For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ZICAM

1.Generic Name

Clonazepam Dispersible Tablets

2. Qualitative and quantitative composition

ZICAM 0.25

Each uncoated dispersible tablet contains:

Clonazepam I.P..... 0.25 mg

Excipients ……. q. s

Colour: Lake of Tartrazine

The excipients used are Mannitol, Lake of Tartrazine, Crospovidone, Citric acid Monohydrate, Colloidal Silicon dioxide, Aspartame, Banana Flavour, Magnesium Stearate, Acetone.

ZICAM 0.5

Each uncoated dispersible tablet contains:

Clonazepam I.P…. 0.5 mg

Excipients ……. q. s

Colour: Lake of Tartrazine

The excipients used are Mannitol, Lake of Tartrazine, Crospovidone, Citric acid Monohydrate, Colloidal Silicon dioxide, Aspartame, Banana Flavour, Magnesium Stearate, Acetone.

ZICAM 1

Each uncoated dispersible tablet contains:

Clonazepam I.P..... 1mg

Excipients ……. q. s

Colour: Lake of Tartrazine

The excipients used are Mannitol, Lake of Tartrazine, Crospovidone, Citric acid Monohydrate, Colloidal Silicon dioxide, Aspartame, Banana Flavour, Magnesium Stearate, Acetone.

ZICAM 2

Each uncoated dispersible tablet contains:

Clonazepam I.P..... 2mg

Excipients ……. q. s

Colour: Lake of Tartrazine

The excipients used are Mannitol, Lake of Tartrazine, Crospovidone, Citric acid Monohydrate, Colloidal Silicon dioxide, Aspartame, Banana Flavour, Magnesium Stearate, Acetone.

3.Dosage Form and Strength

Dosage Form: Uncoated dispersible tablet

Strength :0.25, 0.5, 1 and 2mg

4. Clinical particulars

4.1 Therapeutic indication

In the treatment of petitmal and its variant, akinetic and myoclonic seizures.

4.2 Posology and method of administration

Posology

Dose: As directed by the Physician

Direction for use: Tablets should be dispersed in water before administration.

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

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

Hepatic Impairment

In patients with mild to moderate hepatic impairment the dose should be adjusted to

individual requirements and will probably be lower.

Method of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipient Acute pulmonary insufficiency; severe respiratory insufficiency, sleep apnoea syndrome, myasthenia gravis, severe hepatic insufficiency. Clonazepam must not be used in patients in a coma, or in patients known to be abusing pharmaceuticals, drugs or alcohol.

4.4 Special warnings and precautions for use

Suicidal behaviour:

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for clonazepam.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should sign of suicidal ideation or behaviour emerge.

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

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

Carefully adjust dosage to individual requirements in patients with pre-existing disease of the liver or the respiratory system (e.g. chronic obstructive pulmonary disease) and in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents Do not interrupt treatment abruptly. As with all other antiepileptic drugs, treatment must be withdrawn gradually, by reducing the dose due to the risk of precipitating status epilepticus. This precaution must also be taken when withdrawing another drug while the patient is still receiving clonazepam therapy. Prolonged use of benzodiazepines may result in dependence with withdrawal symptoms on cessation of use. Use with particular caution in patients with spinal or cerebellar ataxia, in the event of acute intoxication with alcohol or drugs and in patients with severe liver damage (e.g. cirrhosis of the liver). 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, clinically relevant respiratory and/or cardio-vascular depression.

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

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 “Interaction with other medicinal products and other forms of interaction “). Clonazepam may cause increased production of saliva and bronchial secretion in infants and small children. Therefore, special attention must be paid to maintaining patency of the airways.

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-porphyrin genic, although there is some conflicting evidence. In rare cases, clonazepam has induced convulsions in patients with porphyria.

