burden increases with higher single doses or on multiple dosing. This results in disproportionate increases in plasma concentrations of paroxetine and hence pharmacokinetic parameters are not constant, resulting in non-linear kinetics. However, the non-linearity is generally small and is confined to those subjects who achieve low plasma levels at low doses.
Steady state systemic levels are attained by 7 to 14 days after starting treatment with immediate or controlled release formulations and pharmacokinetics do not appear to change during long-term therapy.

Distribution
Paroxetine is extensively distributed into tissues and pharmacokinetic calculations indicate that only 1% of the paroxetine in the body resides in the plasma.
Approximately 95% of the paroxetine present is protein bound at therapeutic concentrations.

No correlation has been found between paroxetine plasma concentrations and clinical effect (adverse experiences and efficacy).

Biotransformation
The principal metabolites of paroxetine are polar and conjugated products of oxidation and methylation which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to paroxetine's therapeutic effects.

Metabolism does not compromise paroxetine's selective action on neuronal 5-HT uptake.

Elimination

Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in faeces, probably via the bile, of which unchanged paroxetine represents less than 1% of the dose. Thus paroxetine is eliminated almost entirely by metabolism.

Metabolite excretion is biphasic, being initially a result of first-pass metabolism and subsequently controlled by systemic elimination of paroxetine.

The elimination half-life is variable but is generally about 1 day.

Special populations

Elderly and Renal/Hepatic impairment

Increased plasma concentrations of paroxetine occur in elderly subjects and in those subjects with severe renal impairment or in those with hepatic impairment, but the range of plasma concentrations overlaps that of healthy adult subjects.

Preclinical safety data

CLONAZEPAM

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.

PAROXETINE

Toxicology studies have been conducted in rhesus monkeys and albino rats; in both, the metabolic pathway is similar to that described for humans. As expected with lipophilic amines, including tricyclic antidepressants, phospholipidosis was detected in rats. Phospholipidosis was not observed in primate studies of up to one-year duration at doses that were 6 times higher than the recommended range of clinical doses.

Carcinogenesis: In two-year studies conducted in mice and rats, paroxetine had no tumorigenic effect.

Genotoxicity: Genotoxicity was not observed in a battery of in vitro and in vivo tests.

Reproduction toxicity studies in rats have shown that paroxetine affects male and female fertility by reducing fertility index and pregnancy rate. In rats, increased pup mortality and delayed ossification were observed. The latter effects were likely related to maternal toxicity and are not considered a direct effect on the foetus/neonate.

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

STORAGE
Store at a temperature not exceeding 30^0C, protected from light and moisture.

PRESENTATION
Clonotril P 12.5 is available in Alu-Alu blister pack of 10 Capsules
Clonotril P 25 is available in Alu-Alu blister pack of 10 Capsules

MARKETED BY

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IN/CLONOTRIL P 0.5,12.5,25mg /Sep-17/02/PI