

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clobazam Essential Pharmaceuticals 1 mg/ml oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of suspension contains 1 mg of clobazam.

Excipients with known effect

Each 1 ml suspension contains 2 mg sodium benzoate (E 211).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension

Colourless, slightly hazy liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clobazam Essential Pharmaceuticals may be used as adjunctive therapy in epilepsy in adults and children from 6 months of age, if standard treatment with one or more anticonvulsants has failed.

4.2 Posology and method of administration

Posology

Treatment of epilepsy in association with one or more other anticonvulsants

Adults

A starting dose of 5–15 mg/day is recommended. If needed, the dose may be gradually increased as necessary up to a maximum of 60 mg daily until the required clinical effect is achieved or side effects occur (see sections 4.4 and 4.8). The dose may be divided in 1–3 doses with the largest dose to be taken in the evening. A single dose up to 30 mg can be taken in the evening.

Paediatric population

When prescribed for children, treatment requires low initial doses and gradual dose increments under careful observation since there may be an increased or paradoxical response to the treatment. Plasma drug concentrations may be measured where there is worsening seizures, status epilepticus, suspected noncompliance or suspected toxicity.

Paediatric population aged 6 months–2 years

Data are limited about the use of Clobazam Essential Pharmaceuticals under 2 years of age and it should only be used under the supervision of a paediatrician with experience in the treatment of severe childhood epileptic syndromes.

Use 0.1 mg/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.

Paediatric population aged 2–5 years

Initial dose: 0.1 mg/kg/day.

Maintenance dose: 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 (see sections 4.4 and 4.8).

Usual maintenance dose: 0.3 to 1 mg/kg/day.

Maximum daily dose is 30 mg per day for children aged 2–5 years.

The daily dose can be taken in divided doses 2–3 times a day or as a single dose at night. The largest dose should be taken at night. Single doses should not exceed 1 mg/kg.

Children aged ≥6 years

Initial dose: 5 mg/day.

Maintenance dose: 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 (see sections 4.4 and 4.8).

Usual maintenance dose: 0.3 to 1 mg/kg/day. The daily dose can be divided in 2–3 doses or as a single dose at night. The largest dose should be taken at night. Single doses should not exceed 1 mg/kg or 30 mg.

Maximum daily dose is 60 mg per day for children aged ≥6 years.

Elderly (aged >65 years)

In elderly patients aged >65 years, increased response and increased susceptibility to adverse reactions may occur, so that these patients require low initial doses with gradual increases under careful observation until the required clinical effect is achieved or side effects occur (see sections 4.4 and 4.8). The daily dose can be taken in divided doses or as single dose at night. The largest dose (which should not exceed 30 mg) should be taken at night.

Hepatic impairment

There is no experience of treatment with clobazam in patients with mild and moderate hepatic impairment. The product should not be used in patients with severe hepatic impairment (see section 4.3).

Treatment of patients with hepatic impairment requires low initial doses and gradual dose increments under careful observation (see sections 4.4 and 4.8). For long-term treatment, hepatic function should be checked regularly.

Renal impairment

Clobazam Essential Pharmaceuticals can be used for patients with mild and moderate renal impairment without any dose adjustment. The product is not recommended to be used for patients with severe renal failure.

Treatment of patients with renal impairment requires low initial doses and gradual dose increments under careful observation (see sections 4.4 and 4.8). For long-term treatment, renal function should be checked regularly.

Duration

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.

Method of administration

For oral use only.

This product may settle during storage.

Shake the bottle well for approximately 15 seconds and turn the bottle upside down. Observe the transparency of the bottom. No precipitation sediment or caked sediment should be visible on the bottom of the bottle.

4.3 Contraindications

Clobazam Essential Pharmaceuticals must not be used:

- In patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- In patients with any history of drug or alcohol dependence (increased risk of development of dependence).
- In patients with myasthenia gravis (risk of aggravation of muscle weakness).
- In patients with severe respiratory insufficiency (risk of deterioration).
- In patients with sleep apnoea syndrome (risk of deterioration).
- In patients with severe hepatic insufficiencies (risk of precipitating encephalopathy).
- In breast-feeding women.
- In patients with acute intoxication with alcohol and CNS-active substances.

4.4 Special warnings and precautions for use

Switching between formulations

When taking Clobazam Essential Pharmaceuticals, clobazam reaches higher peak 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. Moreover, the minimum plasma level at steady state ($C_{min,ss}$) may be lower compared to tablet formulation, which can lead to an increased risk of reduced seizure control. Therefore, caution must be taken when switching between different formulations of clobazam, 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 sections 4.5 and 4.8). Clobazam is contraindicated in patients with acute alcohol-intoxication (see section 4.3).

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, spinal or cerebellar ataxia. A dose reduction may be necessary. Clobazam is contraindicated in patients with myasthenia gravis or sleep apnoea syndrome (see section 4.3).

