Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rivotril 0.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms (0.5 mg) clonazepam.

Excipients: Also contains 40mg lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
Round dull pinkish-buff tablets with '0,5' imprinted on one face and a single break mark on the other.
The tablets can be broken into equal halves to facilitate dosing.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rivotril is indicated, primarily as an adjunct or in refractory cases, in most forms of epilepsy especially absence seizures including atypical absence seizures; Lennox-Gastaut syndrome; myoclonic and atonic seizures. For infantile spasms (including West-Syndrome) and tonic-clonic seizures it is only indicated as an adjunct or in refractory cases.

4.2 Posology and method of administration

The scored 0.5 mg tablets facilitate the administration of lower daily doses in the initial stages of treatment.
To break the tablet, hold it with the score facing up and apply downward pressure.

Posology

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

Elderly
The elderly are particularly sensitive to the effects of centrally depressant drugs and may experience confusion. The lowest possible dose should be used in the elderly.It is recommended that the initial dosage of Rivotril should not exceed 0.5 mg/day and particular care should be taken during uptitration.

These are total daily dosages which should be divided into 3 or 4 doses taken at intervals throughout the day. If necessary, larger doses may be given at the discretion of the physician, up to a maximum of 20 mg daily. The maintenance dose should be attained after 2 to 4 weeks of treatment.

Infants and children
To ensure optimum dosage adjustment, children should be given the 0.5 mg tablets.

Initial dosage should not exceed 0.25mg/day for infants and small children (1 to 5 years) and 0.50mg/day for older children.
The maintenance dosage normally falls within the ranges:
School children (5 to 12 years) 3 to 6 mg
Small children (1 to 5 years) 1 to 3 mg
Infants (0 to 1 year) 0.5 mg to 1 mg

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

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

Method 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 dosage of Rivotril 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 equal doses. If doses are not equally divided, the largest dose should be given before retiring. Once the maintenance dose level has been reached, the daily amount may be given in a single dose in the evening.

Simultaneous administration of more than one anti-epileptic drug is a common practice in the treatment of epilepsy and may be undertaken with Rivotril. The dosage of each drug may be required to be adjusted to obtain the optimum effect. Before adding Rivotril to an existing anticonvulsant regimen, it should be considered that the use of multiple anticonvulsants may result in an increase of undesired effects.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with known acute pulmonary insufficiency, severe respiratory insufficiency, medical history of sleep apnoea syndrome and severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy.

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

4.4 Special warnings and precautions for use

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

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

Rivotril 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.

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

<u>Hepatic impairment</u>

Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment. Special caution should be exercised when administering Rivotril to patients with mild to moderate hepatic impairment (see section 4.3).

<u>Central Nervous System (CNS), psychosis and depression</u>

Rivotril should be used with particular caution in patients with ataxia.

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

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

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 signs of suicidal ideation or behaviour emerge.

Myasthenia gravis

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering Rivotril to a patient with myasthenia gravis.

Concomitant use of alcohol / CNS depressants

The concomitant use of Rivotril with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Rivotril possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5 and 4.9).

Rivotril should be used with particular caution in the event of acute intoxication with alcohol or drugs.

Psychiatric and 'paradoxical' reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines (see section 4.8). Should this occur, the use of the drug should be discontinued. Paradoxical reactions are more likely to occur in children and in the elderly.

Amnesia

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 (see 4.8) during long-term treatment is possible.

Sleep apnoea

Benzodiazepines are not recommended for use in patients with sleep apnoea due to possible additive effects on respiratory depression (see section 4.3).

Respiratory disorders

The dosage of Rivotril must be carefully adjusted to individual requirements in patients with pre-existing disease of the respiratory system (e.g. chronic obstructive pulmonary disease). 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.

Epilepsy

The dosage of Rivotril must be carefully adjusted to individual requirements in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents (see section 4.5).

As with all other anti-epileptic drugs, treatment with Rivotril 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 antiepileptics is indicated. This precaution must also be taken when withdrawing another drug while the patient is still receiving Rivotril therapy.

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.

Lactose intolerance

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

Paediatric population

In infants and small children Rivotril may cause increased production of saliva and bronchial secretion. Therefore special attention must be paid to maintaining patency of the airways.

