Safeguarding public health

Public Assessment Report

Decentralised Procedure

Clonazepam 0.5mg and 2mg Tablets

(clonazepam)

UK/H/1890/01-02/DC

UK licence number: PL 20620/0045-6

NRIM Limited

LAY SUMMARY

On 29th June 2010, the MHRA granted NRIM Limited Marketing Authorisations (licences) for the medicinal products Clonazepam 0.5mg and 2mg Tablets (PL 20620/0045-6, UK/H/1890/01-02/DC). These are prescription-only medicines (POM).

Clonazepam tablets contain the active ingredient, clonazepam, which belongs to a group of medicines called 'benzodiazepines'. Clonazepam tablets are used to treat an illness called epilepsy and work by preventing seizures or fits.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Clonazepam 0.5mg and 2mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Information about Initial Procedure

Product Name	Clonazepam 0.5mg and 2mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Clonazepam
Form	Tablets
Strength	0.5mg and 2mg
MA Holder	NRIM Limited Marlborough House 298, Regents Park Road Finchley N3 2UA London, United Kingdom
Reference Member State (RMS)	UK
Concerned Member State (CMS)	Hungary
Procedure Number	UK/H/1890/01-02/DC
Timetable	End of Procedure: Day 210 – 10th June 2010

Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Clonazepam 0.5mg and 2mg Tablets (PL 20620/0045-6) is as follows. Differences between the individual SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Clonazepam 0.5mg Tablets
Clonazepam 2mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains 0.5mg / 2mg of clonazepam.

Also contains 73.0mg of Lactose per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

For Clonazepam 0.5mg Tablets (PL 20620/0045) - Peach coloured flat circular bevelled tablets, cross-scored on one side and plain on the other side.

For Clonazepam 2mg Tablets (PL 20620/0046) – White to off white flat circular bevelled tablets, cross-scored on one side and plain on the other side.

The tablets can be divided in to equal quarters.

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 (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

Route of administration
Oral

Recommended dosage
The scored 0.5mg tablets facilitate the administration of lower daily doses in the initial stages of treatment.

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 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 20mg 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 0.5mg tablets.

Initial dosage should not exceed 0.25mg/day for infants and small children (1 to 5 years) and 0.5mg/day for older children. The maintenance dosage normally falls within the ranges:

School children (5 to 12 years) 3 to 6mg
Small children (1 to 5 years) 1 to 3mg
Infants (0 to 1 year) 0.5 to 1mg

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.

Mode 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 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 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, 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

4.3 Contraindications

Patients with known sensitivity to benzodiazepines; or any of the drugs excipients; acute pulmonary insufficiency; severe respiratory insufficiency, sleep apnoea syndrome, myasthenia gravis, severe hepatic insufficiency.

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

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

Clonazepam may be used only with particular caution in patients with spinal or cerebellar ataxia, in the event of acute intoxication with alcohol or drugs and in patients with severe liver damage (e.g. cirrhosis of the liver).

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

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

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).

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).

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

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

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. In combination with clonazepam, alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects.

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

The antiepileptic drugs phenytoin, phenobarbital, carbamazepine and valproate may induce the metabolism of clonazepam causing higher clearance and lower plasma concentrations of the latter during combined treatment.

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

Known inhibitors of hepatic enzymes, e.g. cimetidine, have been shown to reduce the clearance of benzodiazepines and may potentiate their action and known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines.

In concurrent treatment with phenytoin or primidone, a change, usually a rise in the serum concentration of these two substances has occasionally been observed.

Concurrent use of clonazepam and other centrally acting medications, e.g. other anticonvulsant (antiepileptic) agents, anaesthetics, hypnotics, psychoactive drugs and some analgesics as well as muscle-relaxants may result in mutual potentiation of drug effects. This is especially true in the presence of alcohol. In combination therapy with centrally-acting medications, the dosage of each drug must be adjusted to achieve the optimum effect.

4.6 Pregnancy and lactation

Preclinical studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). From epidemiological evaluations there is evidence that anticonvulsant drugs act as teratogens.

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

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. Therefore clonazepam should not be used in pregnancy unless clearly necessary.

Clonazepam has been found to pass into the maternal milk in small amounts. Therefore clonazepam should not be used in mothers who breastfeed unless clearly necessary.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Clonazepam is well tolerated and adverse reactions have generally been mild and reversible. The following have been reported as adverse events in clinical trials or reported from routine use, but in many cases a relationship to treatment with clonazepam has not been established.

The following definitions of frequencies are used:

Common	$\geq$ 1/100
Uncommon	$\geq$ 1/1000 and < 1/100
Rare	< 1/1000

Common:
Psychiatric: poor concentration, restlessness, confusion and disorientation have been observed. Anterograde amnesia may occur using benzodiazepines at therapeutic dosage, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour.

Neurological: dizziness, ataxia, somnolence, and co-ordination disturbances; such effects are usually transient and disappear spontaneously as treatment continues or with dosage 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.

