Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clobazam Thame 10 mg/5 ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral suspension contains 10mg clobazam
Excipient(s) with known effect:
Each 5ml of oral suspension contains 7.5mg of methyl parahydroxybenzoate (E218)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension

White to off-white viscous suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clobazam Thame 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 Thame must be used only 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 Thame may be used as adjunctive therapy in epilepsy, in adults and 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

Treatment of anxiety
Treatment should be as short as possible. The patient must be re-assessed after a period not exceeding 4 weeks and regularly thereafter in order to evaluate the need for continued treatment, especially where the patient is free of symptoms. Generally the overall duration of treatment (i.e. including tapering-off process) must not exceed 8 to 12 weeks.

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.

Adults:
The usual anxiolytic dose for adults is 20-30mg 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.

Due regard must be paid to the possibility of interference with alertness and reaction time.

Long term chronic use as an anxiolytic is not recommended. 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.

Elderly:

Doses of 10-20mg 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.

Treatment of epilepsy in association with one or more other anticonvulsants
Adults:
In epilepsy a starting dose of 5-15mg/day is recommended, with increases of 10mg increments increasing as necessary up to maximum of 60mg daily.

Elderly:
In elderly patients in the management of epilepsy with clobazam increased response and increased susceptibility to adverse reactions may occur. These patients require low initial doses with gradual increases under careful observation.

Paediatric population aged 2 years and above:
Clobazam Thame doses should be adapted individually. Doses can be taken once a day, or as 2 to 3 divided doses, keeping the total daily dose the same.

When prescribed for children, treatment requires low initial doses and gradual dose increments under careful observation. Clobazam is typically initiated at a low dose, Initially in children aged 6 years and above 5 mg/day 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.

Studies have suggested that slow titration may help to avoid adverse effects and that when present side effects may be reduced or eliminated with dose reduction,

The following up-titration 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 dose by 0.1 to 0.2mg/kg every week up to the target dose.

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

Paediatric population aged 1 month -2 years:
There is a lack of data regarding the use of the product in patients under 2 years old Clobazam Thame should not be used as an anticonvulsant treatment in children from 1 months to 2 years old unless under exceptional situations when there is a clear epilepsy indication. The starting dose in this exceptional circumstance should be the lowest one (0.1mg/kg/day) and titration should be more cautious, not more than 0.1mg/kg/day as in this population the metabolic pathways for clobazam may not be fully mature. Up-to-date no precise dosage recommendations can be made for this population.

During adjunctive therapy in epilepsy, in adults and children aged two years and above, 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), it is recommended to gradually decrease the dosage since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment.

Hepatic and renal impairment (all indications):
Increased responsiveness and higher susceptibility to adverse effects may be present in these patients and require low initial doses and gradual dose increments under careful observation. The maximum dose should not be exceeded.

Clobazam Thame Oral Suspension is particularly recommended for children and adults with swallowing difficulties as it allows a secure and precise dosage.

The patient should be checked regularly at the start of the treatment in order to decrease, if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

Method of administration
For oral use only.
Clobazam Thame can be given with or without food.
This product may settle during storage. Shake the bottle well before use.

4.3 Contraindications

Clobazam Thame must not be used:

- In patients with hypersensitivity to clobazam, benzodiazepines or any of the excipients listed in section 6.1.
- 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.

Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam Thame should not be used in children from 1 month to 2 years old unless under exceptional situations as an anticonvulsant treatment where there is a clear epilepsy indication.

4.4 Special warnings and precautions for use

Switching between formulations
In some individuals taking Clobazam Thame, clobazam 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.

Children under 2 years
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
Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also section 4.8).

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.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.2). Extension beyond these periods should not take place without revaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used (for example Clobazam Thame) it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop

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 affective disorders, it must first be determined whether the patient suffers from a depressive disorder requiring adjunctive or different treatment. In patients with anxiety associated with depression, clobazam must be used only in conjunction with adequate treatments for the underlying disorder. Use of benzodiazepine (such as clobazam) alone, can precipitate suicide in such patients.

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

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). They are more likely to occur in children and the elderly. Should this occur, use of the medicinal product should be discontinued.

Suicidal ideation/suicide attempt/ suicide and depression
Some epidemiological studies suggest an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression, and treated with benzodiazepines and other hypnotics, including clobazam. However, a causal relationship has not been established (see section 4.8).

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.

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 section 4.2).

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (or rebound phenomena). These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur; derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

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).

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. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

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
Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

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 and benzodiazepines
Concomitant use of Clobazam Thame 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 Thame with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Clobazam Thame 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 nonmedicinal products may result in increased exposure to N-desmethylclobazam, leading to increased incidence of somnolence and sedation. Dosage adjustment of clobazam may be necessary. Nonmedicinal products containing cannabidiol must not be taken in combination with Clobazam Thame as they contain unknown quantities of cannabidiol and are of variable quality (see Section 4.5 and 5.2)

Excipients warning
This medicinal product contains **methyl parahydroxybenzoate** (E218), which may cause allergic reactions (possibly delayed).
This medicinal product contains less than 1mmol **sodium** (23mg) per 5ml dose, that is to say 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% and therefore increase the effects of clobazam e.g. sedation (please refer to section 4.5). This affects the ability to drive or use machines.

Central nervous system depressant drugs
Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics , hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines. Special caution is also necessary when clobazam is administered in cases of intoxication with such substances or with lithium.

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs 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).

Anticonvulsants
Addition of clobazam to established anticonvulsant medication (eg, phenytoin, valproic acid) may cause a change in plasma levels of these drugs. If used as an adjuvant in epilepsy the dosage of Clobazam Thame 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 which may result in adverse reactions.

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.

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 nitrous oxide may be enhanced.

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).

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.

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.

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

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 of developing a withdrawal syndrome 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 (see section 4.3).

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.

4.8 Undesirable effects

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

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 (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 functione.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: urticaria; Steven-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)

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 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:** 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.

Other special populations
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

A study in which clobazam (150, 450, or 750 mg/kg/day) was orally administered to pregnant rats throughout the period of organogenesis, embryo-fetal mortality and incidences of fetal skeletal variations were increased at all doses. The low effectdose for developmental toxicity in rats (150 mg/kg/day) was associated with plasma exposures (AUC) for clobazam and desmethylclobazam less than those in humans at the maximum recommended human dose of 60 mg/day.

Oral administration of clobazam (10, 30, or 75 mg/kg/day) to pregnant rabbits throughout the period of organogenesis resulted in decreased fetal body weights, and increased incidences of fetal malformations (visceral and skeletal) at the mid and high doses, and an increase in embryo-fetal mortality at the high dose. Incidences of fetal variations were increased at all doses.

The highest dose tested was associated with severe maternal toxicity (mortality). The low effect dose for embryo-fetal toxicity in rabbits (10 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam less than those in humans at the maximum recommended human dose of 60 mg/day.

Additionally, oral administration of clobazam (50, 350, or 750 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased embryo-fetal mortality at the high dose, decreased pup survival at the mid and high doses and alterations in offspring behaviour (locomotor activity) at all doses.

The low effect dose for pre- and postnatal development in rats (50 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam less than those in humans at the maximum recommended human dose of 60 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

methyl parahydroxybenzoate (E218)
citric acid monohydrate (E330)
sodium citrate (E331)
sucralose (E955)
xanthan gum (E415)
purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

Discard 60 days after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Bottle: Amber glass

Closure: HDPE-EPE wadded, tamper evident, child resistant screw on white plastic polypropylene cap.

Dosing Device: A 5ml polypropylene oral syringe with 0.1ml graduation mark and an adaptor for the syringe. Where higher doses are to be administered, dosing cups should be considered.

Pack size: 100ml and 150ml

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

7 MARKETING AUTHORISATION HOLDER

Syri Pharma Limited t/a Thame Laboratories
Floor 0
1 WML
1 Windmill Lane
Dublin 2
D02 F206
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22697/006/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th February 2016
Date of last renewal: 03rd December 2020

10 DATE OF REVISION OF THE TEXT

January 2026