SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clobazam Atnahs 5mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of suspension contains 5mg of clobazam

Excipients with known effect
Each 5 ml of suspension contains 875mg of sorbitol 15.25mg of sodium, 10.25mg of sodium methyl parahydroxybenzoate (E219) and 1.12mg of sodium propyl parahydroxybenzoate (E217).

For the 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

Clobazam is a 1,5-benzodiazepine indicated for the short-term relief (2-4 weeks) only of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short term psychosomatic, organic or psychotic illness. The use of clobazam to treat short-term “mild” anxiety is inappropriate and unsuitable.

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.
In patients with schizophrenic or other psychotic illnesses, use of benzodiazepines is recommended only for adjunctive, i.e. not for primary treatment.

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

Clobazam oral suspension should only be used in children from 6 month to 2 years old, under exceptional situations, where there is a clear epilepsy indication.

4.2 Posology and method of administration

Posology
If low doses are required, the 5 mg/5ml product is a more suitable presentation. If high doses are required, the 10 mg/ 5 ml strength product is a more suitable presentation.

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; if so it should not take place without re-evaluation of the patient's status with special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependance.

Adults:
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.

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. 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.

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.

Treatment of epilepsy in association with one or more other anticonvulsants

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

In all cases, treatment should be initiated at the lowest effective dose with gradual dose increments under careful observation.

Adults
In epilepsy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily.

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

Paediatric patients aged 6 years and above
When prescribed for children treatment requires low initial doses and gradual dose increments under careful observation. It is recommended that normally treatment should be started at 5mg daily. A maintenance dose of 0.3 to 1mg/kg body weight daily is usually sufficient.

Paediatric population aged 2 and above:
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 6 month-2 years:
Clobazam oral suspension should only be used in children from 6 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.

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. 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.

Patients with impairment of renal or hepatic function: 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.

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.
Once titrated to an effective dose of clobazam, patients should remain on their treatment and care should be exercised when changing between different formulations.

4.3 Contraindications

Clobazam must not be used:

- In patients with hypersensitivity to benzodiazepines or any of the excipients of Clobazam Oral Suspension 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.

Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam must not be used in children between the ages of 6 months to 2 years old, other than in exceptional cases for anticonvulsant treatment where there is a compelling indication. As there is no age appropriate formulation to enable safe and accurate dosing, no dosage recommendations can be made in children under 6 years of age (see section 4.2).

4.4 Special warnings and precautions for use

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 Undesirable Effects).

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.

Depression and personality disorders
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).

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 Posology).
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
A lower dose is also recommended for patients with chronic or acute severe respiratory insufficiency due to the risk of respiratory depression (respiratory functions must be monitored 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. 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 in epilepsy
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).

Benzodiazepines including clobazam, should be used with extreme caution in patients with a history of alcohol or drug abuse.

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).

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 cannabidiol

The concomitant use of clobazam with cannabidiol-containing medicinal and non-medicinal products may result in increased exposure to N-desmethylclobazam, leading to increased incidence of somnolence and sedation. Dosage adjustment of clobazam may be necessary. Non-medicinal products containing cannabidiol must 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).

Excipient warnings in the formulation

Clobazam Oral Suspension contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
The medicine also contains sodium methyl and propyl parahydroxybenzoates 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 - contains 3.05 mg/ml. This should be taken into account by patients on a low sodium diet.

Risks from 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 sedative medicines such as benzodiazepines or related drugs 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 environment to be aware of these symptoms (see section 4.5).

Duration of treatment

The duration of treatment should be as short as possible (see Posology). 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 Frisium) it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

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

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Specific patient groups
Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam must not be used in children between the ages of 6 months and 3 years, other than in exceptional cases for anticonvulsants treatment where there is a compelling indication.

The duration of treatment must be kept to a minimum.

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). This affects the ability to drive or use machines.

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 (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.

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).

Anti-convulsants

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-desmethyl clobazam, which may result in adverse reactions.

Stiripentol increases plasma levels of clobazam and its active metabolite Ndesmethylclobazam, 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.

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

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

MAOIs
Concurrent treatment with drugs that inhibit the cytochrome P-450 enzyme (mono-oxygenase) system (e.g. cimetidine) may enhance and prolong the effect of clobazam.

CYP2C19 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.

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 new born in the postnatal period is recommended.

Breast Feeding

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

Fertility

There is insufficient information to assess effects of clobazam on fertility in humans (see section 5.3).

4.7 Effects on 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).

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a

of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10);uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 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**

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 preexisting 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: **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 the Yellow Card Scheme at 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. The risk of a fatal outcome is increased in cases of combined poisoning with other CNS depressants (including alcohol).

In the management of overdose with any medicinal product, 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: Anxiolytics, Benzodiazepine derivates, 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 (T_{max}) is achieved from 0.5 – 4.0 hrs.

The peak plasma level of clobazam after oral administration of Clobazam Oral Suspension 10mg/5ml was similar to that observed after administration of a reference

10 mg tablet in a single dose, randomised, crossover bioequivalence study (mean C_{max} 238.52 ± 59.43 ng/ml and 243.25 ± 54.34 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 inter individual 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 metabolisers exhibit a 5-fold higher plasma concentration of N-CLB compared to extensive metabolisers.

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

Concomitant administration of 400 mg ketoconazole (CYP3A4 inhibitor) increased clobazam AUC by 54% with no effect on C_{max}. 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.

Elderly

Hepatic metabolism decreases and total clearance decreases with increasing concentrations at equilibrium, it is important to reduce the dose.

Hepatic Impairment

There is a decrease in total clearance.

5.3 Preclinical safety data

Repeat dose 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 reproductive toxicity studies in rats and mice clobazam was reported to be without teratogenic or fertility disturbing effect (see section 4.6).

Genotoxicity and carcinogenicity

Clobazam is not genotoxic or tumorigenic. Follicular cell adenoma wasw 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

Sodium Propyl parahydroxybenzoate (E217)

Sodium Methyl parahydroxybenzoate (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

Unopened: 2 years.

Once opened: 28 days

6.4 Special precautions for storage

Do not store above 25°C. Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Amber glass bottles sealed with tamper evident, child resistant plastic screw caps.

Each pack also contains a 5ml oral syringe (polypropylene body, HDPE plunger) graduated every 0.5ml, syringe adapter (LDPE) and 30ml measuring cup (polypropylene) graduated every 5ml.

Pack sizes: 150ml.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Atnahs Pharma UK Limited

Sovereign House

Miles Gray Road

Basildon

Essex

SS14 3FR

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 43252/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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