Dependence

Use of benzodiazepines such as 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 limbs, tingling, muscle pain, tremor, sweating, nausea, hyperacusis, sensitivity to light, noise and physical contact, as well as epileptic seizures.

A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (e.g. 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 (see 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 (see section 4.3). In long-term treatment renal and hepatic function must be checked regularly. Clobazam is contraindicated in patients with severe hepatic insufficiencies (see section 4.3).

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 (see section 4.8), often with serious consequences in this population. In elderly patients >65 years, increased response and increased susceptibility to adverse reactions may occur (see section 4.2).

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 (see section 4.8). 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.

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 randomised 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-desmethyloclobazam were 9-fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19 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 (see section 4.5).

Tolerance in epilepsy

In the treatment of epilepsy with benzodiazepines such as 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 (see section 4.5). 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 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 sections 4.5 and 4.8).

Excipients in the formulation

Clobazam Essential Pharmaceuticals 1 mg/ml oral suspension contains 2 mg sodium benzoate (E 211) per ml. Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old). Increase of bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

Clobazam Essential Pharmaceuticals 1 mg/ml oral suspension contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacodynamic interactions

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.

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.

Pharmacokinetic interactions

Alcohol

Concomitant consumption of alcohol can increase the bioavailability of clobazam by 50% and therefore increase the effects of clobazam (e.g. sedation). This also affects the ability to drive or use machines (see section 4.7).

Anticonvulsants

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

CYP2C19 inhibitors

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethyloclobazam (N-CLB), the active metabolite of clobazam. This may increase the risk of dose-related adverse reactions (see section 4.8). Dosage adjustment of clobazam may be necessary when co-administered with strong (e.g. fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors (see section 5.2).

CYP2D6 substrates

Clobazam is a weak CYP2D6 inhibitor. Clobazam increased AUC and C_{max} of dextromethorphan by 90% and 59%, respectively, reflecting its inhibition of CYP2D6 *in vivo*. Dose adjustment of drugs metabolised by CYP2D6 (e.g. dextromethorphan, pimozide, nebivolol) may be necessary.

CYP3A4 substrates

Clobazam decreased the AUC and C_{max} of midazolam by 27% and 24%, respectively, and increased the AUC and C_{max} of the metabolite 1-hydroxymidazolam by 4-fold and 2-fold, respectively. Dosage adjustment of drugs that are primarily metabolised by CYP3A4 (e.g. midazolam) is generally not necessary when used concomitantly with clobazam.

CYP3A4 inhibitors

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. Dosage adjustment of clobazam is not necessary when administered with CYP3A4 inhibitor (e.g. ketoconazole, see section 5.2).

Cannabidiol

There is a bi-directional pharmacokinetic interaction between cannabidiol and clobazam, which leads to increases in circulating levels of their respective active metabolites, 7-OH-CBD (approximately 1.5-fold) and N-CLB (approximately 3-fold). Therefore, dose adjustments of cannabidiol or clobazam may be required.

Stiripentol

Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethyloclobazam, 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.

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

Hormonal contraceptives

Clobazam is a weak CYP3A4 inducer. As some hormonal contraceptives are metabolised by CYP3A4, their effectiveness may be diminished when given with clobazam. Additional non-hormonal forms of contraception are recommended when using clobazam.

A population pharmacokinetic analysis indicated clobazam did not affect the exposure of valproic acid (a CYP2C9/2C19 substrate) or lamotrigine (a UGT substrate).

4.6 Fertility, pregnancy and lactation

Pregnancy

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 foetal movement and foetal 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 apnoea), 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 post-natal period is recommended.

Breast-feeding

Clobazam is excreted in the breast milk and due to long half-lives of clobazam and its major metabolite desmethyloclobazam, there is a risk of accumulation. Therefore, clobazam must not be given to breast feeding mothers (see section 4.3).

Fertility

No effects on fertility were observed in animals (see section 5.3). No clinical data are available on the effect of clobazam on human fertility.

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. 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

Summary of the safety profile

In clinical studies the overall incidence of adverse reactions was 33%, of which the most common adverse reactions were related to the CNS and include fatigue, somnolence, restlessness, irritability and aggression. Serious adverse reactions to clobazam include respiratory depression, hallucinations, Stevens-Johnson syndrome and toxic epidermal necrolysis. Drug dependence has been reported and discontinuation of the therapy may result in withdrawal or rebound phenomena. The incidence of adverse reactions was lower in patients under 16 years of age (23.7%) than the incidence in adults (43.1%).

