SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clobazam Wockhardt 2 mg/ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of suspension contains 2 mg of clobazam

Excipient(s) with known effect

Each 1 ml of suspension contains 200 mg of sorbitol, 0.94 mg propylene glycol, 2.1 mg of sodium methyl parahydroxybenzoate and 0.22 mg of sodium propyl parahydroxybenzoate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Suspension

An off white opaque suspension with an odour of raspberry

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clobazam is a 1,5-benzodiazepine indicated in adults for the short-term symptomatic treatment (2-4 weeks) only of anxiety that is severe, disabling or subjecting the individual to unacceptable distress.

In treatment of anxiety states associated with affective disorders, Clobazam must only be used in conjunction with adequate treatments for the underlying disorder.

In patients with schizophrenic or other psychotic illnesses, use of benzodiazepines is recommended only for short term symptomatic management of hyperarousal and agitation. Benzodiazepines do not possess antipsychotic properties.

Clobazam may be used as adjunctive therapy in epilepsy in adults or children over 2 years, if standard treatment with one or more anticonvulsants has failed: Treatment of simple or

complex partial epilepsy with or without secondary generalisation and treatment of all types of generalised epilepsy (tonic/clonic, myoclonic, absence seizures).

4.2 Posology and method of administration

Prior to starting treatment with Clobazam Oral Suspension, a discussion should be held with patients to put in place a strategy for ending treatment with Clobazam Oral Suspension in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

Treatment should be given for the shortest possible duration. If this medicine is being used for the treatment of epilepsy this medicine should be used for as long as the prescriber considers it necessary.

Treatment of anxiety

The usual anxiolytic dose for adults is 20-30 mg daily in divided doses or as a single dose given at night. Doses up to 60mg daily have been used in the treatment of adult in-patients with severe anxiety.

The lowest dose that can control symptoms should be used. After improvement of the symptoms, the dose may be reduced.

It should not be used for longer than 4 weeks. Long term chronic use as an anxiolytic is not recommended. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without re evaluation of the patient's status using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence. Treatment should always be withdrawn gradually. Patients who have taken Clobazam for a long time may require a longer period during which doses are reduced.

Special populations

Elderly:

Doses of 10-20 mg daily in anxiety may be used in the elderly who are more sensitive to the effects of psychoactive agents. Treatment requires low initial doses and gradual dose increments under careful observation.

Hepatic and renal impairment:

Treatment requires low initial doses and gradual dose increments under careful observation, regardless of the age group of the patient.

Treatment of epilepsy in association with one or more other anticonvulsants

Adults:

In epilepsy a starting dose of 5-15 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily.

Special populations

Elderly:

Treatment requires low initial doses and gradual dose increments under careful observation.

Hepatic and renal impairment:

Treatment requires low initial doses and gradual dose increments under careful observation, regardless of the age group of the patient.

Paediatric patients aged 2 years and above:

Clobazam doses should be adapted individually. Doses can be taken once a day or divided in 2 – 3 times a day, keeping the same total dose.

When prescribed for children treatment requires low initial doses and gradual dose increments under careful observation.

Clobazam is typically initiated at a low dose, often 5 mg/day or 0.1 mg/kg/day for younger patients, and increased by step of 0.1 to 0.2 mg/kg/day at 7 days intervals, until a minimum effective dose is reached or side effects occur. Studies have suggested that slow titration may help avoid adverse effects and that when present, side effects may be reduced or eliminated with dose reduction.

The following up-titration regimen has been proposed in the literature in order to take into account the high metabolism variability linked to the P450 system maturation - especially in the presence of inducers and inhibitors - and should be used with increase of the dose by 0.1 to 0.2 mg/kg every week up to the targeted dose.

A maintenance dose of 0.3 to 1mg/kg body weight daily is usually sufficient.

The patient must be re-assessed after a period not exceeding 4 weeks and every 4 weeks thereafter in order to evaluate the need for continued treatment. A break in therapy may be beneficial if drug exhaustion develops, recommencing therapy at a low dose. At the end of treatment (including in poor-responding patients), since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended to gradually decrease the dosage.

