Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epaclob 1 mg/ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Epaclob 1 mg/ml:
1 ml of suspension contains 1 mg of Clobazam.

Excipient (s) with known effect:

Each 1 ml of suspension contains 175 mg of sorbitol, 2.06 mg of sodium methyl hydroxybenzoate, 0.224 mg of sodium propyl hydroxybenzoate and 4.825 mg propylene glycol (as part of the raspberry flavouring agent).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.
An off white viscous suspension with an odour of raspberry.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epaclob oral suspension may be used as adjunctive therapy in epilepsy in adults or children over 2years of age, if standard treatment with one or more anticonvulsants has failed.

Epaclob oral suspension should only be used in children from 1 month to 2 years old, under exceptional situations, when there is a clear epilepsy indication.

4.2 Posology and method of administration

Posology

The oral suspension is suitable for any epilepsy patient in whom the clinician feels an oral suspension is preferable to clobazam tablets.

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.

Treatment of epilepsy in association with one or more other anticonvulsants

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

Paediatric population:
When prescribed for children, there may be increased response and increased susceptibility to adverse reactions, therefore, these patients require low initial doses and gradual increments under careful observation.

Paediatric population aged 2-16 years:

Initial: 5 mg/day (***aged 6 years and above***) or 0.1 mg/kg/day for younger patients. The dose may be increased slowly by steps of 0.1 to 0.2 mg/kg/day at 7 days intervals, until the required clinical effect is achieved or side effects occur.

Maintenance dose: usually 0.3 to 1 mg/kg/day. The daily dose can be taken in divided doses or as single dose at night.

Paediatric population aged 1 month-2 years:
Epaclob oral suspension should only be used in children from 1 month to 2 years old, under exceptional situations, when there is a clear epilepsy indication. Use 0.1mg/kg/day and titrate upwards very slowly (increasing not more often than every 5 days) to achieve required clinical effect, in divided doses twice daily.

Elderly:
In elderly patients increased response and increased susceptibility to adverse reactions may occur, so that these patients require low initial doses with gradual increases under careful observation.

Hepatic and renal failure
Treatment requires low initial doses and gradual dose increments under careful observation (please refer to section 4.3 Contraindications and section 4.4 Switching between formulations).

Duration
The patient's condition should be reassessed during the first 4 weeks of treatment. Thereafter, regular reassessment at every 4 weeks will determine the need for continued treatment. If pharmacological tolerance occurs, it may be beneficial to suspend treatment, then to resume at a lower dose. If the dose is divided throughout the day, take the higher dose at night. Doses up to 30 mg Clobazam may also be administered as a single dose at night.

At the end of treatment, it is recommended to gradually reduce the dose to avoid withdrawal or a rebound phenomenon.

Method of administration with or without food

For oral use only.
Once titrated to an effective dose of clobazam, patients should remain on their treatment and care should be exercised when changing between different
Clobazam formulations (see section 4.4– Switching between formulations).

This product may settle during storage. The bottle should be shaken thoroughly before use.

4.3 Contraindications

Epaclob oral suspension must not be used:

- In patients with hypersensitivity to benzodiazepines or any of the excipients of Epaclob oral suspension.
- 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).
- In breast-feeding women.
- Acute intoxication with alcohol and CNS-active substances

Paediatric population:
Benzodiazepines must not be given to children without careful assessment of the need for their use. Epaclob oral suspension should only be used in children from 1 month to 2 years old, under exceptional situations, when there is a clear epilepsy indication.

4.4 Special warnings and precautions for use

Switching between formulations
When taking Epaclob oral suspension, clobazam reaches higher plasma levels than the same dose 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 doses are not equivalent.

As with other anti-epileptic drugs, some patients may experience an increase in seizure frequency or the onset of new types of seizures with clobazam. These phenomena may be the consequence of an overdose, a decrease in plasma concentrations of concomitantly used anti-epileptics, progress of the disease, or a paradoxical effect.

Alcohol
It is recommended that patients refrain from drinking alcohol during treatment with clobazam (increased risk of sedation and other adverse effects) (see section 4.5).

Amnesia
Benzodiazepines can cause anterograde amnesia when used in the normal dose range, but especially at high doses. In case of loss or bereavement psychological adjustment may be inhibited by benzodiazepines.

