APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

PROPRIETARY NAME (and dosage form):

Clonam 0.5 (Tablets)

Clonam 2 (Tablets)

COMPOSITION:

Each Clonam 0.5 tablet contains 0,5 mg Clonazepam.

Contains lactose.

Excipients: Anhydrous lactose, ferric oxide red (E 172), ferric oxide yellow (E 172), magnesium stearate, microcrystalline cellulose, pregelatinised starch.

Each Clonam 2 tablet contains 2 mg Clonazepam.

Contains lactose.

Excipients: Anhydrous lactose, magnesium stearate, microcrystalline cellulose, pregelatinised starch.

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Anticonvulsants, including anti-epileptics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic Properties:

Clonazepam, a benzodiazepine derivative, exhibits pharmacological properties which include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. These effects are thought to be mediated

mainly by post-synaptic GABA mediated inhibition. Electroencephalographic investigations have shown that clonazepam suppresses the spike and wave discharges in absence seizures (petit mal), slow spike wave, generalised spike waves, spikes with temporal or other locations as well as irregular spikes and waves.

***Pharmacokinetic Properties*:**

Absorption:

Peak plasma concentrations are reached, in most cases, within 1 - 4 hours after an oral dose. Bioavailability is 90 % after oral administration. At a daily dose of 6 mg, divided into 3 doses, steady-state plasma concentrations are 25 - 75 ng/ml. Steady-state plasma concentrations following repeat doses may be four times (following once daily dosing) to eight times (following 3 doses/day) higher than those observed after a single dose.

Distribution:

The mean volume of distribution of clonazepam is estimated at about 3 l/kg. The plasma protein binding of clonazepam is 85 %.

Metabolism:

The biotransformation of clonazepam involves oxidative hydroxylation and reduction of the 7-nitro group, with formation of 7-amino or 7-acetylamino compounds, which may be further conjugated. The main metabolite is 7-amino-clonazepam, which has shown only slight anticonvulsant activity. Four other metabolites present in very small proportions have also been identified. 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. The elimination half-life in neonates is within the range reported for adults.

INDICATIONS:

Epileptic disease

All clinical forms of epileptic disease in children or adults, especially typical or atypical petit mal, focal seizures with elementary or complex symptomatology, generalised primary or secondary tonic-clonic seizures, status epilepticus in all its clinical forms.

Panic disorder

Clonam is indicated for the treatment of Panic Disorder, with or without agoraphobia.

CONTRAINDICATIONS:

- Clonam is contraindicated in patients with known hypersensitivity to clonazepam, other benzodiazepines or to any of the other ingredients of Clonam (see **COMPOSITION**).
- Severe respiratory insufficiency
- Acute pulmonary insufficiency
- Acute narrow angle glaucoma
- Severe hepatic insufficiency
- Myasthenia gravis
- Sleep apnoea

Clonam must not be used in patients in a coma or with spinal or cerebellar ataxia, or in the event of acute intoxication with alcohol, other anti-epileptic medicines, hypnotics, analgesics, neuroleptic agents,

antidepressants or lithium. Clonam must also not be used in patients known to be abusing medicines, other substances, or alcohol.

WARNINGS AND SPECIAL PRECAUTIONS:

Clonam may give rise to salivary or bronchial hypersecretion in small children; supervision is thus required to ensure that the airways remain free of secretions.

Clonam contains lactose and should not be given to patients with rare hereditary problems, or a history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Caution should be exercised in the following patients:

- patients suffering from impairment of renal or hepatic function;
- patients suffering from anxiety accompanied by an underlying depressive disorder;
- patients receiving barbiturates or other central nervous system depressants. There is an additive risk of central nervous system depression when these medicines are taken together;
- patients should be cautioned regarding the additive effect of alcohol.

Tolerance to the anti-epileptic effects of Clonam may develop 1 - 6 months after initiation of therapy and patients may respond to subsequent increases in dose. With certain forms of epilepsy an increase in the frequency of seizures during long term treatments is possible.

There is potential for abuse. Treatment with Clonam can lead to dependence. The risk is greater with higher doses and is particularly pronounced in predisposed patients with a history of alcoholism, substance addiction, personality disorders or other serious psychiatric disease. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (including convulsions). 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.

The following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact or hallucinations. Due to the risk of withdrawal symptoms, Clonam should – even if only of short duration - be terminated by gradually reducing the daily dose.

Depression may occur in patients treated with Clonam.

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

The effect of Clonam on behavioural disturbances in epileptic patients is generally favourable. In certain cases, however, aggressiveness, hyperactivity, anorexia or hyperphagia, irritability, agitation, hostility, anxiety, sleep disturbances, nightmares and vivid dreams may arise during treatment. In patients with a history of aggressiveness, Clonam may aggravate the situation. (See also CONTRAINDICATIONS.)

Paradoxical reactions such as acute hyper-excitability with rage may occur. If these occur, the medicine should be discontinued.

Elderly patients, patients with pre- existing disease of the respiratory system (e.g. chronic obstructive lung disease), liver or kidneys, or who are receiving treatment with other centrally acting medications or anti-convulsant agents, require very careful dosage adjustment.

Since alcohol can provoke epileptic seizures, it is imperative that patients abstain from drinking alcohol while under treatment with Clonam. In combination with Clonam, alcohol may modify the effects of the medicine, compromise the success of therapy, or give rise to unpredictable side-effects.

Clonam can slow reactions to such an extent that the ability to drive a motor vehicle or operate machinery or perform potentially hazardous tasks is seriously impaired. This effect is increased if the

patient has also taken alcohol. Driving, operating machinery and other hazardous activities should therefore be avoided, preferably throughout the duration of treatment or at least during the first few days. The decision should be made in each case on the basis of the patient's response to treatment and the dosage involved.

INTERACTIONS:

Concurrent administration of liver enzyme inducers, such as barbiturates, hydantoins or carbamezapine may accelerate the biotransformation of clonazepam in Clonam without affecting protein binding. By contrast, clonazepam itself seems not to bring about induction of its metabolising enzymes.
In concurrent treatment with phenytoin or primidone, a rise in serum concentration of these two substances has occasionally been observed.

The combination of Clonam with valproic acid may occasionally cause petit mal status epilepticus.

Concurrent use of Clonam and other centrally-acting medications - e.g. other anti-convulsant agents, anaesthetics, hypnotics, psychoactive medicines and some analgesics, and muscle relaxants - can produce mutual potentiation of medicine effects. This is especially true in the presence of alcohol.
Cimetidine reduces clearance of benzodiazepines and potentiates action.
Rifampicin increases clearance of benzodiazepines.
In combination with centrally-acting medications, the dosage of each medicine must be adjusted to achieve the optimum effect.

Epileptic patients must not under any circumstances consume alcohol while being treated with Clonam, since alcohol may alter the effect of clonazepam, reduce the efficacy of treatment, or produce unexpected side-effects.

PREGNANCY AND LACTATION:

Safety in pregnancy has not been established.

Clonam should be used judiciously during pregnancy and preferably avoided. Administration of Clonam in the last trimester of pregnancy or during labour can cause irregularities in the heartbeat of the unborn child. During labour it crosses the placenta and may cause the “floppy-infant” syndrome characterised by central respiratory depression, hypothermia and poor sucking. Clonam must not be used during breastfeeding, since it passes into the breast milk.

DOSAGE AND DIRECTIONS FOR USE:

Dosage of Clonam is essentially individual and depends above all on the age of the patient. It will be determined in each patient according to clinical response and tolerance. In order to avoid initial side effects, it is essential to increase the daily dose progressively until the maintenance dose suited to the individual patient has been reached.

The initial daily dose for children up to the age of 10 years (or up to 30 kg bodyweight):

Initially 0,01 to 0,03 mg/kg, given in two to three divided doses, the dosage being increased by 0,25 to 0,5 mg every third day, until either a maintenance of 0,1 mg per kg of bodyweight per day is reached, or until seizures are controlled or side-effects prevent a further increase. The daily maximum dose in children is 0,2 mg/kg of bodyweight and should not be exceeded.

To obtain optimum adjustment of the dose in children the use of tablets 0,5 mg is recommended.
The single-scored 0,5 mg tablet facilitates administration of low doses in the early phase of treatment.

The following dose can be recommended for children between 10 and 16 years:

The initial dose is 1 – 1,5 mg per day given in 2 – 3 divided doses. The dose may be increased by 0,25 – 0,5 mg every third day, until the individual maintenance dose (usually 3 – 6 mg/day) is reached.

The initial dose for adults:

This should not exceed 1,5 mg/day, divided into 3 doses. The dose may be increased in increments of 0,5 mg every three days, until either seizures are adequately controlled, or undesired effects preclude any further increase. Usually a maintenance dose of 3 - 6 mg per day is sufficient, but, it should be individualized for each patient depending upon response. Maximum recommended daily dose is 20 mg and should not be exceeded.

The daily dose should be divided into 3 equal doses. If doses are not equally divided, the largest dose should he given before retiring. The maintenance dose level is best attained after 2 to 4 weeks of treatment. Once the maintenance dose level has been reached, the daily amount may be given in a single dose in the evening.

Special dosage instructions:

Clonam can be administered concurrently with one or several other anti-epileptic agents, in which case the dosage of each medicine must be adjusted to achieve the optimum effect.

Treatment with Clonam must not be stopped abruptly, but must be reduced in a stepwise fashion (see **SIDE-EFFECTS**).

SIDE-EFFECTS*:*

Immune system disorders:

Less frequent: Allergic reactions, angioedema.

Gastrointestinal disorders:

Less frequent: Nausea, epigastric symptoms, gastrointestinal symptoms (constipation, diarrhoea).

Psychiatric disorders:

Less frequent: Depression, impaired concentration, restlessness, confusional state, disorientation, excitability, irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares, vivid dreams, psychotic disorders, activation of new types of seizures. Paradoxical reactions such as hyper-excitability with rage. (See **WARNINGS AND SPECIAL PRECAUTIONS**.)

Nervous system disorders:

Frequent: Drowsiness, dizziness, ataxia, dysarthria, fatigue, somnolence, and anterograde amnesia, slowed reaction, over-sedation.

Drowsiness is more common in elderly and debilitated patients and those receiving higher doses.

Less frequent: Headaches, generalised fits, amnesia, lethargy.

Cardiac disorders:

Less frequent: Cardiac failure including arrest.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Muscle weakness.

Less frequent: Muscular hypotonia and co-ordination disturbances.

These effects are generally transitory and disappear spontaneously as treatment continues. They tend to occur early in treatment and can to a certain extent be avoided by gradual increase of dosage.

Blood and lymphatic system disorders:

Less frequent: A reduction in blood platelets (thrombocytopenia), blood dyscrasias.

Skin and subcutaneous tissue disorders:

Less frequent: Urticaria, pruritus, skin rash, pharyngeal edema, temporary hair loss and pigmentation changes.

The following side-effect has been reported and frequency is unknown: Anaphylactic shock.

Eye disorders:

Less frequent: Disorders of vision (double vision, nystagmus).

Respiratory, thoracic and mediastinal disorders:

Less frequent: Chest pain, respiratory depression, increased salivation and bronchial secretion in children (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Injury and poisoning:

Less frequent: Falls and fractures in the elderly.

Investigations:

Less frequent: Abnormal liver function tests.

Renal and urinary disorders:

Less frequent: Urinary incontinence.

Reproductive system and breast disorders:

Frequent: Loss of libido and impotence.

Less frequent: Erectile dysfunction.

Endocrine disorders:

The following side-effect has been reported and frequency is unknown: Reversible development of premature secondary sex characteristics in children.

General disorders and administration site conditions:

Frequent: Fatigue (tiredness, lassitude), dependence and withdrawal (see **WARNINGS AND SPECIAL PRECAUTIONS**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Main symptoms of overdosage may include one or more of the following: somnolence and confusion, co-ordination disturbances and muscular hypotonia, diminished reflexes and coma. Paradoxical reactions may occur. Depressive effects on respiration, pulse rate and blood pressure except in cases of extreme overdosage.

Treatment should consist of general symptomatic and supportive measures. These should include early gastric lavage and *IV* fluids.

Maintain adequate airway and administer oxygen if necessary. The respiration rate, pulse rate and blood pressure should also be monitored. Hypotension may be treated with sympathomimetic agents.

Warning: The benzodiazepine antagonist (flumazenil) is not indicated in patients with epilepsy who have been given benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

In small children it is important to monitor the airways due to possible hypersalivation and disturbance of swallowing. Excitation and hyperactivity may appear during the recovery phase.

IDENTIFICATION:

Clonam 0.5 Tablets**:** Peach coloured, flat, circular, bevelled tablets with cross-scored on one side, plain on the other side.

Clonam 2 Tablets: White to off white, flat, circular, bevelled tablets with cross-scored on one side, plain on the other side.

PRESENTATION:

Clonam 0.5 Tablets are available as clear, PVC/PVDC-Aluminium foil blister strips with VMCH heat seal coating containing either 7, 14 or 10 tablets per blister each in a pack size of 84, 90 or 100 tablets packed in an outer carton.

Clonam 2 Tablets are available as clear, PVC/PVDC-Aluminium foil blister strips with VMCH heat seal coating containing either 7, 14 or 10 tablets per blister each in a pack size of 84, 90 or 100 tablets packed in an outer carton.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light.

Do not remove the blister from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

Clonam 0.5: 45/2.5/0820

Clonam 2: 45/2.5/0821

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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