The oral suspension is particularly recommended for children and adults with swallowing difficulties, as it allows a secure and precise dosage.

Clobazam should not be used as an anticonvulsivant treatment in children from 6 months to 2 years old, unless under exceptional situations, when there is a clear epilepsy indication. The starting dose in this exceptional circumstances should be the lowest one (0.1 mg/kg/day) and titration should be even more cautious, not more than 0.1 mg/kg/day as in this population the metabolic pathways for clobazam may not be fully mature. Up-to-date, no precise dosage recommendation can be made in this population.

Available products

- Clobazam Wockhardt 1 mg/ml Oral Suspension
- Clobazam Wockhardt 2mg/ml Oral Suspension

If low doses are required, the 1 mg/ml strength product is the most suitable presentation. If high doses are required, the 2 mg/ml strength product is the most suitable presentation. In all cases, treatment should be initiated at the lowest effective dose with gradual dose increments under careful observation. Clobazam Wockhardt 2mg/ml Oral Suspension is recommended for doses over 20mg.

Method of administration

For oral use only.

Shake the bottle thoroughly before use

4.3 Contraindications

Clobazam must not be used:

- In patients with hypersensitivity to benzodiazepines or to any of the excipients listed in section 6.1
- In patients with any history of drug or alcohol dependence (increased risk of development of dependence).
- In patients with myasthenia gravis (risk of aggravation of muscle weakness).
- In patients with severe respiratory insufficiency (risk of deterioration).
- In patients with sleep apnoea syndrome (risk of deterioration).
- In patients with severe hepatic insufficiencies (risk of precipitating encephalopathy).
- During the first trimester of pregnancy (for use during second and third trimester, see section 4.6 Pregnancy and Lactation).
- In breast-feeding women.
- During acute intoxication with alcohol or CNS-active substances

Benzodiazepines must not be given to children without careful assessment of the need for their use.

Clobazam should not be used in children from 6 months to 2 years old, unless under exceptional situations as an anticonvulsant treatment, when there is a clear epilepsy indication.

4.4 Special warnings and precautions for use

Switching between formulations

In some individuals taking Clobazam Oral Suspension, the drug reaches higher plasma levels than the same dose taken as a tablet. This may lead to an increased risk of respiratory depression and sedation which may be most noticeable when switching to this medicine from tablets. Therefore, caution must be taken when switching between clobazam products as the mean Cmax on single dose administration for the suspension is higher than that observed for the tablet formulation.

Children

There is a lack of data regarding the use of the product in patients under 2 years old. For this reason, careful assessment and monitoring is required by the treating physician for use in children under 2 years for anticonvulsant treatment.

Amnesia

Amnesia may occur with benzodiazepines. In case of loss or bereavement psychological adjustment may be inhibited by benzodiazepines.

Muscle weakness

Clobazam can cause muscle weakness. Therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia or sleep apnoea, special observation is required and a dose reduction may be necessary. Clobazam is contraindicated in patients with myasthenia gravis.

Patients with schizophrenic or other psychotic illnesses

Benzodiazepines are not recommended for the primary treatment of patients with schizophrenic or other psychotic illnesses.

Paradoxical reactions

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines (See section 4.8). Should this occur, use of the medicinal product should be discontinued. They are more likely to occur in children and the elderly.

Suicidal Ideation and 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 clobazam. 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.

Depression and personality disorders

Disinhibiting effects may be manifested in various ways. Suicide may be precipitated in patients who are depressed and aggressive behaviour towards self and others may be precipitated. Extreme caution should therefore be used in prescribing benzodiazepines in patients with personality disorders.
Before treatment of anxiety states associated with emotional instability, it must first be determined whether the patient suffers from a depressive disorder requiring adjunctive or different treatment. Indeed, in patients with anxiety associated with depression, Clobazam must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepine (such as Clobazam) alone, can precipitate suicide in such patients.