Elderly

Benzodiazepine pharmacologic effects appear to be greater in elderly patients than in younger patients even at similar plasma benzodiazepine concentrations, possibly because of age-related changes in drug–receptor interactions, post-receptor mechanisms and organ function.

Dependence

Use of benzodiazepines may lead to the development of physical and psychologicaldependence upon these products (see 4.8). 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).

The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcoholism and/or drug abuse. Abuse has been reported in poly-drug abusers.

Rivotril should be used with extreme caution in patients with a history of alcohol 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, diarrhoea, muscle pain, extreme anxiety, tension, restlessness, mood changes, 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).

4.5 Interaction with other medicinal products and other forms of interactions

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 Rivotril, alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects.

See section 4.9 Overdose for warning of other central nervous system depressants, including alcohol.

Enhanced side effects such as sedation and cardio-respiratory depression may also occur when Rivotril 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 Rivotril is used in conjunction with other anti-epileptic drugs, side-effects such as sedation and apathy and toxicity may be more evident, particularly with hydantoins or phenobarbital and combinations including them. In such cases, the dosage of each drug must be adjusted to achieve the optimum desired effect, particularly in the initial stages of treatment. The combination of Rivotril 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, lamotrigine and to a lesser extent valproate may increase the clearance of clonazepam thereby decreasing the plasma concentrations of the latter by up to 38% during combined treatment.

Rivotril has the potential to influence concentrations of phenytoin. Due to the bi-directional nature of the clonazepam-phenytoin interaction, phenytoin levels have been found to be unchanged, increased or decreased upon coadministration with Rivotril depending on dosing and patient factors.

Rivotril itself does not induce the enzymes responsible for its own metabolism. The enzymes involved in the metabolism of Rivotril have not been clearly identified but include CYP3A4. Inhibitors of CYP3A4 (e.g., fluconazole) may impair the metabolism of Rivotril and lead to exaggerated concentrations and effects.

The selective serotonin reuptake inhibitors sertraline (weak CYP3A4 inducer), fluoxetine (CYP2D6 inhibitor) and the anti-epileptic drug felbamate (CYP2C19 inhibitor; CYP3A4 inducer) 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 (see section 5.3). 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 newborn. 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. Rivotril should only be administered to pregnant women if the potential benefits outweigh the risk to the foetus.

During pregnancy, Rivotril may be administered only if there is a compelling indication. Rivotril has harmful pharmacological effects on pregnancy and the foetus/newborn 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 a 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.

Breast feeding
Although, the active ingredient of Rivotril 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 Rivotril, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

As a general rule, epileptic patients are not allowed to drive. Even when adequately controlled on Rivotril, 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 (see section 4.5 and 4.8).

4.8 Undesirable effects

The following have been observed:

Immune System Disorders
Allergic reactions and very rare cases of anaphylaxis 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
Emotional and mood disturbances, confusional state, disorientation have been observed. Depression may occur in patients treated with Rivotril, but it may be also associated with the underlying disease. The following paradoxical reactions have been observed: restlessness, irritability, aggressiveness, agitation, nervousness, hostility, anxiety, delusion, anger, sleep disturbances, nightmares, abnormal dreams, hallucinations, psychoses, hyperactivity, inappropriate behaviour and other adverse behavioural effects and activation of new types of seizures are known to occur. If these occur, the drug should be discontinued. Paradoxical reactions are more likely to occur in children and in the elderly. The addition to the regimen of another suitable drug may be necessary or, in some cases, it may be advisable to discontinue Rivotril therapy. In rare cases changes in libido may occur.

Nervous System Disorders
Impaired concentration, somnolence, slowed reaction, muscular hypotonia, dizziness, ataxia and co-ordination disturbance. These undesirable effects occur relatively frequently and are usually transient and generally disappear spontaneously in the course of the treatment or on reduction of the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment.

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

Particularly in long-term or high-dose treatment, reversible disorders such as dysarthria, reduced coordination of movements and gait disorder (ataxia) and nystagmus may occur. Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour. With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible.