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)

Use in epileptic patients

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

Galactose intolerance

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

Dependence

Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products (see 4.8). In particular, long-term or high-dose treatment, may lead to reversible disorders such as dysarthria, reduced coordination of movements and gait disorder (ataxia), nystagmus and double vision (diplopia). Furthermore, the risk of anterograde amnesia, which may occur using benzodiazepines at therapeutic dosages, increases at higher dosages. Amnestic effects may be associated with inappropriate behaviour. With certain forms of epilepsy, an increase in the frequency of seizures (see 4.8) during long-term treatment is possible. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. During long-term treatment, withdrawal

symptoms may develop after a lengthy period of use, especially with high doses or if the daily dose is reduced rapidly or abruptly discontinued. The symptoms include tremor, sweating, agitation, sleep disturbances and anxiety, headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability and epileptic seizures which may be associated with the underlying disease. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact or hallucinations. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, abrupt withdrawal of the drug should therefore be avoided and treatment - even if only of short duration - should be terminated by gradually reducing the daily dose. The risk of withdrawal symptoms is increased when benzodiazepines are used together with day-time sedatives (crossed tolerance).

4.5 Drugs interactions

Coadministration with alcohol

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

Antiepileptic drugs

When used in conjunction with other antiepileptic drugs, side-effects such as sedation and apathy, and toxicity may be more evident, particularly with hydantoins or phenobarbital and combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment. The combination of clonazepam and sodium valproate has, rarely, been associated

with the development of absence status epilepticus. Although some patients tolerate and benefit from this combination of drugs, this potential hazard should be borne in mind when its use is considered.

The antiepileptic drugs phenytoin, phenobarbital, carbamazepine and valproate may increase the clearance of clonazepam thereby decreasing the plasma concentrations of the latter during combined treatment**.**

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

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

Special Precautions

The plasma concentration of clonazepam is often reduced by carbamazepine, phenobarbital, phenytoin or primidone, and possibly by theophylline. Concurrent treatment with phenytoin or primidone can change the plasma concentration of phenytoin or primidone (usually increases).

There is an increased risk of prolonged sedation and respiratory depression when clonazepam is given with amprenavir. Metabolism of clonazepam is inhibited (i.e. increased plasma concentration) by cimetidine, disulfiram, fluvoxamine and ritonavir. Metabolism of clonazepam may possibly be accelerated by rifampicin.

Clonazepam may possibly antagonise effects of levodopa.

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

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

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

Opioids:

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

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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

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

Clonazepam should not be used during pregnancy unless clearly necessary. Administration of high doses in the last trimester of pregnancy or during labour can cause irregularities in the heart beat of the unborn child and hypothermia, hypotonia, mild respiratory depression and poor sucking in the neonate. Infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the post-natal period. It should be borne in mind that both pregnancy itself and abrupt discontinuation of the medication can cause exacerbation of epilepsy.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

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

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

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory 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

The adverse experiences for ZICAM are provided separately for patients with seizure disorders and with panic disorder.

Seizure Disorders: The most frequently occurring side effects of ZICAM are preferable to CNS depression. Experience in treatment of seizures has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients. Others, listed by system, including those identified during post approval use of ZICAM are:

Cardiovascular: Palpitations

Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema

Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums

Genitourinary: Dysuria, enuresis, nocturia, urinary retention

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia

Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase

Musculoskeletal: Muscle weakness, pains

Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, ‘‘glassy-eyed’’ appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo

Psychiatric: Confusion, depression, amnesia, hysteria, increased libido, insomnia, psychosis (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances).

The following paradoxical reactions have been observed: irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares, abnormal dreams, hallucinations.

Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages

Panic Disorder: Adverse events during exposure to ZICAM were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, CIGY dictionary terminology has been used to classify reported adverse events, except in certain cases in which redundant terms were collapsed into more meaningful terms, as noted below.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials:

Adverse Events Associated with Discontinuation of Treatment:

Overall, the incidence of discontinuation due to adverse events was 17% in ZICAM compared to 9% for placebo in the combined data of two 6-to 9-week trials. The most common events (≥1%) associated with discontinuation and a dropout rate twice or greater for ZICAM than that of placebo included the following:

Table 1 Most Common Adverse Events (≥1%) Associated with Discontinuation of Treatment

Adverse Event	**ZICAM (N=574)**	**Placebo (N=294)**
Somnolence	7%	1%
Depression	4%	1%
Dizziness	1%	<1%
Nervousness	1%	0%
Ataxia	1%	0%
Intellectual Ability Reduced	1%	0%

Adverse Events Occurring at an Incidence of 1% or More among ZICAM -Treated Patients:

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of panic disorder from a pool of two 6to 9-week trials. Events reported in 1% or more of patients treated with ZICAM (doses ranging from 0.5 to 4 mg/day) and for which the incidence was greater than that in placebo-treated patients are included.