Musculoskeletal: muscle weakness

General: fatigue, light-headedness

Uncommon:
Musculoskeletal: occasional muscular hypotonia

Psychiatric: 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.

Rare:
Haematological: as with other benzodiazepines, isolated cases of blood dyscrasias have been reported.

Psychiatric: depression may occur in patients treated with clonazepam, but it may be also associated with the underlying disease

Neurological: particularly in long-term use, or with high-dose treatment, there are reports of reversible disorders such as a slowing or slurring of speech (dysarthria), reduced co-ordination of movements and gait (ataxia). Seizures may also occur in pre-disposed patients (see *Special Warnings and Precautions for Use*).

Eye Disorders: double vision and nystagmus.

Gastrointestinal: gastrointestinal symptoms including nausea.

Respiratory: respiratory depression may occur with intravenous clonazepam, particularly if other depressant drugs have been administered. As a rule, this effect can be avoided by careful adjustment of the dose in individual requirements.

Hepatic: abnormal liver function tests have been reported.

Skin: there are a few reports of urticaria, pruritus, transient hair loss and pigmentation changes. Allergic reactions including a very few cases of anaphylaxis and angioedema have been reported to occur with benzodiazepines.

Urinary: urinary incontinence.

Reproductive: decrease in sexual drive (loss of libido), and impotence have been reported. Isolated cases of reversible development of premature secondary sex characteristics in children (incomplete precocious puberty) have also been reported.

General: headache.

Withdrawal symptoms: once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. During long-term treatment, withdrawal symptoms may develop, 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 which may be extreme, headaches, muscle pain, 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.

Special Warnings and Special Precautions for Use.

In infants and small children, and particularly those with a degree of mental impairment, clonazepam may give rise to salivary or bronchial hyper secretion with drooling. Supervision of the airway may be required.

With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible. Clonazepam generally has a beneficial effect on behaviour disturbances in epileptic patients. In certain cases, 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 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.

Although clonazepam has been given uneventfully to patients with porphyria, there are rare reports of induced convulsions in these patients.

An increased risk of falls and fractures has been recorded in elderly benzodiazepine users.

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 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:
Maintain a clear airway and adequate ventilation if indicated.

1. 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.
2. Gastric lavage is unnecessary if these drugs have been taken alone.
3. Patients who are asymptomatic at 4 hours are unlikely to develop symptoms.
4. 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.
5. Flumazenil (Anexate), a benzodiazepine antagonist is available but should rarely be required. It has a short half-life (about an hour). Flumazenil is **NOT TO BE USED 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

Pharmcotherapeutic group: benzodiazepine derivative

ATC Code: N03AE01

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 of clonazepam. Peak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. Bioavailability is 90% after oral administration.

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

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

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

Within 4 - 10 days 50 - 70% of the total radioactivity of a radiolabelled 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.

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

In preclinical murine studies there was at least a two fold increase in 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

Anhydrous Lactose
Pregelatinised Starch
Microcrystalline Cellulose
Ferric Oxide Yellow (E 172)
Ferric Oxide Red (E 172)
Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf life of the medicinal product as packaged for sale: 2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original packaging.

6.5 Nature and contents of container

For Clonazepam 0.5mg Tablets (PL 20620/0045)
Tablets are packed in Clear PVC-PVDC/Aluminium blisters containing 50, 100 or 150 tablets. Not all pack sizes will be marketed.

For Clonazepam 2mg Tablets (PL 20620/0046)
Tablets are packed in Clear PVC-PVDC/Aluminium blisters containing 30 or 100 tablets. Not all pack sizes will be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

NRIM Limited
Marlborough House
298, Regents Park Road
Finchley N3 2UA
London, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20620/0045
PL 20620/0046

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/06/2010

10 DATE OF REVISION OF THE TEXT

29/06/2010

Module 3

Patient Information Leaflet

NRIM

CLONAZEPAM 0.5MG & 2MG TABLETS

PATIENT INFORMATION LEAFLET

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START USING THIS MEDICINE.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

THE LEAFLET CONTAINS INFORMATION ON:

1. What Clonazepam Tablets are and what they are used for
2. Before you take Clonazepam Tablets
3. How to take Clonazepam Tablets
4. Possible side effects
5. How to store Clonazepam Tablets
6. Further Information

1. WHAT CLONAZEPAM TABLETS ARE AND WHAT THEY ARE USED FOR?

The name of your medicine is Clonazepam 0.5mg or 2mg Tablets (called Clonazepam tablets throughout this leaflet). Clonazepam tablets belongs to a group of medicines called 'benzodiazepines'. They are used to treat an illness called epilepsy. Clonazepam works by preventing seizures or fits.

2. BEFORE YOU TAKE CLONAZEPAM TABLETS

You should not take Clonazepam tablets until you are sure it is safe for you to do so.