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

Respiratory depression may occur, particularly on i.v. administration of clonazepam. This effect may be aggravated by pre-existing airways obstruction or brain damage or if other medications which depress respiration have been given. As a rule, this effect can be avoided by careful adjustment of the dose to individual requirements.

In infants and young children, particularly those with a degree of mental impairment, Rivotril may cause increased production of saliva or of bronchial secretion. Particular attention should therefore be paid to maintaining patency of the airways.

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 hairloss, pigmentation changes and angioedema.

Musculoskeletal and Connective Tissue Disorders
Muscle weakness, this undesirable effect occurs relatively frequently and isusually transient and generally disappears spontaneously in the course of thetreatment or on reduction of the dosage. It can be partially prevented byincreasing the dose slowly at the start of treatment.

Renal and Urinary Disorders
In rare cases urinary incontinence may occur.

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

Dependence and withdrawal (see section 4.4)
Although Rivotril has been given uneventfully to patients with porphyria, rarely it may induce convulsions in these patients.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517, Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms
The symptoms of overdosage 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 Rivotril 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 a few hours but it may be more protracted and cyclical, particularly in elderly

patients. Increased frequency of seizures may occur in patients at supratherapeutic plasma concentrations (see section 5.2). 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 its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug. Flumazenil is **NOT TO BE USED IN MIXED OVERDOSE OR AS A "DIAGNOSTIC TEST"**

Warning

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

If excitation occurs, barbiturates should not be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N03AE01

Mechanism of action

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux. 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 absences 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 focal EEG abnormalities such as focal spikes. Clonazepam has beneficial effects in generalised and focal epilepsies.

5.2 Pharmacokinetic properties

Absorption

Clonazepam is quickly and completely absorbed after oral administration of Rivotril. Peak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. The absolute bioavailability is around 90% after oral administration with large differences between individuals.

Plasma concentrations of clonazepam at steady state for a once-daily dosage regimen are 3-fold higher than those after a single oral dose; the predicted accumulation ratios for two times and three times daily regimens are 5 and 7, respectively. Following multiple oral doses of 2 mg three times daily steady-state pre-dose plasma concentrations of clonazepam averaged 55 ng/mL. The plasma concentration-dose relationship of clonazepam is linear. The target anticonvulsant plasma concentrations of clonazepam range from 20 to 70 ng/mL. Severe toxic effects including increased frequency of seizures developed in the majority of patients with steady state plasma concentrations above 100 ng/mL.

Routine monitoring of plasma concentrations of Rivotril 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.

Biotransformation
The biotransformation of clonazepam involves oxidative hydroxylation and reduction of the 7-nitro group by the liver with formation of 7-amino or 7-acetamido 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 30-40 hours) and is independent of the dose.

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

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

Hepatic Impairment
Although the influence of hepatic impairment on clonazepam pharmacokinetics has not been further investigated, experience with nitrazepam indicates that clearance of unbound clonazepam might be reduced in liver cirrhosis.

Paediatric patients
Overall the elimination kinetics in children are similar to those observed in adults.

5.3 Preclinical safety data

Carcinogenicity
No 2-year carcinogenicity studies have been conducted with clonazepam.
However, in an 18-month chronic study in rats no treatment-related histopathological changes were seen up to the highest tested dose of 300 mg/kg/day.

Mutagenicity
Genotoxicity tests using bacterial systems with in vitro or host mediated metabolic activation did not indicate a genotoxic liability for clonazepam.

Impairment of Fertility
Studies assessing fertility and general reproductive performance in rats showed a reduced pregnancy rate and impaired pup survival at doses of 10 and 100 mg/kg/day.

Teratogenicity
No adverse maternal or embryo-foetal 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 (see section *4.6 Pregnancy and Lactation*).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Pregelatinised starch
Magnesium stearate
Iron oxide red E172
Iron oxide yellow E172
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original package and in the outer carton, protected from light

6.5 Nature and contents of container

Amber glass bottles with polyethylene screw closures, containing 50, 100 or 150 tablets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Arzneimittel GmbH
Ziegelhof 24
17489
Greifswald
Germany

8 MARKETING AUTHORISATION NUMBER

PA2239/020/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1977
Date of last renewal: 1st April 2007

10 DATE OF REVISION OF THE TEXT

November 2021