The prescriber should be aware that the figures in Table 3 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 2 Treatment-Emergent Adverse Event Incidence in 6-to 9-Week Placebo-Controlled Clinical Trials* Clonazepam Maximum Daily Dose						
Adverse Event by Body System	<1mg n=96 %	**1<2mg n=129 %**	**2<3mg n=113 %**	≥3mg n=235 %	**All ZICAM Groups**	**Placebo N=294 %**

					N=574 %	
Central & Peripheral Nervous System						
Somnolence†	26	35	50	36	37	10
Dizziness	5	5	12	8	8	4
Coordination Abnormal†	1	2	7	9	6	0
Ataxia†	2	1	8	8	5	0
Dysarthria†	0	0	4	3	2	0
Psychiatric						
Depression	7	6	8	8	7	1
Memory Disturbance	2	5	2	5	4	2
Nervousness	1	4	3	4	3	2
Intellectual Ability Reduced	0	2	4	3	2	0
Emotional Lability	0	1	2	2	1	1
Libido Decreased	0	1	3	1	1	0
Confusion	0	2	2	1	1	0
Respiratory System						
Upper Respiratory Tract Infection†	10	10	7	6	8	4
Sinusitis	4	2	8	4	4	3
Rhinitis	3	2	4	2	2	1
Coughing	2	2	4	0	2	0

Clonazepam Maximum Daily Dose

Adverse Event by Body System	**<1mg n=96 %**	**1<2mg n=129 %**	**2<3mg n=113 %**	**≥3mg n=235 %**	**All ZICAM Groups N=574 %**	**Placebo N=294 %**
Pharyngitis Bronchitis	1 1	1 0	3 2	2 2	2 1	1 1
Gastrointestinal System						
Constipation†	0	1	5	3	2	2
Appetite Decreased	1	1	0	3	1	1
Abdominal Pain†	2	2	2	0	1	1
Body as a Whole						
Fatigue	9	6	7	7	7	4
Allergic Reaction	3	1	4	2	2	1
Musculoskeletal						
Myalgia	2	1	4	0	1	1
Resistance Mechanism Disorders						
Influenza	3	2	5	5	4	3
Urinary System Micturition Frequency Urinary Tract Infection†	1 0	2 0	2 2	1 2	1 1	0 0
Vision Disorders						
Blurred Vision	1	2	3	0	1	1
Reproductive Disorders Female						
Dysmenorrhea	0	6	5	2	3	2
Colpitis Male	4	0	2	1	1	1
Ejaculation Delayed	0	0	2	2	1	0
Impotence	3	0	2	1	1	0

***** Events reported by at least 1% of patients treated with ZICAM and for which the incidence was greater than that for placebo.

† Indicates that the p-value for the dose-trend test (Cochran-Mantel-Haenszel) for adverse event incidence was ≤0.10.

‡ Denominators for events in gender-specific systems are: n=240 (clonazepam), 102 (placebo) for male, and 334 (clonazepam), 192 (placebo) for female.

Commonly Observed Adverse Events:

Table 4 Incidence of Most Commonly Observed Adverse Events* in Acute Therapy in Pool of 6-to 9-Week Trials

Adverse Event (N=574)	**Clonazepam (N=294)**	**Placebo**
Somnolence	37%	10%
Depression	7%	1%
Coordination Abnormal	6%	0%
Ataxia	5%	0%

* Treatment-emergent events for which the incidence in the clonazepam patients was ≥5% and at least twice that in the placebo patients.