Do not take this medicine and tell your doctor if:

- You are allergic (hypersensitive) to clonazepam or any of the other ingredients of Clonazepam tablets (listed in Section 6 below) or to other benzodiazepines (such as diazepam, chlordiazepoxide, bromazepam, or flurazepam).
- If you are allergic to any of the ingredients it contains.
- If you suffer from lung disease.
- If you suffer from myasthenia gravis (severe muscle tiredness).
- If you suffer from sleeping disorders, such as difficulty breathing while asleep.
- If you have a severe liver condition.

Take special care with Clonazepam Tablets and check with your doctor or pharmacist before taking your medicine if you:

- have a lung, liver or kidney condition.
- regularly drink alcohol or use recreational drugs.
- suffer from a form of inco-ordination of the muscles called cerebellar ataxia.
- have a history of depression and/or suicide attempts.
- suffer from the disease which affects the skin and/or nervous system called porphyria.
- have recently suffered a death of a near friend or relative.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Clonazepam tablets.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you buy without a prescription, including herbal medicines. This is because Clonazepam tablets affect the way some other medicines work. Also some medicines can affect the way Clonazepam tablets work.

Tell your doctor if you are taking any of the following medicines;

- hydantoins, phenobarbital, sodium valproate or carbamazepine (medicines used to treat epilepsy). The effect of Clonazepam tablets may be increased by these drugs.
- cimetidine (medicine used to treat stomach problems).
- rifampicin (an antibiotic).
- anaesthetics.
- hypnotics (sleep inducing drugs).
- tranquillisers.
- analgesics (drugs that relieve pain).
- baclofen, tizanidine (muscle relaxants).

Taking phenytoin or primidone with Clonazepam tablets may affect the amount of drug in your blood.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Clonazepam tablets.

Taking Clonazepam tablets with food or drink

Clonazepam tablets should be taken with a drink that does not contain alcohol. Do not drink alcohol while you are taking clonazepam tablets as it may cause fits (epileptic seizures) and increase the risk of having side effects.

Pregnancy or breast-feeding

Do not take this medicine if you are pregnant, might become pregnant unless your doctor tells you to. Contact your doctor if you think you may be pregnant, or are intending to become pregnant. If advised to take this medicine during late pregnancy or during labour, your baby might have a low body temperature, floppiness, breathing and feeding difficulties, an irregular heart beat. The baby may have become dependent on clonazepam and could suffer withdrawal symptoms.

Do not take this medicine if you are breast-feeding or planning to breast-feed as clonazepam passes into breast milk.

Driving and using machines:

Clonazepam may affect your ability to drive, operate machinery and carry out other hazardous activities and should therefore be avoided altogether or at least during the first few days of treatment. This may be made worse if you take alcoholic drinks. If you increase your dose or change the timings of when you take your medication this may also modify your reactions.
You must not drink alcohol whilst taking Clonazepam tablets as this may provoke epileptic seizures.

Important information about some of the ingredients of Clonazepam tablets

Clonazepam Tablets contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE CLONAZEPAM TABLETS

Always take Clonazepam tablets exactly as your doctor has told you. You should check with your doctor if you are not sure.

How much to take

The dose your doctor prescribes will depend on your illness. Follow your doctor's instructions carefully.
Clonazepam tablets are taken 3 – 4 times a day. They are started at a low dose and increased over 2-4 weeks until the right dose for you is reached (the maintenance dose). The maximum dose is 20mg in a 24 hour period. The

tablets should be swallowed with water and can be broken in half to give a smaller dose.

Adults

- The starting dose should be no more than 1.0mg in a 24 hour period.
- The maintenance dose is usually a total of 4 to 8mg in a 24 hour period however your doctor may tell you to take more.

Elderly

- The starting dose should be no more than 0.5mg in a 24 hour period, as elderly people are particularly sensitive to the effects of clonazepam and may become confused to begin with.
- The maintenance dose is usually a total of 4 to 8mg in a 24 hour period however your doctor may tell you to take more.

Children and Infants

Infants: The starting dose should be no more than 0.25mg in a 24 hour period (half a 0.5mg Tablet) and the maintenance dose is usually a total of 0.5 – 1mg in a 24 hour period.
Children 1 – 5 years: The starting dose should be no more than 0.25mg in a 24 hour period (half a 0.5mg Tablet) and the maintenance dose is usually a total of 1 – 3mg in a 24 hour period.
Children 5 – 12 years: The starting dose should be no more than 0.5mg in a 24 hour period and the maintenance dose is usually a total of 3 – 6mg in a 24 hour period.

If you take more Clonazepam tablets than you should

It is important to stick to the dose on the label of the medicine. If you or someone else takes too much medicine, contact your doctor or nearest hospital emergency department immediately. Always take any medicine left over with you and also the box, as this will allow easier identification of the medicine.

If you forget to take Clonazepam tablets

If you forget to take a dose, simply take the next dose when it is due. Never take an extra dose to make up for a forgotten dose.