Muscle weakness
Clobazam can cause muscle weakness. Special caution is necessary if clobazam is used in patients with pre-existing muscle weakness myasthenia gravis, spinal or cerebellar ataxia or sleep apnoea. A dose reduction may be necessary. Clobazam is contraindicated in patients with myasthenia gravis or sleep apnoea syndrome.

Dependence
Use of benzodiazepines - including clobazam - may lead to the development of physical and psychological 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 section 4.2).

Various factors appear to increase the risk of addiction:

- duration of treatment
- dose
- history of other drug dependencies, including alcohol

With cessation of use of benzodiazepines, especially if it is done suddenly, there may be interruption syndrome or withdrawal syndrome:

- Interrupt syndrome associated with original clobazam treatment leading to return of symptoms acutely (e.g. agitation, seizures). This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness.

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 which originally led to clobazam treatment. This may be accompanied by other reactions including headache, sleep disturbances, increased dreaming, extreme anxiety, tension, restlessness, confusion and excitability, derealisation, depersonalisation, hallucinations and symptomatic psychoses (e.g. "withdrawal delirium"), numbness of the limb tingling, muscle pain, tremor, sweating, nausea, hyperacusis, sensitivity to light, noise and physical contact from, as well as epileptic seizures.

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.

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 (please refer to section 4.3 Contraindications).

Elderly

Benzodiazepines should be used with caution in the elderly because the risk of sedation and/or muscle relaxant that can promote the risk of falls, often with serious consequences in this population. A dose reduction is recommended.

Serious skin reactions
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 period. A majority of the reported cases involved the concomitant use of other drugs, including anti-epileptic 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).

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.

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo controlled trials of antiepileptic medicinal products 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.

Psychiatric and 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.
These reactions are more common in children and elderly patients.

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).

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.

Concomitant use of opioids and benzodiazepines
Concomitant use of clobazam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of benzodiazepines such as clobazam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe clobazam 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).

Concomitant use of cannabidiol
The concomitant use of clobazam with cannabidiol-containing medicinal and non-medicinal products may result in increased exposure to N-desmethylclobazam, which may lead to an increased incidence of somnolence and sedation. Dosage adjustment of clobazam may be necessary. Non-medicinal products containing cannabidiol should not be taken in combination with clobazam as they contain unknown quantities of cannabidiol and are of variable quality (see sections 4.5 and 5.2).

Excipientsin the formulation

- Sorbitol: The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Sorbitol may cause gastrointestinal discomfort and mild laxative effect. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.
- Sodium: This medicinal product contains 3.33 mg of sodium per ml oral suspension, equivalent to 10% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

- Propylene Glycol: Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old. While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case-by-case basis. Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attribute to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

- The medicine also contains 2,06 mg sodium methyl hydroxybenzoate and 0,224 mg propyl hydroxybenzoate per ml of oral suspension which can cause allergic reactions (possibly delayed).

- Benzoate: This medicine contains 1.57 mg benzoate in each ml of oral suspension.

4.5 Interaction with other medicinal products and other forms of interaction

Depressant Drugs for Central Nervous System
Especially when clobazam is administered at higher doses, an enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), 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.

Alcohol
Concomitant consumption of alcohol can increase the bioavailability of clobazam by 50 % (see section 5.2) and therefore increase the effects of clobazam (e.g.; sedation) (see section 4.5).. This affects the ability to drive or use machines.

Anticonvulsants
Addition of clobazam to established anticonvulsant medication (eg, phenytoin, valproic acid) may cause a change in plasma levels of these drugs. The dosage of clobazam if used as an adjuvant in epilepsy, 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-desmethyl clobazam.

Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels 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.

Opioids

The concomitant use of benzodiazepines such as clobazam 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).

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

Cytochrome P-450 enzyme inhibitors
Concurrent treatment with drugs that inhibit the cytochrome P-450 enzyme (mono- oxygenase) system (eg cimetidine and the antibiotic erythromycin) may enhance and prolong the effect of clobazam.

CYP2C219 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).

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

Cannabidiol
When cannabidiol and clobazam are co-administered, bi-directional PK interactions occur. Based on a healthy volunteer study, elevated levels (3- to 4-fold) of N-desmethylclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition. Increased systemic levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions. Concomitant use of cannabidiol and clobazam increases the incidence of somnolence and sedation. Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co-administered with cannabidiol.
Metabolism of clobazam is reduced by concomitant use of cimetidine, disulfiram and estrogenes.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited amount of data from the use of clobazam in pregnant women. Nevertheless, a large amount of data collected from cohort studies has not demonstrated evidence of the occurrence of major malformations following exposure to benzodiazepines during the first trimester of pregnancy, although incidences of cleft lip and palate were reported in certain case-control studies.

Clobazam is not recommended during pregnancy and in women of childbearing potential not using contraception.

Clobazam crosses the placenta. Animal studies have demonstrated reproductive toxicity (see section 5.3). Women of childbearing potential should be informed of the risks and benefits of the use of clobazam during pregnancy.

Women of childbearing potential should be informed to contact her physician regarding discontinuation of the product if they are pregnant or intend to become pregnant. If clobazam treatment is continued, it should be used at the lowest effective dose.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy.

If clobazam is administered during the late phase of pregnancy or during childbirth, effects on the neonate, such as respiratory depression (including respiratory distress and apnea), sedation signs, hypothermia, hypotonia, and feeding difficulties in the newborn (so-called "floppy infant syndrome") are to be expected.

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
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 Interactions). It is not advisable to drive or use machinery which requires special attention or concentration, until it is verified that the ability to perform these activities is not affected.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following:
Very common (> 1/10), Common (≥1/100, < 1/10), Uncommon (≥1/1000, < 1/100), Rare (≥1/10,000, < 1/1000), Very Rare (< 1/10,000), not known (cannot be estimated from the available data).

Metabolism and nutrition disorder	
Common	• Decreased appetite
Psychiatric Disorders	
Common	• irritability • aggression • restlessness • depression (pre-existing depression may be unmasked) • drug tolerance[1] • agitation
Uncommon:	• abnormal behaviour • confusional state • anxiety • delusion • nightmare • loss of libido[2,3]
Notknown	• dependence [1] • initial insomnia • anger • hallucinations • psychotic disorder • poor sleep quality • suicidal ideation • discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4 Warnings and Precautions). Abuse of benzodiazepines has been reported.
Nervous system disorders	
Very common	• Somnolence[4]
Common:	• Sedation • dizziness • disturbance in attention • slow speech/dysarthria/speech disorder [2,3] • headache • tremor • ataxia
Uncommon	• emotional poverty

	• amnesia (may be associated with abnormal behaviour), • memory impairment • anterograde amnesia[5]
Not known	• cognitive disorder • altered state of consciousness[6] • nystagmus[2] • gait disturbance [2,3]
Eye disorder	
Uncommon:	• diplopia [2,3]
Respiratory, thoracic and mediastinal disorder	
Not known	• respiratory depression, respiratory failure particularly in patients with pre-existing compromised respiratory function e.g. in patients with bronchial ***asthma or brain injury*** (see section 4.3 and 4.4)
Gastrointestinal disorder	
Common	• dryness of the mouth • constipation • nausea
Skin and subcutaneous tissue disorders	
Uncommon:	rash
Notknown	• photosensitivity reaction • urticaria • Stevens-Johnson syndrome • toxic epidermal necrolysis (including some • cases with fatal outcome)
Musculoskeletal and connective tissue disorders	
Notknown	• muscle spasm • muscle weakness
General disorders and administration site condition	
Very common	• fatigue [4]
Not known:	• slow response to stimuli • hypothermia
Uncommon:	• weight increased [2,3]
Injury, poisoning and procedural complications	
Uncommon	• fall

1. especially during prolonged use (see section 4.4)
2. particularly with high doses or in long-term treatment
3. is reversible
4. especially at the beginning of treatment and when higher doses are used
5. in the normal dose range, but especially at higher dose levels
6. particularly in elderly patients, may be combined with respiratory disorders

As with other benzodiazepines, the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use.

Reportingof suspected adversereactions
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:
HPRA Pharmacovigilance,
Website: www.hpra.ie

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives
ATC code: N05BA

Clobazam is a 1,5-benzodiazepine and the pharmacodynamic activity is qualitatively similar to that of other compounds of this class:
• Muscle relaxant
• Anxiolytic
• Sedative
• Hypnotic
• Anticonvulsant
• Amnesic.
The peak plasma level of clobazam after oral administration of Epaclob oral suspension 2 mg/ml was higher than that observed after administration of a reference 10 mg tablet in a single dose, randomised, crossover bioequivalence study (mean Cmax 267.5 ± 64.5 ng/ml and 220.4 ± 49.9 ng/ml, respectively).

5.2 Pharmacokinetic properties

Absorption
After administration of Epaclob oral suspension, clobazam is rapidly and extensively absorbed. Time to peak plasma concentrations (Tmax) is achieved in an average (median) of 0.67 hours *(*from 0.667h to 1.667h).

Absorption of clobazam is virtually complete after oral administration.

Approximately 85% is protein bound in man. It is metabolised by demethylation and hydroxylation. It is excreted unchanged and as metabolites in the urine (87%) and faeces.

The peak plasma level of clobazam after oral administration of Epaclob oral suspension 2 mg/ml was higher than that observed after administration of a reference 10 mg tablet in a single dose, randomised, crossover bioequivalence study (mean Cmax 267.5 ± 64.5 ng/ml and 220.4 ± 49.9 ng/ml, respectively).

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.

Metabolism
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.

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

Breast feeding
Clobazam crosses the placental barrier and is found in breast milk. Pharmacologically active concentrations may be recovered from both fetal blood and breast milk.

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.

In another fertility study in which clobazam (50, 350, or 750 mg / kg / day) was administered orally to male and female rats before and during mating, and continued in females until gestation day 6, the No-Observed-Adverse-Effect Level was (NOAEL) for fertility and early fetal development in rats 750 mg / kg / day, and was associated with lower plasma exposure (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, than in humans at the maximum recommended human dose of 80 mg / day.

Oral administration of clobazam (10, 30, or 75 mg / kg / day) to pregnant rabbits throughout the organogenesis resulted in decreased fetal weight and increased incidence of fetal malformations (visceral and skeletal) at medium and high doses, and in an increase in embryo -fetal mortality at the high dose. Incidence of fetal variations was increased at all doses. The highest dose tested was associated with severe maternal toxicity (mortality). The NOAEL for embryo-fetal toxicity in rabbits (10 mg / kg / day) was associated with lower plasma exposures to clobazam and N-desmethylclobazam than in humans at the maximum recommended human dose of 80 mg / day.

Genotoxicty 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

Sorbitol (E420) Xanthan Gum (E415)
Acesulfame Potassium (E950)
Raspberry Flavour (containing propylene glycol E 1520)
Sodium Propyl Hydroxybenzoate (E217) Sodium Methyl Hydroxybenzoate (E219)
Disodium Hydrogen Phosphate Dihydrate (for pH-adjustment) Sodium Dihydrogen Phosphate Dihydrate (for pH-adjustment)
Purified Water

6.2 Incompatibilities

None.

6.3 Shelf life

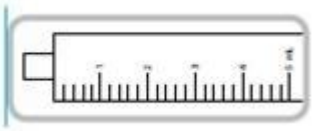
2 years
28 days after first opening.

6.4 Special precautions for storage

Do not store above 25 ºC.

6.5 Nature and contents of container

Amberglass bottles sealed with tamper evident, child-proof plastic screw caps. The bottle is packed in a cardboard carton containing a 5 ml syringe with an adaptor and a 30 ml measuring cup along with the patient information leaflet for both Epaclob
1 mg/ml and 2 mg/ml oral suspension.



5 ml syringe- each numbered increment is 1 ml equivalent to 1 mg of Epaclob 1 mg/ml oral suspension and 2 mg of Epaclob 2 mg/ml oral suspension. The smaller increments are 0.2 ml or 0.2 mg of Epaclob 1 mg/ml oral suspension and 0.4 mg of Epaclob 2 mg/ml oral suspension.

30 ml dosing cup- each numbered increment is 5 ml - equivalent to 5 mg of Epaclob 1 mg/ml oral suspension and 10 mg of Epaclob 2 mg/ml oral suspension.

Packsizes:100 ml,150 ml and 250 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

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

7 MARKETING AUTHORISATION HOLDER

Ethypharm
194 Bureaux de la Colline - Bâtiment D
92213 Saint-Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0549/026/001

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10 DATE OF REVISION OF THE TEXT

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