Tabulated summary of adverse reactions

The frequencies of adverse events are ranked according to the following:

Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Metabolism and nutrition disorders	
<i>Common</i>	<ul style="list-style-type: none"> decreased appetite
Psychiatric disorders	
<i>Common</i>	<ul style="list-style-type: none"> irritability aggression restlessness depression (including that pre-existing depression may be unmasked) drug tolerance¹ agitation
<i>Uncommon</i>	<ul style="list-style-type: none"> abnormal behaviour confusional state anxiety delusion nightmare

	<ul style="list-style-type: none"> loss of libido^{2,3}
<i>Not known</i>	<ul style="list-style-type: none"> dependence¹ 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)
Nervous system disorders	
<i>Very common</i>	<ul style="list-style-type: none"> somnolence⁴
<i>Common</i>	<ul style="list-style-type: none"> sedation dizziness disturbances in attention slow speech/dysarthria/speech disorder^{2,3} headache tremor ataxia
<i>Uncommon</i>	<ul style="list-style-type: none"> emotional poverty amnesia (may be associated with abnormal behaviour) memory impairment anterograde amnesia⁵
<i>Not known</i>	<ul style="list-style-type: none"> cognitive disorder altered state of consciousness⁶ nystagmus² gait disturbances^{2,3}
Eye disorders	
<i>Uncommon</i>	<ul style="list-style-type: none"> diplopia^{2,3}
Respiratory, thoracic and mediastinal disorders	
<i>Not known</i>	<ul style="list-style-type: none"> respiratory depression, respiratory failure particularly in patients with pre-existing compromised respiratory function e.g. in patients with bronchial asthma or brain injury (see sections 4.3 and 4.4)
Gastrointestinal disorders	
<i>Common</i>	<ul style="list-style-type: none"> dryness of the mouth constipation nausea
Skin and subcutaneous tissue disorders	
<i>Uncommon</i>	<ul style="list-style-type: none"> rash
<i>Not known</i>	<ul style="list-style-type: none"> photosensitivity reaction

	<ul style="list-style-type: none"> • urticaria • Stevens-Johnson syndrome • toxic epidermal necrolysis (including some cases with fatal outcome)
Musculoskeletal and connective tissue disorders	
<i>Rare</i>	<ul style="list-style-type: none"> • muscle weakness
<i>Not known</i>	<ul style="list-style-type: none"> • muscle spasm
General disorders and administration site conditions	
<i>Very common</i>	<ul style="list-style-type: none"> • fatigue⁴
<i>Uncommon</i>	<ul style="list-style-type: none"> • weight increased^{2,3}
<i>Not known</i>	<ul style="list-style-type: none"> • slow response to stimuli • hypothermia
Injury, poisoning and procedural complications	
<i>Uncommon</i>	<ul style="list-style-type: none"> • 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

Description of selected adverse reactions

Skin reactions

Serious skin reactions (some also fatal), such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported with the use of clobazam. Patients should be monitored for the condition during treatment (see section 4.4).

Habituation and dependence during prolonged use

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

In cases of prolonged use, patients may develop tolerance to the drug. Abrupt discontinuation of clobazam therapy may result in withdrawal or rebound phenomena (see section 4.4).

Paradoxical and psychiatric reactions

Paradoxical and psychiatric reactions, such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations and psychoses have been described with the use of clobazam. The reactions are more commonly reported in children (see section 4.4).

Respiratory depression

Clobazam may cause respiratory depression (especially if administered in high doses), particularly in patients with pre-existing compromised respiratory function (e.g. in patients with bronchial asthma or brain damage) (see section 4.4).

Paediatric population

Paradoxical reactions may occur, especially in children and in the elderly. These may include restlessness, difficulty falling asleep or sleeping through, irritability, acute agitational states, anxiety, aggressiveness, delusion, fits of rage, nightmares, hallucinations, psychotic reactions, suicidal tendencies, or frequent muscle spasms. In the event of such reactions, treatment with clobazam must be discontinued.

Other special population(s) including elderly

Clobazam should be used with caution in elderly and debilitated patients, and those with organic brain disorders, with treatment initiated at the lowest possible dose due to the increased susceptibility to the CNS depressant activity of benzodiazepines even after low doses (see section 4.4). In elderly patients aged >65 years, increased susceptibility to adverse reactions may occur, so that these patients require low initial doses (see section 4.2). Paradoxical reactions may occur, especially in the elderly and in children.

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.

Intravenous administration of fluid and generally supportive measures can be used as an adjunct to monitoring vital parameters including consciousness, respiration, heart rate, blood pressure, oxygen saturation and neurological state. Activated charcoal could be given to reduce absorption.

Equipment should be available to treat complications such as airway obstruction or respiratory distress. Hypotension can be treated with plasma substitutes and, if necessary, with sympathomimetics. 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.

5.2 Pharmacokinetic propertiesAbsorption

After administration of Clobazam Essential Pharmaceuticals, clobazam is rapidly and extensively absorbed. Time to peak plasma concentrations (T_{max}) is achieved in an average (median) of 0.67 hours (from 0.667 hours to 1.667 hours).