If you stop taking Clonazepam tablets

Keep taking Clonazepam tablets until your doctor tells you to stop. Treatment with clonazepam may last all your life, therefore you must always tell your doctor if you want to stop taking clonazepam, as sudden discontinuation of treatment can cause the reappearance of seizures as well as withdrawal symptoms.
After a period of usage it is advisable to reduce dosage gradually.

Sometimes withdrawal effects occur if the medicine is stopped suddenly and these may include sleep disturbances, muscle pain, extreme anxiety, tension, restlessness, confusion, mood changes, irritability, sweating, tremor, headaches and agitation. In serious cases, withdrawal effects can also include being oversensitive to light, noise and physical contact, hallucinations, tingling and numbness and a feeling of being unreal.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Clonazepam Tablets can cause side effects although not everybody gets them.

Tell your doctor immediately if you experience any of the following as he/she may want you to stop taking this medicine:

- Rarely, changes in behaviour may occur including aggression, excitement, irritability, nervousness, hostility, agitation, anxiety, sleep disturbances, nightmares, vivid dreams, psychotic disorders, severe behavioural disturbances, and new types of seizure may arise.

The following side effects have been reported:

- feeling drowsy or tired, especially at the start of treatment, muscle weakness, dizziness, light-headedness, floppiness of the muscles or bad co-ordination and unsteadiness when walking. In rare cases breathing difficulties may occur. Your doctor can help to avoid most of these effects by adjusting the dose. The effects are temporary and disappear over the course of treatment.
- poor concentration, restlessness, confusion, disorientation and memory loss.
- increased salivation and secretion from the lungs in infants and small children. Children should therefore be watched carefully as this might cause difficulties in breathing and/or severe choking and coughing.
- hives or itching, swelling of the soft tissue, especially around the eyes, lips and hands, hairloss, changes in your colouring (i.e. skin), nausea, headache, loss of sexual desire, impotence, urinary incontinence, early sexual development in children (this is reversible), abdominal problems or allergic reactions including severe hypersensitivity and shock.
- seizures as a result of long-term treatment (only with certain forms of epilepsy), slowing or slurring of speech, reduced co-ordination of movements or changes in vision (e.g. double vision, involuntary jerky movements of the eye).
- Depression, but it may also be associated with the underlying disease.
- Rarely, changes in your blood and liver may occur and your doctor will monitor for these.
- convulsions in patients with a metabolic disorder called porphyria.
- development of physical and psychological dependence may make it difficult to come off or stop treatment if taken for too long.
- increased risk of falls and consequent injury, especially if you are elderly as benzodiazepines have a muscle relaxing effect.

If any of the side effects get serious or lasts longer than a few days, or if you notice other unwanted effects, tell your doctor or pharmacist.

5. HOW TO STORE CLONAZEPAM TABLETS

- Keep out of the reach and sight of children.
- Do not use Clonazepam tablets after the expiry date, which is stated on the end of the carton. The expiry date refers to the last day of the month.
- Do not store above 25°C. Store in the original packaging.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Clonazepam Tablets contains?

The name of this medicine is Clonazepam 0.5mg or 2mg Tablets. The active substance in your tablet is clonazepam. Each Tablet contains 0.5mg or 2mg of clonazepam respectively. Other ingredients include anhydrous lactose, pregelatinized starch, microcrystalline cellulose, magnesium stearate. Clonazepam 0.5mg Tablets also contain ferric oxide yellow (E172) and ferric oxide red (E172).

What Clonazepam looks like and contents of the pack

Clonazepam 0.5mg Tablets are peach coloured flat circular bevelled tablets with cross scoring on one side and plain on the other side. The tablets can be divided in to equal quarters.
Clonazepam 2mg Tablets are white to off white flat circular bevelled tablets with cross scoring on one side and plain on the other side. The tablets can be divided in to equal quarters.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation holder and manufacturer of this medicine is NRIM Limited Marlborough House, 298 Regents Park Road, Finchley, London, N3 2UA, United Kingdom

