SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clonazepam Celix 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is clonazepam.

Each tablet contains 2 mg of clonazepam

Excipients with known effect:

Each 2 mg tablet contains 121.5 mg of lactose monohydrate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

Clonazepam 2 mg Tablets are white to off white circular tablets, debossed with ‘CL2’ on one side and cross breakline on other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

All clinical forms of epileptic disease and seizures in infants, children and adults, especially absence seizures (petit mal), including atypical absence; primary or secondarily generalised tonic-clonic seizures (grand mal); tonic or clonic seizures;

partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

4.2 Posology and method of administration

Posology

Adults

Initial dose not to exceed 1 mg/day.

The maintenance dosage for adults normally falls with the range 4 – 8 mg.

Elderly

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

Children and Infants

Children should receive the 0.5 mg tablets to ensure optimum dosage adjustment.

Initial dose should not exceed 0.25 mg/day for infants and small children (1-5 yrs).

Initial dose should not exceed 0.5 mg/day for older children.

The maintenance dosage normally falls within the ranges:

Infants (0 - 1 year) 0.5 – 1 mg/day

Small children (1 – 5 years) 1 – 3 mg/day

School children (5-12 years) 3 – 6 mg/day

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

Hepatic Impairment

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

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

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

The daily dose should be divided into 3 or 4 doses throughout the day. If doses are not equally divided, the largest dose should be given before retiring. Once the maintenance dose level has been reached, the daily amount may be given in a single dose in the evening.

Simultaneous administration of more than one antiepileptic drug is a common practice in the treatment of epilepsy and may be undertaken with clonazepam. The dosage of each drug may be required to be adjusted to obtain the optimum effect. If status epilepticus occurs in a patient receiving oral clonazepam, intravenous clonazepam may still control the status. Before adding clonazepam to an existing anticonvulsant regimen, it should be considered that the use of multiple anticonvulsants may result in an increase of undesired effects. If necessary, larger doses may be given at the discretion of the physician, up to a maximum of 20 mg daily. The maintenance dose should be attained after 2-4 weeks of treatment.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Suicidal behaviour:

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

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

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

Carefully adjust dosage to individual requirements in patients with pre-existing disease of the liver or the respiratory system (e.g. chronic obstructive pulmonary disease) and in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents (see section 4.5. Interaction with other medicinal products and other forms of interaction).

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.

Do not interrupt treatment abruptly. As with all other antiepileptic drugs, treatment must be withdrawn gradually, by reducing the dose due to the risk of precipitating status epilepticus. 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 with withdrawal symptoms on cessation of use.

Use 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).

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

Concomitant use with alcohol / CNS depressants

The concomitant use of Clonazepam Tablets 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 (see section 4.5).

Use with extreme caution in patients with a history of alcohol or drug abuse.

Risk from concomitant use of opioids:

Concomitant use of Clonazepam Tablets and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Clonazepam Tablets concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Paediatric population

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

Porphyria

Clonazepam is considered to be probably non porphyrinogenic, although there is some conflicting evidence. In rare cases, clonazepam has induced convulsions in patients with porphyria.

Driving

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) (see section 4.7).

As a general rule, epileptic patients are not allowed to drive. Even when adequately controlled on Clonazepam Tablets, it should be remembered that any increase in dosage or alteration in timings of dosage may modify patients' reactions, depending on individual susceptibility.

Dependence

Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products (see section 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 double 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 behavior. With certain forms of epilepsy, an increase in the frequency of seizures (see section 4.8) during long-term treatment is possible. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse.

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).

Excipients

Lactose

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Coadministration with alcohol

Alcohol in combination with clonazepam may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects (see also section 4.4). Under no circumstances should alcohol be consumed while under treatment with clonazepam.

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

Antiepileptic drugs

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

The antiepileptic drugs phenytoin, phenobarbital, carbamazepine and valproate may increase the clearance of clonazepam there by 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.

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

Special Precautions

The plasma concentration of clonazepam is often reduced by theophylline.

Concurrent treatment with phenytoin or primidone can change the plasma concentration of phenytoin or primidone (usually increases).

There is an increased risk of prolonged sedation and respiratory depression when clonazepam is given with amprenavir.

Clonazepam may possibly antagonize effects of levodopa.

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

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

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

Opioids:

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as clonazepam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Hepatic enzyme inhibitors and inducers

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

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

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

4.6 Fertility, pregnancy and lactation

Fertility

Preclinical studies in animals have shown reproductive toxicity and from preclinical studies it cannot be excluded that clonazepam possesses the possibility of producing congenital malformations (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. Clonazepam should only be administered to pregnant women if the potential benefits outweigh the risk to the fetus.

Pregnancy

Clonazepam has harmful pharmacological effects on pregnancy and the foetus/newborn child.

Clonazepam should not be used during pregnancy unless clearly necessary.

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 sucking 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.

Breastfeeding

Clonazepam passes into the maternal milk in small amounts. Therefore, clonazepam should not be used in mothers who breastfeed unless clearly necessary.

If there is a compelling indication for clonazepam, breastfeeding should be discontinued. Mothers undergoing treatment with this drug should not breastfeed.

4.7 Effects on ability to drive and use machines

Driving, operating machinery and other hazardous activities should be avoided when using clonazepam especially during the first few days of treatment. Even when adequately controlled on clonazepam, increases in dosage or alteration in timings of dosage may modify patients' reactions, depending on individual susceptibility. Clonazepam can slow reaction to such an extent that the ability to drive a vehicle or operate machinery is impaired. This effect is aggravated by consumption of alcohol. Driving, operating machinery and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment.