Absorption of clobazam is virtually complete after oral administration.

Distribution

After a single dose of 20 mg clobazam, marked interindividual variability in maximum plasma concentrations (222–709 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-desmethyclobazam (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 metabolised in the liver. Clobazam metabolism occurs primarily by hepatic demethylation to N-desmethyclobazam (N-CLB), mediated by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. 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-desmethyclobazam, 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}.

Clobazam decreased the AUC and C_{max} of midazolam by 27% and 24%, respectively, and increased the AUC and C_{max} of the metabolite 1-hydroxymidazolam by 4-fold and 2-fold, respectively. This level of induction does not call for dosage adjustment of drugs that are primarily metabolised by CYP3A4 when used concomitantly with clobazam.

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 foetal 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

Rat studies were performed for up to 18 months with daily doses of up to 1,000 mg/kg body weight. In the dose range of 12–1,000 mg/kg body weight, a dose-dependent reduction in spontaneous activity occurred, and in the highest dose group, minor weight-gain as well as respiratory depression and hypothermia were observed.

Studies in dogs were conducted for periods up to 12 months. At a daily dose of 2.5–80 mg/kg body weight, dose-dependent sedation, somnolence, ataxia and mild tremor were initially seen. Later, these symptoms had almost disappeared.

In monkeys, similar dose-dependent reactions were observed in studies of up to 12 months with daily doses of 2.5–20 mg/kg body weight.

Mutagenicity

No genotoxic or mutagenic effects of clobazam have been demonstrated.

Carcinogenicity

In a carcinogenicity study, a significant increase in the incidence of thyroid follicle cell adenoma was observed in rats in the highest dose group (100 mg/kg body weight).

Like other benzodiazepines, clobazam activates the thyroid gland in rats. These changes have not been observed in studies with other species.

Teratogenicity

Studies in mice, rats and thalidomide-sensitive rabbits with daily doses up to 100 mg/kg body weight showed no evidence of teratogenic effects.

In another study, where clobazam (150, 450 or 750 mg/kg/day) was administered orally to pregnant rats throughout the organogenesis, embryo-foetal mortality and the occurrence of foetal skeletal variations were increased at all doses. The low dose effect on developmental toxicity in rats (150 mg/kg/day) was associated with lower plasma exposure (AUC) for clobazam and desmethyloclobazam 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 organogenesis resulted in decreased foetal weight and increased incidence of foetal malformations (visceral and skeletal) at medium and high doses, and in an increase in embryo-foetal mortality at the high dose. Incidence of foetal variations was increased at all doses. The highest dose tested was associated with severe maternal toxicity (mortality). The No-Observed-Adverse-Effect Level (NOAEL) for embryo-foetal toxicity in rabbits (10 mg/kg/day) was associated with lower plasma exposures to clobazam and N-desmethyloclobazam than in humans at the maximum recommended human dose of 80 mg/day.

In addition, oral administration of clobazam (50, 350, or 750 mg/kg/day) to rats throughout the pregnancy and during lactation resulted in increased embryo-foetal mortality at the high dose, decreased survival of the offspring at medium and high doses, as well as changes in the offspring's behaviour (movement activity) at all doses. The low dose effect of pre- and postnatal development in rats (50 mg/kg/day) was associated with lower plasma exposures to clobazam and N-desmethyloclobazam than in humans at the maximum recommended human dose of 80 mg/day.

Fertility

In fertility studies in mice with daily doses of 200 mg/kg body weight and rats with daily doses of 85 mg/kg body weight, no effect on fertility and pregnancy 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 (NOAEL) for fertility and early foetal development in rats was 750 mg/kg/day, and was associated with lower plasma exposure (AUC) of clobazam and its major active metabolite, N-desmethyloclobazam, than in humans at the maximum recommended human dose of 80 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E 422)
Hydroxyethylcellulose
Sodium benzoate (E 211)
Citric acid monohydrate (for pH-adjustment)
Colloidal anhydrous silica
Polysorbate 80
Purified water

6.2 Incompatibilities

None.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

150 ml oral suspension in an amber (type III) glass bottle with child resistant PP/LDPE cap.

The bottle is packed in a cardboard carton containing a 3 ml dosing syringe (PP) with an adaptor and a 30 ml graduated measuring cup (PP) along with the patient information leaflet.

The 3 ml dosing syringe is graduated every 0.1 ml and is to be used in the dosing range of 0.4 ml–5 ml. The 30 ml measuring cup is graduated every 2 ml up to 10 ml and every 2.5 ml up to 30 ml and is to be used in the dosing range of 5 ml–60 ml.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Essential Pharmaceuticals Limited
Vision Exchange Building
Triq It-Territorjals Zone 1
Central Business District
Birkirkara
CBD 1070
Malta

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT