1. NAME OF THE MEDICINAL PRODUCT

Clonazepam Rosemont 0.5mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 0.5mg Clonazepam

Excipient with known effect
Ethanol – 100mg/5ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

A clear, pale straw coloured oily solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

All clinical forms of epileptic disease and seizures in adults, especially absence seizures (petit mal) including atypical absence; primary or secondarily generalised tonic-clonic (grand mal), tonic or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

4.2 Posology and method of administration

Posology

The 0.5mg/5ml oral solution may facilitate the administration of lower daily doses in the initial stages of treatment or treatment for the elderly.

The 2mg/5ml oral solution should be used for maintenance and maximum dosage regimens.

Adults

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

Elderly

The elderly are particularly sensitive to the effects of centrally depressant drugs and may experience confusion. It is recommended that the initial dosage of clonazepam should not exceed 0.5mg/day.

These are total daily dosages which should be divided into 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 20mg daily. The maintenance dose should be attained after 2 to 4 weeks of treatment.

Paediatric Population

Due to the presence of ethanol in the formulation, this product is not indicated for paediatric use.

Method of administration

A 2.5ml/ 5ml double ended spoon with a further 1.25ml graduation is supplied with the pack.
Suitable for administration via non-PVC nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes. For further instructions see section 6.6. When these instructions are followed over 95% of the dose is delivered.

The product is incompatible with polystyrene or PVC and therefore, other devices may react with the product.

It should be noted that for oral syringes, the product may cause the plunger to stop moving smoothly or the markings may fade over time.

Treatment should be started with low doses. The dose may be increased progressively until the maintenance dose suited to the individual patient has been found.

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

The daily dose should be divided into 4 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 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, administration of an intravenous clonazepam injection 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.

4.3 Contraindications

Patients with known sensitivity to benzodiazepines; or hypersensitivity to the active substance or to any of the excipients listed in section 6.1; acute pulmonary insufficiency; severe respiratory insufficiency, sleep apnoea syndrome, myasthenia gravis, severe hepatic insufficiency as benzodiazepines may precipitate hepatic encephalopathy.

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 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.

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 antiepileptics is indicated. This precaution must also be taken when withdrawing another drug while the patient is still receiving clonazepam therapy.

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.

Clonazepam may be used only with particular caution in patients with spinal or cerebellar ataxia, in the event of acute intoxication with alcohol.

Hepatic impairment

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

Myasthenia gravis

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

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 that could result in coma or death, clinically relevant respiratory and/or cardio-vascular depression (see *sections 4.5 and 4.9*).

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 (see *section 4.5*). 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 non-porphyrinogenic, 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) (see *section 4.7*).

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

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.

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).

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 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 (see section 4.8) 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).

Due to the oily nature of this medicine caution should be used when administering this medicine via a nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes. This could lead to under dosing due to medicine remaining in the tube. For accurate delivery the instructions in section 6.6 should be followed.

Risk from concomitant use of opioids:

Concomitant use of Clonazepam 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 such as Clonazepam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Clonazepam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

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).

Excipient warnings:

This product contains the following excipients:
Ethanol: This medicinal product contains 2.6% (v/v) ethanol (alcohol). This is equivalent to 100 mg of ethanol in 5 ml, which is equivalent to 20 mg/ml.
A dose of 10 ml of this medicine administered to an adult weighing 70 kg would result in exposure to 2.9 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 0.5 mg/100 ml.

For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.
As this product is indicated for epilepsy, special consideration should be given to the amount of ethanol administered in the dose (see section 4.2).
Harmful for those suffering from alcoholism.
To be taken into account in pregnant or breast-feeding women.

4.5 Interaction with other medicinal products and other forms of interaction

Since alcohol can provoke epileptic seizures, irrespective of therapy, patients must under no circumstances drink alcohol while under treatment with antiepileptic drugs. In combination with clonazepam, alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects.

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

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. In such cases, the dosage of each drug must be adjusted to achieve the optimum desired effect, particularly in the initial stages of treatment. 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, lamotrigineand to a lesser extent valproate may induce the metabolism of clonazepam causing higher clearance and lower plasma concentrations of the latter during combined treatment. Clonazepam 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 clonazepam depending on dosing and patient factors.

In concurrent treatment with primidone, a change, usually a rise in the serum concentration has occasionally been observed.

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

The selective serotonin reuptake inhibitors sertraline (weak CYP3A4 inhibitor) and 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.

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).

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 Preclinical safety data*). 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 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/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 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.

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 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:

- 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 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

4.8 Undesirable effects

Immune System Disorders

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

Endocrine Disorders

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

Psychiatric Disorders

Impaired concentration, restlessness, emotional and mood disturbances, 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, restlessness, hallucinations 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. Paradoxical reactions are more likely to occur in children and in the elderly.

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 (see section 4.4)

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

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 at 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 60mg 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. 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, 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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, Benzodiazepine derivatives

ATC Code: N03 AE01

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. Animal data and electroencephalographic investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spike and wave discharge in absence seizures (petit mal), slow spike wave, generalised spike wave, spikes with temporal or other locations as well as irregular spikes and waves.

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

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.

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-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.

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-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 (see section 4.6 Pregnancy and Lactation).

In preclinical murine studies there was at least a two fold increase in teratogenic birth defects at dose levels of 3, 9 and 18 times the human therapeutic dose compared to the controls.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Saccharin

Ethanol

Levomenthol

Medium chain triglycerides

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

This product should not be mixed with water.

This product is incompatible with polystyrene and PVC.

6.3 Shelf life

12 months

1 month once open

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Bottle: Amber (Type III) glass

Closure: HDPE, EPE wadded, tamper evident, child resistant closure

Pack size: 150ml

Dosing Device: 2.5ml/ 5ml double ended spoon with a 1.25ml graduation mark

6.6 Special precautions for disposal and other handling

Instruction for administration via nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes:

Clonazepam Oral Solution is suitable for use with the following types of NG and PEG tubes:

Material	External Bore Size (Fr Unit)	Internal Diameter (mm)	Maximum Length (cm)
Silicone	6	1.0	125
	10	2.0	125
Polyurethane	8	1.5	100
	12	2.6	75
	18	4.0	75

This product is not compatible with PVC or polystyrene and therefore should not be used with NG or PEG tubes made from these materials.

Care should be taken during administration due to the oily nature of the product. It is recommended to administer the dose prior to delivering feed through the NG or PEG tub and to follow the instruction below:

Ensure that the enteral feeding tube is free from obstruction before administration.

1) Flush the enteral tube with water, a minimum flush volume of 10mL is required.

2) Administer the required dose of Clonazepam Oral Solution with a suitable measuring device.

3) Flush the enteral tube again by either of the methods below:

i) Flush the enteral tube 3 consecutive times, using a minimum volume of 5mL of water each time.

ii) Flush the enteral tube using a minimum volume of 5mL of water and then immediately deliver a minimum of 10ml of feed.

Healthcare professionals should be aware that if the instructions above cannot be followed (e.g. longer or wider tubes are used or in a specific clinical situations) there is a risk of under dosing (up to 15%) as the oily medicine may adsorb to the wall of the feeding tube.. Extra flushing with water or feed may combat this. In these situations the patient should be monitored closely.

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

7 MARKETING AUTHORISATION HOLDER

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LS11 9XE

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00427/0157

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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