Driving

Complex behaviours such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in patients taking sedative hypnotics. These events can occur in sedative-hypnotic-naive as well as in sedative-hypnotic experienced persons. Although behaviours such as sleep-driving may occur with a sedative-hypnotic alone at therapeutic doses, the use of alcohol and other central nervous system (CNS) depressants with sedative-hypnotics appears to increase the risk of such behaviours, as does exceeding the maximum recommended dose.

Dependence

Use of benzodiazepines - including clobazam - may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse. Therefore the duration of treatment should be as short as possible (see Posology).

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (or rebound phenomena). Rebound phenomena are characterised by a recurrence in enhanced form of the symptoms wihich originally led to clobazam treatment. This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness.

A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (for example, Clobazam) to one with a short duration of action.

Serious Skin Reaction

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with clobazam in both children and adults during the post-marketing experience. A majority of the reported cases involved the concomitant use of other drugs, including antiepileptic drugs that are associated with serious skin reactions.

SJS/TEN could be associated with a fatal outcome. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment. Clobazam should be immediately discontinued when SJS/TEN is

suspected. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered (see section 4.8).

Respiratory Depression

Respiratory function should be monitored in patients with chronic or acute severe respiratory insufficiency and a dose reduction of clobazam may be necessary. Clobazam is contraindicated in patients with severe respiratory insufficiency (please refer to section 4.3 Contraindications).

Renal and hepatic impairment

In patients with impairment of renal or hepatic function, responsiveness to clobazam and susceptibility to adverse effects are increased, and a dose reduction may be necessary. In long-term treatment renal and hepatic function must be checked regularly.

Elderly patients

In the elderly. due to the increased sensitivity to adverse reactions such as drowsiness, dizziness, muscle weakness, there is an increased risk of fall that may result in serious injury. A dose reduction is recommended.

Tolerance in epilepsy

In the treatment of epilepsy with benzodiazepines -including clobazam -consideration must be given to the possibility of a decrease in anticonvulsant efficacy (development of tolerance) in the course of treatment.

CYP2C19 poor metabolisers

In patients who are CYP2C19 poor metabolisers, levels of the active metabolite N-desmethylclobazam are expected to be increased as compared to extensive metabolisers. As this may lead to increased side effects, dosage adjustment of clobazam may be necessary (e.g. low starting dose with careful dose titration (please refer to section 5.2)).

Alcohol

It is recommended that patients abstain from drinking alcohol during treatment with clobazam (increased risk of sedation and other adverse effects) (please refer to section 4.5).

Risk from concomitant use of opioids*:*

Concomitant use of Clobazam Oral Suspension and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Clobazam Oral Suspension with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Clobazam Oral Suspension concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

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

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with Clobazam Oral Suspension should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Drug withdrawal syndrome

Prior to starting treatment with Clobazam Oral Suspension, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with Clobazam Oral Suspension should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care, and for use in epilepsy).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take

in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.
a slow stepwise rate of reduction proportionate to the existing dose is recommended, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

Excipients in the formulation, this medicinal product contains:

Propylene glycol: 4.7 mg propylene glycol per 5ml dose which is equivalent to 0.94 mg/ml.

Sorbitol: 1000 mg sorbitol per 5 ml dose which is equivalent to 200 mg/ml**;** patients with rare hereditary problems of fructose intolerance should not take this medicine. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

Parahydroxybenzoates and their esters: which may cause allergic reactions, the signs may include a rash, swallowing or breathing problems and swelling of the lips, face, throat or tongue.

Sodium: 5.75 mg sodium per 5 ml, equivalent to 0.29 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. The maximum daily dose of 60 ml contains 69 mg sodium equivalent to 3.45% WHO maximum daily intake sodium for an adult. Doses up to 15 ml per day can be considered essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol

Concomitant consumption of alcohol can increase the bioavailability of clobazam by 50% (please refer to Section 5.2) and therefore increase the effects of clobazam e.g. sedation (please refer to section 4.5).