This leaflet was prepared in 01/2010

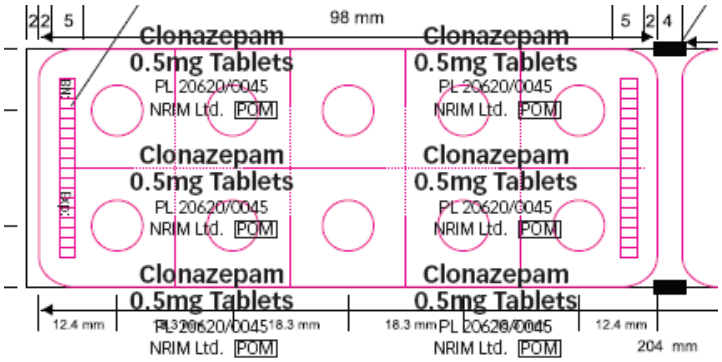
Module 4

Labelling

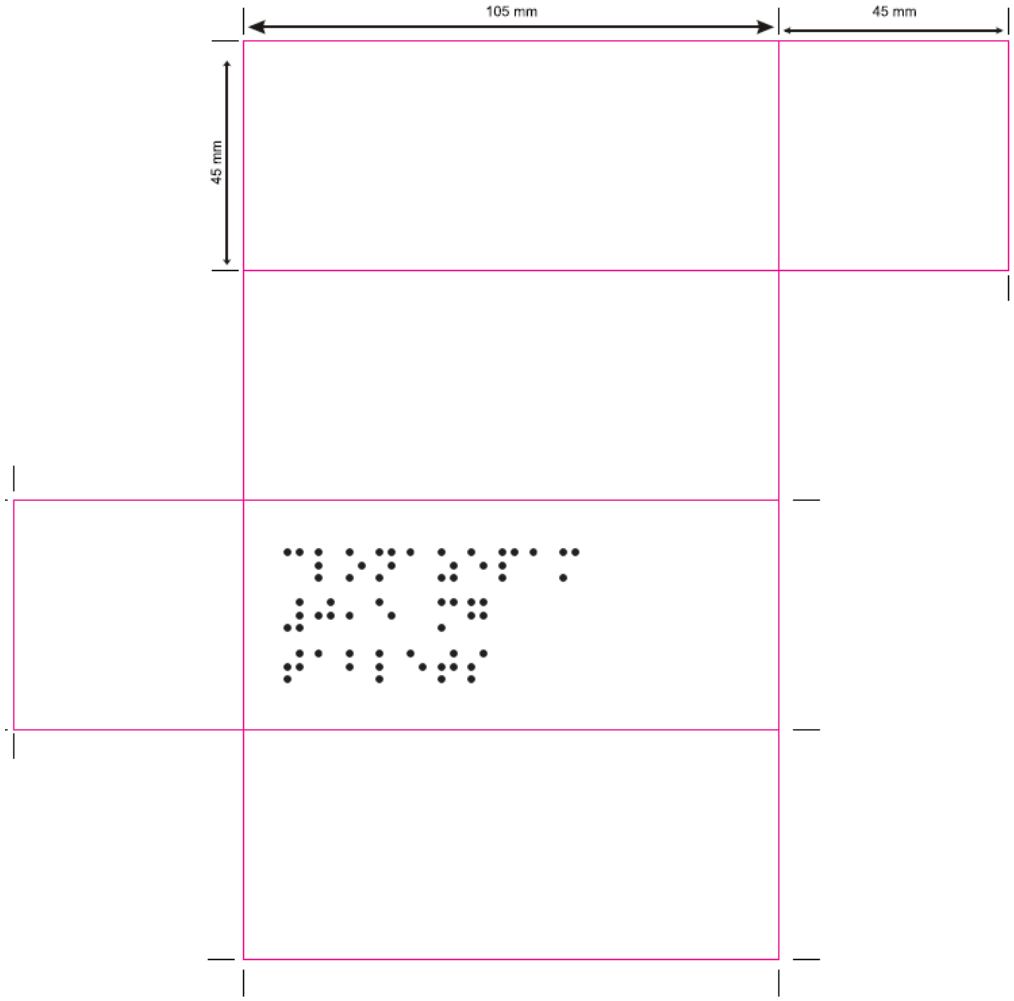
Clonazepam 0.5mg Tablets – PL 20620/0045