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

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

- The medicine is likely to affect your ability to drive
- 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 defense') 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

4.8 Undesirable effects

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).

The side effects marked with an asterisk (*) are usually transitory and disappear spontaneously as treatment continues or with dose reduction. They tend to occur early in treatment and can be greatly reduced, if not avoided, by commencing with low dosages followed by progressive increases.

Blood and the lymphatic system disorders

Isolated cases of blood dyscrasias.

Immune system disorders

Allergic reaction and a very few cases of anaphylaxis and angioedema.

Endocrine disorders

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

Psychiatric disorders and Paradoxical Reactions

Anterograde amnesia (risk increases at higher dosages). Amnestic effects may be associated with inappropriate behaviour. Depression, loss of libido, impotence.

Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment and is particularly pronounced in predisposed patients with a history of alcoholism or drug abuse (see section 4.4).

Paradoxical effects such as aggressiveness, excitability, nervousness, hostility, anxiety, sleep disturbances, nightmares, vivid dreams, irritability, agitation, psychotic

disorders and activation of new types of seizures may occur. If these occur, the benefit of continuing the drug should be weighed against the adverse effect. It may be necessary to add another suitable drug to the regimen or to discontinue clonazepam therapy.

Nervous system disorders

Dizziness*, light-headedness*, somnolence*, fatigue*, co-ordination disturbances*, poor concentration, restlessness, confusion and disorientation, headache.

Dysarthria and ataxia* are reversible disorders and occur particularly in long-term or high-dose treatment.

These undesirable effects occur relatively frequently and may disappear gradually 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 generalized 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 behavior. Although clonazepam has been given uneventfully to patients with porphyria, rarely it may induce convulsions in these patients.

With certain forms of epilepsy, an increase in the frequency of seizures during long term treatment is possible.

Rarely, convulsions may be induced in patients with porphyria.

Eye disorders

Double vision and nystagmus are reversible disorders and occur particularly in long term or high-dose treatment.

Common: nystagmus

Cardiac Disorders

Cardiac failure including cardiac arrest has been reported.

Respiratory, thoracic and mediastinal disorders

Rarely respiratory depression may occur with intravenous clonazepam, particularly if other depressant drugs have been administered. This effect may be aggravated by pre-

existing airways obstruction or brain damage or if other medications which depress respiration have been given. This effect can usually 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, salivary or bronchial hypersecretion with drooling may occur. Supervision of the airway may be required.

Gastrointestinal disorders

Rarely: nausea, gastrointestinal and epigastric symptoms.

Hepato-biliary disorders

Isolated cases of abnormal liver function tests have been reported.

Skin and subcutaneous tissue disorders

Rarely: urticaria, pruritus, rash, transient hair loss, pigmentation changes.

Musculoskeletal, connective tissue and bone disorders

Muscle weakness*, occasional muscular hypotonia*

Renal and urinary disorders

Rarely: urinary incontinence.

Reproductive System and Breast Disorders

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

General disorders and administration site conditions

Withdrawal: Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. During long-term treatment, withdrawal symptoms may develop, especially withdrawing from 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, discontinuation should be carried out by gradually reducing the daily dose.

Injury, Poisoning and Procedural Complications

An increased risk for falls and fractures has been reported in elderly benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages)

Investigations

In rare cases decreased platelet count may occur. As with other benzodiazepines, isolated cases of blood dyscrasias. Dependence and withdrawal, (see section 4.4).

Pediatric population

For pediatric 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 the Yellow Card Scheme; website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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. Coma, areflexia, apnoea, hypotension and cardiorespiratory depression occasionally occur but are seldom serious if these drugs are taken alone. Coma 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. The benefit of gastric decontamination is uncertain. Consider activated charcoal (50 g for an adult, 10-15 g for a child) in adults or children who have taken more than 0.4mg/kg within 1 hour, provided they are not too drowsy.

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. Gastric lavage is unnecessary if these drugs have been taken alone. 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. 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.

7. Flumazenil (Anexate), a benzodiazepine antagonist is available but should rarely be required. It has a short half-life (about an hour). If CNS depression is severe consider the use of flumazenil. This should only be administered under closely monitored conditions 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 USE IN MIXED OVERDOSE OR AS A "DIAGNOSTIC TEST"** (see separate prescribing information).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, benzodiazepine derivate.

ATC code: N03AE01

Mechanism of action

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, generalized spike wave, spikes with temporal or other locations as well as irregular spikes and waves.

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

5.2 Pharmacokinetic properties

Absorption

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

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

Distribution

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

Metabolism

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

Within 4 - 10 days 50 - 70% of the total radioactivity of a radio labelled oral dose of clonazepam is excreted in the urine and 10 - 30% in the faces, almost exclusively in the form of free or conjugated metabolites. Less than 0.5% appears as unchanged clonazepam in the urine.

Elimination

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

Pharmacokinetics in special clinical situations

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

5.3 Preclinical safety data

Carcinogenicity

Conventional studies of carcinogenic potential have not 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).

As toxicokinetic evaluations have not been performed with clonazepam, it is not possible to determine the safety margin for the adverse effects observed in the

nonclinical studies. The relevance of these findings to the patient population is unclear therefore a potential risk to man cannot be ruled out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Microcrystalline cellulose, Starch pregelatinized, Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Clonazepam Tablets are marketed in blister pack (aluminium-PVC).

Pack size: 100 tablets

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Celix Pharma Ltd.,
12 Constance street,
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 53835/0026

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10 DATE OF REVISION OF THE TEXT

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