Treatment-Emergent Depressive Symptoms:

In the pool of two short-term placebo-controlled trials, adverse events classified under the preferred term "depression" were reported in 7% of ZICAM -treated patients compared to 1% of placebo-treated patients, without any clear pattern of dose relatedness. In these same trials, adverse events classified under the preferred term "depression" were reported as leading to discontinuation in 4% of ZICAM -treated patients compared to 1% of placebo-treated patients. While these findings are noteworthy, Hamilton Depression Rating Scale (HAM-D) data collected in these trials revealed a larger decline in HAM-D scores in the clonazepam group than the placebo group suggesting that clonazepam treated patients were not experiencing a worsening or emergence of clinical depression.

Other Adverse Events Observed During the Premarketing Evaluation of ZICAM in Panic Disorder:

Following is a list of modified CIGY terms that reflect treatment-emergent adverse events reported by patients treated with ZICAM at multiple doses during clinical trials. All reported events are included except those already listed in Table 3 or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of

being acutely life-threatening. It is important to emphasize that, although the events occurred during treatment with ZICAM, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency. These adverse events were reported infrequently, which is defined as occurring in 1/100 to 1/1000 patients.

Body as a Whole: weight increase, accident, weight decrease, wound, edema, fever, shivering, abrasions, ankle edema, edema foot, edema periorbital, injury, malaise, pain, cellulitis, inflammation localized

Cardiovascular Disorders: chest pain, hypotension postural

Central and Peripheral Nervous System Disorders: migraine, paresthesia, drunkenness, feeling of enuresis, paresis, tremor, burning skin, falling, head fullness, hoarseness, hyperactivity, hypoesthesia, tongue thick, twitching

Gastrointestinal System Disorders: abdominal discomfort, gastrointestinal inflammation, stomach upset, toothache, flatulence, pyrosis, saliva increased, tooth disorder, bowel movements frequent, pain pelvic, dyspepsia, hemorrhoids

Hearing and Vestibular Disorders: vertigo, otitis, earache, motion sickness

Heart Rate and Rhythm Disorders: palpitation *Metabolic and Nutritional Disorders:* thirst, gout *Musculoskeletal System Disorders:* back pain, fracture traumatic, sprains and strains, pain leg, pain nape, cramps muscle, cramps leg, pain ankle, pain shoulder, tendinitis, arthralgia, hypertonia, lumbago, pain feet, pain jaw, pain knee, swelling knee

Platelet, Bleeding and Clotting Disorders: bleeding dermal

Psychiatric Disorders: insomnia, organic disinhibition, anxiety, depersonalization, dreaming excessive, libido loss, appetite increased, libido increased, reactions decreased, aggression, apathy, disturbance in attention, excitement, anger, hunger abnormal, illusion, nightmares, sleep disorder, suicide ideation, yawning

Reproductive Disorders, Female: breast pain, menstrual irregularity *Reproductive Disorders, Male:* ejaculation decreased *Resistance Mechanism Disorders:* infection mycotic, infection viral, infection

streptococcal, herpes simplex infection, infectious mononucleosis, moniliasis

Respiratory System Disorders: sneezing excessive, asthmatic attack, dyspnea, nosebleed, pneumonia, pleurisy *Skin and Appendages Disorders:* acne flare, alopecia, xeroderma, dermatitis contact,

flushing, pruritus, pustular reaction, skin burns, skin disorder *Special Senses Other, Disorders:* taste loss *Urinary System Disorders:* dysuria, cystitis, polyuria, urinary incontinence, bladder

dysfunction, urinary retention, urinary tract bleeding, urine discoloration *Vascular (Extracardiac) Disorders:* thrombophlebitis leg *Vision Disorders:* eye irritation, visual disturbance, diplopia, eye twitching, styes, visual field defect, xerophthalmia

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Clonazepam is a Schedule IV controlled substance.

Physical and Psychological Dependence: Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (e.g., convulsions, psychosis, hallucinations, behavioral disorder, mood changes, tremor, abdominal and muscle cramps) have occurred following abrupt discontinuance of clonazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed (see DOSAGE AND ADMINISTRATION). Addiction-prone

4.9 Overdose

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability. General supportive measures should be initiated in all cases of overdose.