Carton

Blister foil



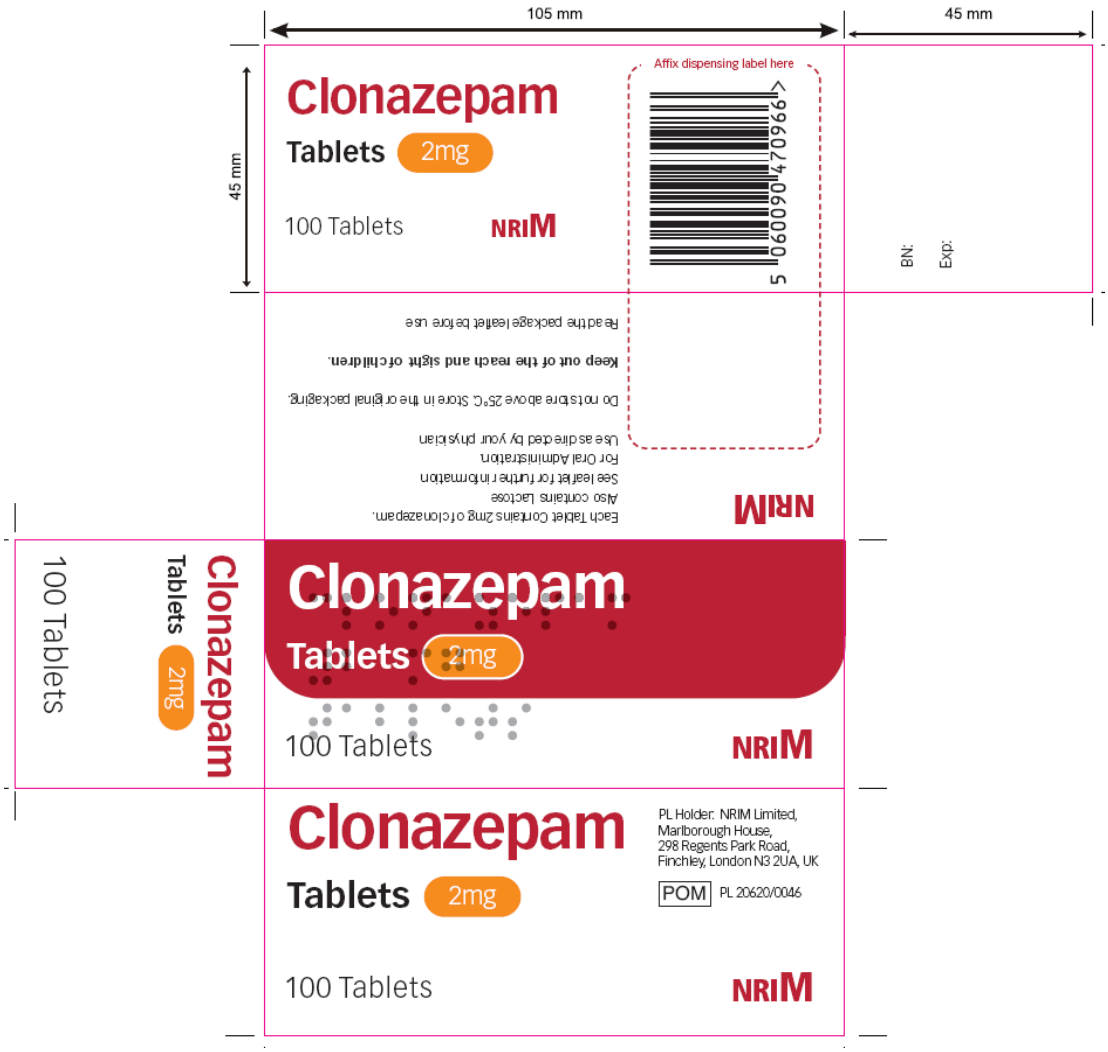
Carton outline showing Braille



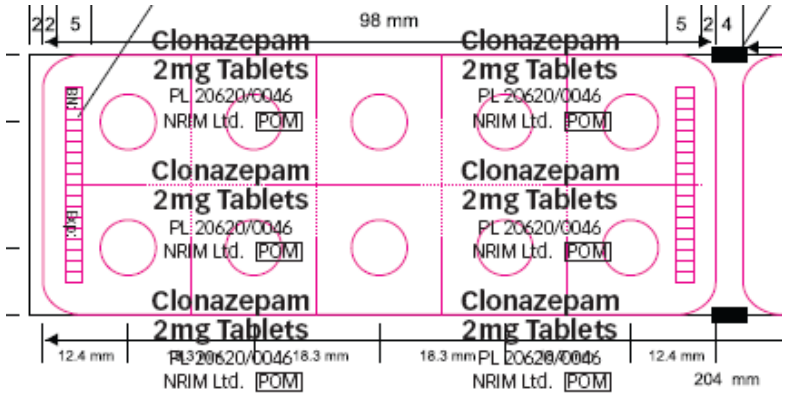
CLONAZEPAM
#0.5 MG
TABLETS

Clonazepam 2mg Tablets – PL 20620/0046

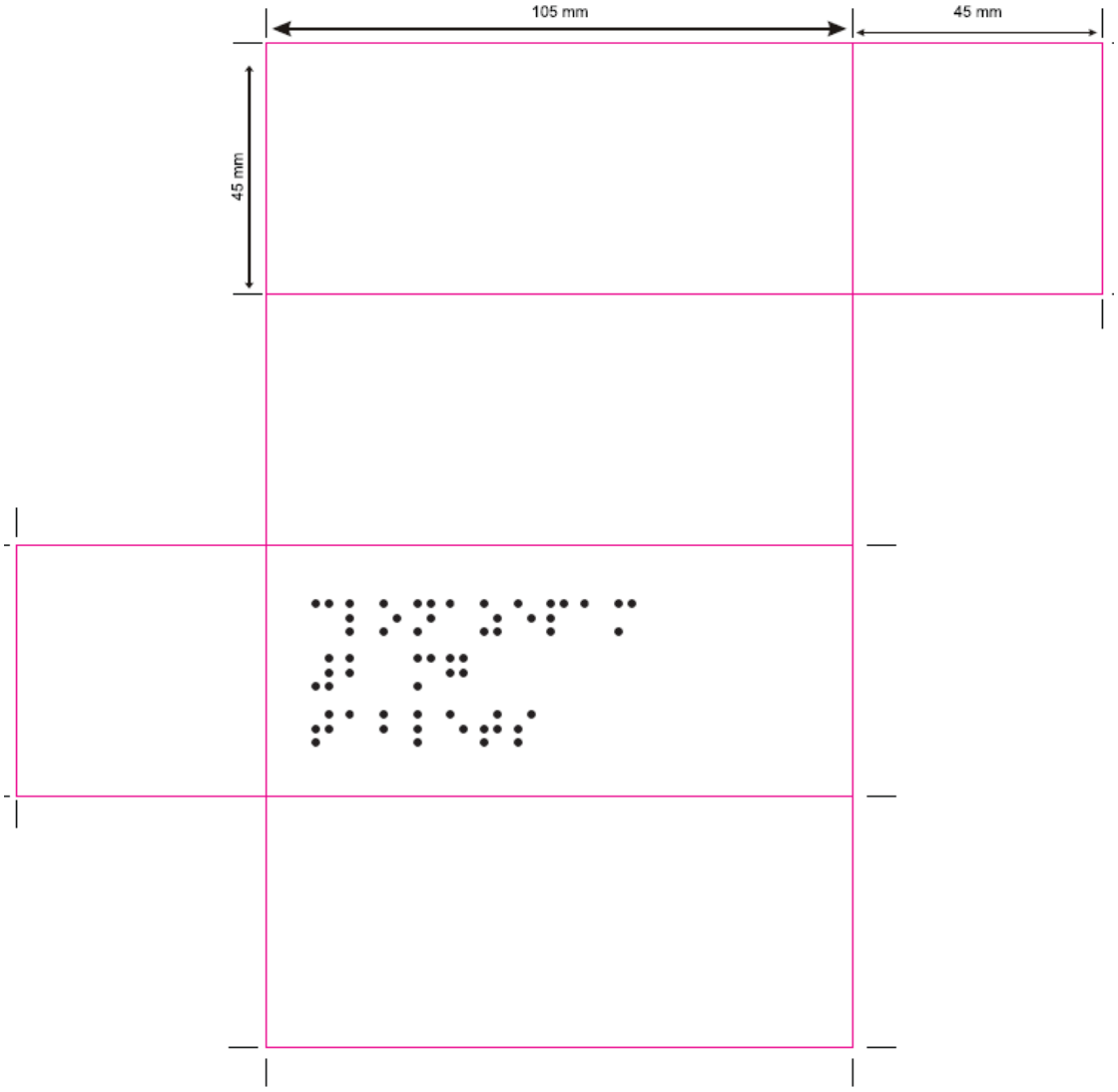
Carton



Blister foil



Carton outline showing Braille



CLONAZEPAM
#2 MG
TABLETS

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted NRIM Limited Marketing Authorisations for the medicinal products Clonazepam 0.5mg and 2mg Tablets (PL 20620/0045-6, UK/H/1890/01-02/DC) on 29th June 2010. The products are prescription-only medicines.

These are abridged applications for Clonazepam 0.5mg and 2mg Tablets, submitted under Article 10.1 of Directive 2001/83 EC, as amended. The applications refer to the UK products, Rivotril 0.5mg and 2mg Tablets respectively (PL 00031/0076R and 0077R), which were authorised to Roche Products Limited on 8th February 1989. The reference products have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired. With the UK as the Reference Member State (RMS) in this Decentralised Procedure, NRIM Limited applied for Marketing Authorisations for Clonazepam 0.5mg and 2mg Tablets in Hungary.

Clonazepam 0.5mg and 2mg Tablets are indicated for all clinical forms of epileptic disease and seizures in infants, children and adults, especially absence seizures (petit mal) including atypical absence; primary or secondarily generalised tonic-clonic (grand mal), tonic or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anti-convulsive, sedative, muscle relaxing and anxiolytic effects. Animal data and electroencephalographic (EEG) 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.