Opioids:

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

Central nervous system depressant drugs

Especially when clobazam is administered at higher doses, an enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics , hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anticonvulsant drugs, anaesthetics and sedative antihistamines. Special caution is also

necessary when clobazam is administered in cases of intoxication with such substances or with lithium.

Anticonvulsants

Addition of clobazam to established anticonvulsant medication (e.g. phenytoin, valproic acid) may cause a change in plasma levels of these drugs. If used as an adjuvant in epilepsy the dosage of Clobazam should be determined by monitoring the EEG and the plasma levels of the other drugs checked.

Phenytoin and carbamazepine may cause an increase in the metabolic conversion of clobazam to the active metabolite N-desmethylclobazam.

Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels of clobazam and active metabolite is recommended, prior to initiation of stiripentol, and then once new steady-state concentration has been reached, i.e. after 2 weeks approximately.

Clinical monitoring is recommended and dose adjustment may be necessary.

Narcotic analgesics

If clobazam is used concomitantly with narcotic analgesics, possible euphoria may be enhanced; this may lead to increased psychological dependence.

Muscle relaxants

The effects of muscle relaxants, analgesics and nitrious oxide may be enhanced.

Cytochrome P-450 enzyme inhibitors

Concomitant administration of medicinal products that inhibit the Cytochrome P-450 enzyme (monooxygenase) system, such as cimetidine and erythromycin, can enhance and prolong the effects of clobazam.

CYP 2C19 inhibitors

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethylclobazam (N-CLB), the active metabolite of clobazam. Dosage adjustment of clobazam may be necessary when co-administered with strong (e.g. fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors (please refer to Section 5.2).

CYP 2D6 substrates

Clobazam is a weak CYP2D6 inhibitor. Dose adjustment of drugs metabolized by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol) may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of Clobazam in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). As a precautionary measure, Clobazam Oral Suspension should not be used during the first trimester of pregnancy, unless the clinical condition of the woman requires the treatment with clobazam.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become pregnant or suspects that she is pregnant.

Administration of clobazam before or during childbirth can result in the occurrence of respiratory depression (including respiratory distress and apnea), which may be associated with other disorders such as sedation signs, hypothermia, hypotonia, and feeding difficulties in the new born (signs and symptoms of the so-called “floppy infant syndrome").

In the later stages of pregnancy, it must only be used if there are compelling indications.

Moreover, infants born to mothers who have taken benzodiazepines over longer periods during the later stages of pregnancy may have developed physical dependence and may be at risk for developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

Breast-feeding

Since benzodiazepines are found in the breast milk, benzodiazepines must not be given to breast feeding mothers.

Fertility

No clinical data on fertility are available. In a fertility study in male and female rats no effect on fertility was observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Clobazam has major influence on the ability to drive and use machines.

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also section 4.5). Patients should not drive or use machinery until it is verified that the ability to perform these activities is not affected.

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:

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 and in the information provided with the medicine and

o It was not affecting your ability to drive safely.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very common (≥ 1/10);
Common (≥ 1/100, < 1/10);
Uncommon (≥ 1/1,000, < 1/100);
Rare (≥1/10,000, < 1/1,000);
Very rare (<1/10,000);
Not known (cannot be estimated from the available data).

Metabolism and nutrition disorders

Common: decreased appetite

Psychiatric disorders

Common: irritability, aggression, restlessness, depression (pre-existing depression may be unmasked), drug tolerance (especially during prolonged use), agitation

Uncommon: abnormal behaviour, confusional state, anxiety, delusion, nightmare, loss of libido (particularly with high doses or in long-term treatment and is reversible)

Not known: dependence (especially during prolonged use), initial insomnia, anger, hallucination, psychotic disorder, poor quality sleep, suicidal ideation

Drug dependence (see section 4.4)

<u>General disorders and administration site conditions:</u>

Drug withdrawal symptoms (see 4.4 Special warnings and precautions).

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of "rebound" phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.
In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

Nervous system disorders
Very common: somnolence, especially at the beginning of treatment and when higher doses are used
Common: sedation, dizziness, disturbance in attention, slow speech/dysarthria/ speech disorder (particularly with high doses or in long-term treatment, and are reversible), headache, tremor, ataxia

Uncommon: emotional poverty, amnesia (may be associated with abnormal behaviour), memory impairment, anterograde amnesia (in the normal dose range, but especially at higher dose levels)

Not known: cognitive disorder, altered state of consciousness (particularly in elderly patients, may be combined with respiratory disorders), nystagmus (particularly with high doses or in long-term treatment), gait disturbance (particularly with high doses or in long-term treatment and is reversible)

Eye Disorders
Uncommon: diplopia **(**particularly with high doses or in long-term treatment and is reversible)

Respiratory, thoracic and mediastinal disorders
Not known: respiratory depression respiratory failure (particularly in patients with pre-existing compromised respiratory function e.g. in patients with bronchial asthma or brain damage) (see Sections 4.3 Contraindications and 4.4 Warnings and Precautions)

Gastrointestinal disorders
Common: dry mouth, nausea, constipation

Skin and subcutaneous tissue disorders
Uncommon: rash

Not known: photosensitivity reaction; urticaria; Stevens-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome)

Musculoskeletal and connective tissue disorders
Not known: muscle spasms, muscle weakness

General disorders and administration site conditions
Very common: fatigue, especially at the beginning of treatment and when higher doses are used

Not known: slow response to stimuli, hypothermia

Investigations
Uncommon: weight increased (particularly with high doses or in long-term treatment), which is reversible.

Injury poisoning and procedural complications
Uncommon: fall

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

In the management of overdose, it is recommended that the possible involvement of multiple agents be taken into consideration.

Following overdose with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious, or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Secondary elimination of clobazam (by forced diuresis or haemodialysis) is ineffective. Consideration should be given to the use of flumazenil as a benzodiazepine antagonist.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: benzodiazepine derivatives, ATC code: N05BA09

Clobazam is a 1,5-benzodiazepine. In single doses up to 20mg or in divided doses up to 30mg, clobazam does not affect psychomotor function, skilled performance, memory or higher mental functions.

5.2 Pharmacokinetic properties

Absorption

After oral administration, clobazam is rapidly and extensively absorbed.

Time to peak plasma concentrations (Tmax) is achieved from 0.5-4.0 hrs.

The administration of clobazam tablets with food or crushed in applesauce slows the rate of absorption by approximately 1 hour, but it does not affect the overall extent of absorption. Clobazam can be given without regard to meals.

Concomitant intake of alcohol can increase the bioavailability of clobazam by 50%.

Distribution

After a single dose of 20 mg clobazam, marked interindividual variability in maximum plasma concentrations (222 to 709 ng/ml) was observed after 0.25 to 4 hours. Clobazam is lipophilic and distributes rapidly throughout the body. Based on a population pharmacokinetic analysis, the apparent volume of distribution at steady-state was approximately 102 L, and is concentration independent over the therapeutic range. Approximately 80 - 90% of clobazam is bound to plasma protein.

Clobazam accumulates approximately 2-3 fold to steady-state while the active metabolite N-desmethylclobazam (N- CLB) accumulates approximately 20-fold following clobazam twice daily administration. Steady state concentrations are reached within approximately 2 weeks.

Biotransformation

Clobazam is rapidly and extensively metabolized in the liver. Clobazam metabolism occurs primarily by hepatic demethylation to N-desmethylclobazam (N-CLB),

mediated by CYP3A4 and to a lesser extent by CYP2C19. N-CLB is an active metabolite and the main circulating metabolite found in human plasma.

N-CLB undergoes further biotransformation in the liver to form 4-hydroxy-N-desmethylclobazam, primarily mediated by CYP2C19.

CYP2C19 poor metabolizers exhibit a 5-fold higher plasma concentration of N-CLB compared to extensive metabolizers.

Clobazam is a weak CYP2D6 inhibitor. Co-administration with dextromethorphan led to increases of 90% in AUC and 59% in Cmax values for dextromethorphan.

Concomitant administration of 400 mg ketoconazole (CYP3A4 inhibitor) increased Clobazam AUC by 54% with no effect on Cmax. These changes are not considered clinically relevant.

Elimination

Based on a population pharmacokinetic analysis, plasma elimination half-lives of clobazam and N-CLB were estimated to be 36 hours and 79 hours respectively.

Clobazam is cleared mainly by hepatic metabolism with subsequent renal elimination. In a mass balance study, approximately 80% of the administered dose was recovered in urine and about 11% in the faeces. Less than 1 % of unchanged clobazam and less than 10% of unchanged N-CLB are excreted through the kidneys.

Populations at Risk

Elderly

Elderly persons are susceptible to lower clearance after oral administration. The terminal half-life is extended and the volume of distribution is increased. This can cause a greater clobazam accumulation after multiple administration than in younger people. Age also seems to affect the clearance and accumulation of active metabolite for elderly patients.

Hepatic Impairment

In patients with severe liver disease clobazam distribution volume is increased and the terminal half-life is prolonged.

Renal Impairment

In patients with renal impairment, clobazam concentration in plasma decreases probably due to impaired absorption of the drug. The terminal half-life is largely not dependent on renal function.

5.3 Preclinical safety data

Chronic toxicity

In chronic toxicity studies in rats with daily oral clobazam administration of 12-1000 mg/kg, spontaneous activity was dose-dependently reduced, whereas respiratory depression and hypothermia were observed at the high dose level. Dose-dependent sedation, somnolence, ataxia and tremor were initially evident in dogs receiving daily oral doses of 2.5-80 mg/kg clobazam, which almost completely reversed in the course of the study. Similar dose-dependent effects were noted in monkeys after daily oral administration of 2.5-20 mg/kg.

Reproduction toxicity

In fertility studies in mice with daily administration of 200 mg/kg clobazam and in rats receiving daily doses of 85 mg/kg, no impairment of fertility and gravidity was observed.

Oral administration of clobazam to pregnant rats and rabbits throughout the period of organogenesis resulted in increased embryofetal mortality and increased incidences of fetal skeletal variations. In rabbits clobazam also decreased fetal body weights and increased the incidence of fetal malformations (visceral and skeletal). Additionally, oral administration of clobazam to rats throughout pregnancy and lactation resulted in decreased pup survival and alterations in offspring behaviour (locomotor activity). The observed embryo-fetal effects were associated with plasma exposures for clobazam and its major active metabolite N-desmethylclobazam less than those in humans at the maximum recommended dose.

Genotoxicity and carcinogenicity

Clobazam is not genotoxic or tumorigenic. Follicular cell adenoma were significantly increased in rats at the 100 mg/kg clobazam high dose. In contrast to other species (mouse, dog, monkey), clobazam is known to activate the thyroid gland in rats like other benzodiazepine-containing agents. No effects on human thyroid function were noted at clinically relevant doses (20-80 mg).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid sorbitol (non-crystallising) (E420)
Raspberry flavour (contains propylene glycol E1520)
Sodium Propyl parahydroxybenzoate (E217)

Sodium methyl parahydroxybenzoate (E219)
Sucralose
Xanthan gum (E415)
Sodium dihydrogen phosphate dihydrate
Sodium hydroxide *(for pH-adjustment)*
Phosphoric acid *(for pH-adjustment)*
Purified water

6.2 Incompatibilities

None

6.3 Shelf life

3 years

8 weeks after first opening

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Amber soda glass bottles (type III) sealed with tamper evident caps.

The bottle is packed in a cardboard carton containing a 5ml dosing syringe with an adaptor and a 30ml graduated measuring cup along with the patient information leaflet.

Pack sizes: 150 ml and 300 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This product may settle during storage. Please shake the bottle thoroughly before use.

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

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Ltd

Ash Road North

Wrexham, UK

LL13 9UF

8 MARKETING AUTHORISATION NUMBER(S)

PL 29831/0672

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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