5. Pharmacological properties

5.1 Mechanism of Action

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

5.2Pharmacodynamicproperties

The precise mechanism by which clonazepam exerts its anti-seizure and anti-panic effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system.

5.3 Pharmacokinetic properties

Clonazepam is rapidly and completely absorbed after oral administration. The absolute bioavailability of clonazepam is about 90%. Maximum plasma concentrations of clonazepam are reached within 1 to 4 hours after oral administration. Clonazepam is approximately 85% bound to plasma proteins. Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group to the 4-amino derivative. This derivative can be acetylated, hydroxylated and glucuronidated. Cytochrome P-450 including CYP3A, may play an important role in clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically 30 to 40 hours. Clonazepam pharmacokinetics are dose-independent throughout the dosing range. There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans.

Pharmacokinetics in Demographic Subpopulations and in Disease States: Controlled studies examining the influence of gender and age on clonazepam pharmacokinetics have not been

conducted, nor have the effects of renal or liver disease on clonazepam pharmacokinetics been studied. Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Thus, caution should be exercised when administering clonazepam to these patients (see CONTRAINDICATIONS).

In children, clearance values of 0.42 ± 0.32 mL/min/kg (ages 2 – 18 years) and 0.88 ± 0.4 mL/min/kg (ages 7 – 12 years) were reported; these values decreased with increasing body weight. Ketogenic diet in children does not affect clonazepam concentrations.

Clinical Trials:

Panic Disorder: The effectiveness of ZICAM in the treatment of panic disorder was demonstrated in two double-blind, placebo-controlled studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IIIR) with or without agoraphobia. In these studies, ZICAM was shown to be significantly more effective than placebo in treating panic disorder on change from baseline in panic attack frequency, the Clinician's Global Impression Severity of Illness Score and the Clinician's Global Impression Improvement Score.

Study 1 was a 9-week, fixed-dose study involving ZICAM doses of 0.5, 1, 2, 3 or 4 mg/day or placebo. This study was conducted in four phases: a 1-week placebo lead-in, a 3-week upward titration, a 6-week fixed dose, and a 7-week discontinuance phase. A significant difference from placebo was observed consistently only for the 1 mg/day group. The difference between the 1 mg dose group and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 74% of patients receiving clonazepam 1 mg/day were free of full panic attacks, compared to 56% of placebo-treated patients.

Study 2 was a 6-week, flexible-dose study involving ZICAM in a dose range of 0.5 to 4 mg/day or placebo. This study was conducted in three phases: a 1-week placebo lead-in, a 6-week optimal-dose, and a 6-week discontinuance phase. The mean clonazepam dose during the optimal dosing period was 2.3 mg/day. The difference between ZICAM and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 62% of patients receiving clonazepam were free of full panic attacks, compared to 37% of placebo-treated patients.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of race or gender.

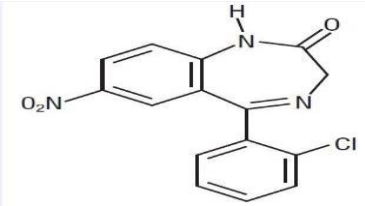
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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.

7. Description

Clonazepam is 5-(2-chlorophenyl)-1, 3-dihydro-7-nitro-2H-1, 4-benzodiazepin-2-one. Its molecular formula is $C_{15}H_{10}ClN_3O_3$ and its molecular weight is 315.7. The structural formula is:



It is slightly yellowish crystalline powder. It is slightly soluble in ethanol (95%), in methanol and practically insoluble in water.

Clonazepam dispersible tablets are yellow coloured, round, flat uncoated tablets with breakline on one side. The excipients used are Mannitol, Lake of Tartrazine, Crospovidone, Citric acid Monohydrate, Colloidal Silicon dioxide, Aspartame, Banana Flavour, Magnesium Stearate, Acetone.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

ZICAM is available in blister strips of 15 tablets.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C, Protected from moisture.

Keep the medicines out of reach of children.

9. Patient Counselling Information

ZICAM

Information for the patient

Clonazepam 0.25, 5.0, 1 and 2 mg Tablets

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

· 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 only. Do not pass it on to others; it may harm them, even if their signs of illness are the same as yours.

· If you get any side effects, talk to your doctor or pharmacist. This includes any possible side

effects not listed in this leaflet.

What is in this leaflet

What is in this leaflet

1. What ZICAM is and what it is used for

The name of your medicine is. Clonazepam belongs to a group of medicines called 'benzodiazepines'. It is used to treat epilepsy. Clonazepam works by preventing seizures or fits.:

2. What you need to know before you take ZICAM

Do not take ZICAM:

• if you are allergic to clonazepam or any of the other ingredients of this medicine (listed in section 6).

• if you are allergic to other benzodiazepine medicines. These include diazepam, chlordiazepoxide, bromazepam and flurazepam.

• if you have lung disease.

• if you have myasthenia gravis (severe muscle weakness)

• if you suffer from sleeping disorders, such as difficulty breathing while asleep (sleep apnoea)

• if you have a severe liver condition

• if you have problems with alcohol or drug (prescription or recreational) use

Warnings and precautions

Talk to your doctor or pharmacist before taking Clonazepam if:

- you have a lung, liver or kidney condition

- you have a history of depression or have attempted suicide

- you have recently suffered a death of a close friend or relative

- you regularly drink alcohol or use recreational drugs

- you have porphyria (a disease that affects the skin and/or nervous system)

- you suffer from cerebellar ataxia (you have a problem co-ordinating movement)

A small number of people being treated with anti-epileptics such as Clonazepam have had thoughts of harming or killing themselves. If at any time you have these thoughts, contact your doctor immediately.

Other medicines and ZICAM

Tell your doctor of pharmacist if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor of pharmacist if you are taking any of the following medicines:

- other medicines to treat epilepsy, such as carbamazepine, hydantoins, phenobarbital, phenytoin, primidone or sodium

valproate

- cimetidine (medicine used to treat stomach problems)

- rifampicin (an antibiotic)

- anaesthetics

- medicines to make you sleep (hypnotics)

- medicines that help with anxiety (tranquillisers)

- pain killers (analgesics) or medicines to relax your muscles (muscle relaxants)

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

Concomitant use of Clonazepam and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.

However, if your doctor does prescribe Clonazepam together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.

Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

Clonazepam with alcohol

Do not drink alcohol whilst taking Clonazepam as it may cause fits (epileptic seizures) and increase the risk of having side effects.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Clonazepam may affect your ability to drive, operate machinery and other hazardous activities, particularly in the first few days of treatment. This may be made worse if you drink alcohol. Increasing the dose of clonazepam or changing the time that you take it may also slow your reactions. You should not drive unless your doctor says you can. The medicine can affect your ability to drive as it may make you sleepy or dizzy.

• Do not drive while taking this medicine until you know how it affects you.

• It is an offence to drive if this medicine affects your ability to drive.

• However, you would not be committing an offence if:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and

o It was not affecting your ability to drive safely.

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine

Dependence

When taking this medicine there is a risk of dependence which increases with the dose and duration of treatment and also in patients with a history of alcohol and/or drug abuse.

3. How to take ZICAM

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

As directed by the Physician**.**

If you take more ZICAM than you should

If you take too many tablets or someone else accidentally takes your medicine, contact you doctor, pharmacist or nearest hospital immediately**.**

If you forget to take ZICAM If you forget to take a dose, simply take the next dose when it is due. Do not take a double dose to make up for a forgotten dose.

If you stop taking ZICAM Do not suddenly stop taking Clonazepam. If you need to stop taking Clonazepam, your doctor will tell you how to stop **slowly** to reduce any side effects as you can get withdrawal symptoms if you stop suddenly. These symptoms may include problems with sleeping, muscle pain, anxiety (sometimes severe), tension, restlessness, confusion, severe mood changes, irritability, sweating, shakes (tremor), headaches and agitation. In serious cases, withdrawal effects can also include being oversensitive to light, noise and touch, hallucinations, tingling, numbness and a feeling of being unreal.

If you think the effect of Clonazepam is too strong or too weak, talk to your doctor. Do NOT change the dose yourself.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you experience any of the following serious side effects – you may need urgent medical treatment:

• Changes in behaviour: aggressiveness, excitability, nervousness, hostility, anxiety, problems sleeping, nightmares, vivid dreams, irritability, agitation, extreme mood changes and new types of seizures may occur.

• Allergic reactions can occur (such as itching, swelling of the tongue, eyes, lips and hands).

The following side effects have been reported:

• Memory loss (amnesia) after a traumatic event which may be linked with some strange behaviour (more likely with higher doses).

• Depression.

• Loss of sex drive, impotence.

• Dependence on clonazepam – this is more of a risk when the dose is high or the treatment is for a long time, and is especially likely to occur in patients with a history of alcoholism or drug abuse.

• Dizziness, light-headedness, sleepiness, tiredness, lack of co-ordination, poor concentration, restlessness, confusion, disorientation, floppiness and weakness of the muscles, headache. Particularly at the start of treatment. The side effects are usually short-lived and may disappear by adjusting the dose.

• Breathlessness, swelling of the ankles, cough, tiredness and a racing heart.

• Chest pain which may spread to your neck and shoulders and down your left arm.

• Feeling unsteady when walking.

• Platelet count bruising easily, being short of breath and nose bleeds.

• Slurring of speech, lack of co-ordination of movement, double vision, rapid eye movements are all reversible effects that may occur particularly if on long-term or high-dose treatment.

• Increase in number of fits (epileptic seizures) may occur during long-term treatment or in patients with a rare condition called porphyria.

• Infants and small children may start to dribble or drool because of increased production of saliva and secretions from the airways. Children should therefore be watched carefully as this might cause problems in breathing and/or severe choking and coughing.

• Rarely, nausea and stomach problems can occur.

• Rarely there may be hives, rashes, short-term hair loss or change in skin colouring.

• Rarely, urinary incontinence (not being able to control when to pass water) may occur. There have been some isolated reports of:

• changes to your blood or liver function (seen in test results).

• early development of puberty in children. This effect is reversible.

Withdrawal symptoms

Stopping Clonazepam suddenly may cause withdrawal symptoms. These include, shakes (tremors), sweating, agitation, problems sleeping, anxiety (sometimes severe), headaches, muscle pain, tension, restlessness, confusion, irritability and fits (epileptic seizures). In severe cases the following effects may happen: a feeling of being unreal, oversensitivity to noise, light and touch, numbness and tingling of the hands and feet or hallucinations. Gradual withdrawal of Clonazepam will help to reduce these effects.

Injury

Patients taking benzodiazepine medicines are at risk of falling and breaking bones. The risk is increased in the elderly and those taking other sedatives (including alcohol).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store ZICAM Store at a temperature not exceeding 30°C, Protected from moisture. Keep all medicines out of reach of children.

6. Contents of the pack and other information

What Clonazepam contains

- The active substance is clonazepam.

- The excipients used are Mannitol, Lake of Tartrazine, Crospovidone, Citric acid Monohydrate, Colloidal Silicon dioxide, Aspartame, Banana Flavour, Magnesium Stearate, Acetone.

10. Details of manufacturer

Manufactured by:

Torrent Pharmaceuticals Ltd

32 No. Middle Camp, NH-10, East District, Gangtok, Sikkim-737 135.

11. Details of permission or licence number with date

Zicam 0.25 – Mfg Licence No. M/563/2010 issued on 17.12.2018

Zicam 0.5 – Mfg Licence No. M/563/2010 issued on 17.12.2018

Zicam 1 – Mfg Licence No. M/563/2010 issued on 17.12.2018

Zicam 2 – Mfg Licence No. M/563/2010 issued on 17.12.2018

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Indrad-382 721, Dist. Mehsana, INDIA.

IN/ ZICAM 0.25,0.5,1 and 2 mg Tablets /JUN-19/01/PI