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by the single bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Clonazepam 2mg Tablets, to that of the reference product, Rivotril 2mg Tablets (Roche Products Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, issued by the MHRA, as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Clonazepam 0.5mg and 2mg Tablets
Name(s) of the active substance(s) (INN)	Clonazepam
Pharmacotherapeutic classification (ATC code)	Benzodiazepine derivatives (N03A E01)
Pharmaceutical form and strength(s)	Tablets 0.5mg and 2mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1890/01-02/DC
Reference Member State	United Kingdom
Member States concerned	Hungary
Marketing Authorisation Number(s)	PL 20620/0045-6
Name and address of the authorisation holder	NRIM Limited Marlborough House 298, Regents Park Road Finchley N3 2UA London, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

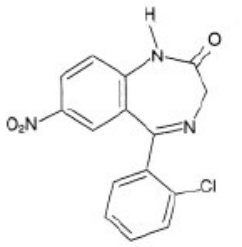
ACTIVE SUBSTANCE

Clonazepam

Nomenclature:

INN:	Clonazepam
Chemical name:	5-(2-Chlorophenyl)-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one

Structure:



Molecular formula:	$C_{15}H_{10}ClN_3O_3$
Molecular weight:	315.7 g/mol
CAS No:	1622-61-3
Physical form:	Slightly yellowish, crystalline powder
Solubility:	Practically insoluble in water, slightly soluble in alcohol and in methanol
Melting point:	About 239°C

The active substance, clonazepam, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of clonazepam are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of clonazepam for inclusion in this medicinal product.

MEDICINAL PRODUCT

Description and Composition

Clonazepam 0.5mg Tablets are presented as peach-coloured, flat, circular, bevelled tablets, cross-scored on one side and plain on the other side, each containing 0.5mg of clonazepam. Clonazepam 2mg Tablets are presented as white to off-white, flat, circular, bevelled tablets, cross-scored on one side and plain on the other side, each containing 2mg of clonazepam.

Other ingredients consist of pharmaceutical excipients, namely anhydrous lactose, pregelatinised starch, microcrystalline cellulose, ferric oxide yellow (E172), ferric oxide red (E172) and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of ferric oxide yellow and red (E172) which comply with the requirements of the US Pharmacopoeia and National Formulary (NF). Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory.

Comparative dissolution and impurity data were provided for both strengths of the test and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. All in-process control limits were met.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for the 0.5mg and 2mg strength finished products. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished products are licensed for marketing in polyvinylchloride (PVC) - polyvinylidene chloride (PVdC) / aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 50, 100 or 150 tablets (0.5mg strength), and 30 or 100 tablets (2mg strength). The MA Holder has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are ‘Do not store above 25°C. Store in the original packaging’.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Clonazepam 2mg Tablets, to the reference product, Rivotril 2mg Tablets (Roche Products Limited).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Quality Overall Summary

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), and labelling are satisfactory. Mock-ups of the labelling and PIL have been provided. The PIL user test report has been evaluated and is satisfactory. The labelling fulfils the statutory requirements for Braille.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Clonazepam 0.5mg and 2mg Tablets from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of clonazepam, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal products, Rivotril 0.5mg and 2mg Tablets (Roche Products Limited).

There are no objections to approval of Clonazepam 0.5mg and 2mg Tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

Clonazepam 0.5mg and 2mg Tablets are indicated for all clinical forms of epileptic disease and seizures in infants, children and adults, especially absence seizures (petit mal) including atypical absence; primary or secondarily generalised tonic-clonic (grand mal), tonic or clonic seizures; partial (focal) seizures with elementary or complex symptomatology; various forms of myoclonic seizures, myoclonus and associated abnormal movements.

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

The toxicology of clonazepam is well known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of clonazepam is well known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics – bioequivalence study

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Clonazepam 2mg Tablets (test) and Rivotril 2mg Tablets - Roche Products Limited (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for the test and reference products.

This was a randomised, open-label, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study conducted in 26 healthy adult human male subjects under fasting conditions. Following an overnight fast of at least 10 hours, a single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 28 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 192.0 hours after administration of test or reference product. Plasma levels of clonazepam were detected by a validated LC/MS/MS analytical method.

The primary pharmacokinetic parameters for this study were C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Results:

26 subjects commenced the study and 21 subjects completed the clinical phase of the study. The omissions of subjects from the analysis were in keeping with the pre-specified protocol criteria.

A total of 34 Adverse Events (AEs) occurred during the study, consisting of: headache, drowsiness, nausea and /or vomiting. Both formulations were well tolerated with no serious AEs reported. No relevant differences in safety profiles were observed between the preparations, particularly with respect to the pattern of AEs.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for clonazepam for a randomised, two-way, single dose crossover study between the test and reference products. n=21 healthy subjects, dosed fasted; t=192 hours. Wash-out period: 28 days.

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC_{0-inf}	678.14	684.17	99.12	94.03	104.48
AUC_{0-t}	626.47	630.78	99.32	93.52	105.48
C_{max}	16.43	15.64	105.04	93.84	117.58

*Geometric mean has been taken as the antilog (exponential) of the least square mean of the log-transformed data.

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

Satisfactory justification is provided for a bio-waiver for Clonazepam 0.5mg Tablets. As Clonazepam 0.5mg and 2mg Tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 2mg strength can be extrapolated to the 0.5mg tablets.

Clinical efficacy

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of clonazepam is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of clonazepam is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those for the reference products, and are acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

Clinical overview

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSIONS

For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal products, Rivotril 0.5mg and 2mg Tablets (Roche Products Limited).

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Clonazepam 0.5mg and 2mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Clonazepam 2mg Tablets, and the reference product, Rivotril 2mg Tablets (Roche Products Limited).

As the proposed products, Clonazepam 0.5mg and 2mg Tablets, meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 2mg strength were extrapolated to the 0.5mg strength tablets.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs are satisfactory and consistent with those for the reference products.

The PIL is in line with the SmPCs and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are marketed.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's products, Clonazepam 0.5mg and 2mg Tablets, and their respective reference products, Rivotril 0.5mg and 2mg Tablets (Roche Products Limited), are interchangeable. Extensive clinical experience with clonazepam is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome