Folding: 38 x 160 mm

320 mm

38 mm

520 mm

CLOCENT 10

Clobazam Tablets BP 10mg

1. NAME OF THE MEDICINAL PRODUCT :
Clocent 10/Clobazam Tablets BP 10 mg

2. Qualitative and quantitative composition
Each tablet contains: Clobazam Ph.Eur. (10 mg)
Excipient with known effect
Each tablet contains 68.900 mg Lactose.
For the full list of excipients, see section 6.1.

3 Pharmaceutical form
Clobazam 10mg, tablets
Description
"White to off white round tablets with break line and debossed with 'C' & '1' on one side and plain on other side."

4. Clinical particulars
4.1 Therapeutic indications
Acute and chronic anxiety states, which may produce the following symptoms in particular: Anxiety, tension, restlessness, excitement, irritability, sleep disturbances from emotional causes, psychovegetative and psychosomatic disorders (for example, in the cardiovascular or gastrointestinal area), and emotional instability. In cases of psychovegetative and psychosomatic disorders, the possibility of an organic cause must be investigated. In patients with depression or anxiety associated with depression, Clocent 10 must only be used inconjunction with adequate concomitant treatment, since the use of benzodiazepines (e.g. Clocent 10) alone can precipitate suicide. 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. In patients with schizophrenic or other psychotic illnesses, use of benzodiazepines isrecommended only for adjunctive, i.e. not for primary, treatment.
As adjunctive therapy in patients with epilepsy not adequately stabilised with their basic medication.

4.2 Posology and method of administration
Dosage
The pharmaceutical form, dose and duration of use must be adapted to the response of the individual, the therapeutic indication and the severity of the disease. It is important to watch for possible impairment of reactions. The principle of keeping the dose as low as possible applies.

Treatment of anxiety:
In general, the starting dose is 20 mg of clobazam per day. The daily dose can be increased to 30 mg of clobazam if required.

Elderly patients
As elderly patients may react more strongly to treatment with Clocent 10 and may be more prone to undesirable effects, it is necessary to start with a low dose and increase it gradually under careful observation (see secction 4.4).
A daily dose of 10-15 mg of clobazam is often sufficient for elderly patients.

Withdrawal of treatment for anxiety:
Once the symptoms have improved, the dose can be reduced. Clocent 10 should not be withdrawn suddenly after prolonged use. The dose should be reduced gradually under medical supervision, otherwise symptoms such as restlessness, anxiety and insomnia may recur.
Combination with an anti-epileptic or several other anti-epileptics for treatment of epilepsy:
In common with other benzodiazepines, the anti-epileptic efficacy of Clocent 10 may decline over the course of the treatment.

Adults
A starting dose of 5-15 mg of clobazam per day is increased gradually to a maximum daily dose of approx. 80 mg of clobazam.
Constant doses (e.g. 20 mg/day) and intermittent treatment (temporarily withdrawing and then represcribing Clocent) have also proved effective.

Children from 6 years of age:
It is recommended that normally treatment be started at 5 mg daily. A maintenance dose of 0.3 to 1.0 mg/kg body weight daily is usually sufficient.
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.

Elderly patients
Higher susceptibility to adverse effects may be present in elderly patients and require low initial dose and gradual dose increments under careful observation (see section 4.4).

Withdrawal of combination treatment for epilepsy:
Even if it has been unsuccessful, the treatment should be withdrawn by reducing the dose gradually, otherwise an increased tendency to seizures cannot be ruled out.

Patients with impaired hepatic and renal function:
As patients with impaired hepatic and renal function may react more strongly to treatment with Clocent 10 and may be more prone to undesirable effects, it is necessary to start with a low dose and increase it gradually under careful observation. In the event of long-term treatment, hepatic and renal function should be monitored as a precaution.

Method of administration
The tablets can be administered whole, or crushed and mixed in apple puree. Clobazam10 mg tablets can be divided into equal doses of 5 mg. Clocent 10 can be given with or without food. If the dose is spread out over the day, the higher portion should be taken in the evening. Doses of up to 30 mg of clobazam may also be prescribed as a single evening dose.
If stress-related sleep disturbances predominate, a single evening dose is recommended.

Duration of administration
In cases involving acute states of tension, agitation and anxiety, the use of Clocent 10 should be confined to single doses or a few days.
In cases involving chronic states of tension, agitation and anxiety, the duration of use depends on the course of the disorder. The doctor should assess the condition of the patient no more than two weeks after the start of treatment and regularly thereafter in order to decide whether the treatment should be continued, especially if the patient is free of symptoms.
In general, the total duration of treatment should not exceed 8-12 weeks (including the period in which the dose is reduced). In certain cases, it may be necessary to extend the maximum treatment period. In such cases, the treatment should not be extended without reassessing the condition of the patient. Continuous long term use should be avoided because it can lead to dependence.
In cases involving combination treatment for epilepsy, the doctor should assess the condition of the patient no more than four weeks after the start of treatment and regularly thereafter in order to decide whether the treatment should be continued.
A break in therapy may be beneficial if drug exhaustion develops, recommencing therapy at a low dose.
At the end of treatment (including 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.

4.3 Contraindications
Clocent 10 must not be used in any of the following circumstances:
- Hypersensitivity to the active substance, other benzodiazipines or any of the excipients,
- Myasthenia gravis,
- Severe respiratory insufficiency
- Sleep apnoea syndrome,
- Severe liver dysfunction
- Acute intoxication with alcohol or other centrally acting substances,
- History of dependence on alcohol, medicinal products or drugs,
- Lactation.

4.4 Special warnings and precautions for use
In patients with schizophrenia or other psychoses, benzodiazepines are recommended only as an additional medicinal product, i.e. not as the primary form of treatment.
In patients with depression or anxiety linked to depression, Clocent 10 may only be used in combination with an appropriate concomitant medicinal product.
Not all states of tension, agitation and anxiety require treatment with a medicinal product. They are often a manifestation of physical or mental illness and can be influenced by other measures or treatment of the underlying disease.
Clocent 10 may only be taken if prescribed by a doctor and under constant medical supervision. It is irresponsible to pass medicinal products prescribed for personal use on to others.

Concomitant use with cannabidiol
The concurrent use of clobazam with medicinal and non-medicinal products containing cannabidiol can increase levels of n–desmethylclobazam, which leads to an increased incidence of drowsiness and sedation. It may be necessary to adjust the dose of clobazam. Non-medicinal products containing cannabidiol must not be used in combination with clobazam since they contain unknown quantities of cannabidiol and differ in terms of quality (see sections 4.5 and 5.2).

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

Amnesia
Anterograde amnesia may occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels.

Dependence
As with other medicinal products containing benzodiazepines, administration should only be continued if absolutely essential and after careful evaluation of the therapeutic benefit against the risk of habituation and dependence.
All benzodiazepines can lead to physical and psychological dependence, the risk of which increases with the dose and duration of treatment.
Even daily administration for a few weeks puts the patient at risk of developing dependence. This applies not only to the misuse of high doses but also to the therapeutic dose range. Patients with a known history of alcohol or medicinal product abuse have a higher risk of developing dependence.

Rebound phenomena/withdrawal symptoms
A rebound phenomenon or withdrawal syndrome can occur, especially if benzodiazepines are withdrawn suddenly. For this reason, the treatment should end with a gradual reduction in the dose.
The reappearance of symptoms that originally led to treatment with Clocent 10 in an intensified form (e.g. states of anxiety, epileptic seizures) is characteristic of a rebound phenomenon. This may be accompanied by reactions such as mood swings, sleep disturbances and restlessness.

Once physical dependence has developed, sudden withdrawal of treatment with Clocent 10 leads to withdrawal symptoms. Such symptoms include headache, muscle pain, sleep disturbances, increased dreaming, anxiety, states of tension, restlessness, confusion and agitation, tremor, sweating, symptomatic psychoses (e.g. withdrawal delirium) and epileptic seizures.
A withdrawal syndrome can also occur if treatment switches suddenly from a long-acting benzodiazepine (e.g. Clocent) to one with a short duration of action.
When Clocent 10 is withdrawn after a prolonged period of use (more than a week), the dose should be reduced gradually. Consideration should be given to the possibility of temporary withdrawal phenomena. Abrupt withdrawal may provoke convulsions, especially if the medicinal product has been used as an anticonvulsant.

Development of tolerance
Patients should be expected to develop tolerance if Clocent 10 is used as an anti-convulsant for several months.

Paradoxical reactions
During the use of benzodiazepines the occurrence of paradoxical reactions such as restlessness, irritability, aggression, delusion, anger, nightmares, hallucinations, psychotic disorders, agitation, sleep disturbances, suicidal ideation, increased muscle spasms and anxiety has been reported. Such reactions are to be especially expected in children and elderly people. If paradoxical reactions occur, treatment with clobazam should be discontinued.

Serious Skin Reactions
Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with Clocent 10 in both children and adults during post-marketing surveillance. A majority of the reported cases involved the concomitant use of other drugs, including antiepileptic drugs, that are associated with serious skin reactions. SJS and 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. In this case clobazam must no longer be used and alternative therapeutic options should be considered.

CYP2C19 poor metabolizers
In patients who are CYP2C19 poor metabolizers, levels of the active metabolite N-desmethylclobazam are expected0 to be increased as compared to extensive metabolizers. Dosage adjustment of clobazam may be necessary (e.g. low starting dose with careful dose titration).

High risk patients
At the start of treatment, the treating doctor should monitor the individual response of the patient to the medicinal product in order to detect any relative overdoses as quickly as possible. This applies particularly to children, elderly patients and patients in poor general condition as well as to patients with organic brain changes, circulatory failure or respiratory failure. Patients should also be told exactly how to behave in everyday life, taking into account their specific situation (e.g. occupation).

Patients with renal and hepatic impairment
In patients with impairment of renal or hepatic function, responsiveness to clobazam (intensified and prolonged effect) and susceptibility to adverse effects might be increased and therefore dose reduction might be necessary. In long-term treatment renal and hepatic function must be checked regularly.

Elderly patients
In elderly patients there might be an increased sensitivity to adverse reactions such as drowsiness, dizziness and muscle weakness.
Therefore, a dose reduction is recommended (see section 4.2 and 4.8). Care should be taken in elderly patients especially when getting up at night due to risk of fall.

Children
Benzodiazepines must not be given to children without careful assessment of the need for their use (see section 4.2).

Respiratory depression
Clobazam can cause respiratory depression, especially if administered in high doses. Therefore, in patients with chronic or acute respiratory sufficiency respiratory function must be monitored and a dose reduction may be necessary. Clobazam is contraindicated in patients with severe respiratory insufficiency (see section 4.3).

Muscle weakness
Clobazam can cause muscle weakness. Therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia, Clocent 10 should only be used with particular caution and if necessary with reduced dose, Clobazam is contraindicated in patients with myasthenia gravis (see section 4.3).

Long-term treatment
As a precaution, hepatic and renal function should be monitored during long-term treatment. Clocent 10 contains lactose. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose-malabsorption should not take this medicine.

This is a medicament
- Medicament is a product which affects your health, and this consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Please note the following information for the patient:
This preparation contains a “benzodiazepine”. Benzodiazepines are medicines for the treatment of, e.g., certain disorders which are associated with restlessness and anxiety states, inner tension or insomnia. When using benzodiazepines, there is a risk of developing or furthering dependence.
To minimise this risk, please follow strictly these instructions:
1 Benzodiazepines have been developed solely for the treatment of a specific group of illnesses, and may only be taken on your doctor's instructions.
2 When these medicines have been taken for a maximum of four weeks, the doctor should decide whether to continue the treatment. An uninterrupted, prolonged period of administration should be avoided, as it may lead to dependence. If you take these drugs without consulting your doctor, you will reduce your chances of benefiting from them.
3 On no account increase the dose prescribed by your doctor, even if the effect has weakened. Treatment will not have the desired effect if you increase the dose on your own.
4 When benzodiazepines are discontinued after prolonged use, restlessness, anxiety states, and insomnia may occur, often after a delay of several days. These withdrawal symptoms usually disappear after 2–3 weeks.
5 Tell your doctor if you have suffered or are still suffering from alcohol or drug dependence. If this is the case, you must not take benzodiazepines, except in rare situations determined only by the doctor.
6 Never take benzodiazepine-containing medicines because “they have been such a help to someone else”, and do not pass these preparations on to others.
7 Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucosegalactose-malabsorption should not take this medicine.

Benzodiazepine
Risks from concomitant use of opioids and benzodiazepines
Concomitant use of benzodiazepines, including clobazam, and opioids may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.
If a decision is made to prescribe clobazam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction
Central nervous system depressant drugs/alcohol
If other medicinal products with a depressant effect on the central nervous system (e.g. neuroleptics, tranquillisers, antidepressants, hypnotics/sedatives, anaesthetics, beta blockers, opiate analgesics, sedative antihistamines, antiepileptics) are taken at the same time as high doses of Clocent 10 in particular, each is likely to intensify the effect of the other. This applies particularly to concomitant alcohol consumption, which can alter or intensify the effects in an unpredictable way. Alcohol can increase the bioavailability of clobazam by 50%, thereby intensifying the effect of Clobazam. For this reason, the patient should refrain from drinking alcohol during treatment with Clobazam.

MAO inhibitors
If medicinal products that inhibit the monooxygenase system, such as cimetidine and erythromycin, are taken concurrently, the effect of Clocent 10 may be intensified and prolonged.

Anticonvulsants
If anti-epileptics are also being taken for seizures, the treatment must be commenced under medical supervision (EEG monitoring), as the medicinal product may interact with the primary anti-epileptic treatment:
Concomitant administration of valproic acid and Clocent 10 may result in a slight to moderate increase in the plasma concentration of valproic acid. Blood levels of phenytoin may rise if patients are treated with Clocent 10 simultaneously. If possible, blood levels of valproic acid and phenytoin should be determined in such cases.
Carbamazepine and phenytoin can lead to an increase in the biotransformation of clobazam into the active metabolite – desmethylclobazam. Stiripentol increases plasma levels of clobazam and its active metabolite N.desmethylclobazam through inhibition of CYP3A4 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/nitrous oxide
By concomitant use of muscle relaxants the muscle relaxing effect may be enhanced, especially in elderly patients and in case of higher dosage (risk of fall!).
The effects of muscle relaxants and nitrous oxide may be enhanced.

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 coadministered with strong (e.g fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors.
CYP2D6 substrates
Clobazam is a weak CYP2D6 inhibitor. Dose adjustment of drugs metabolized by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol) may be necessary.

Benzodiazepine
Opioids
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions). Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Cannabidiol
Concurrent administration of cannabidiol and clobazam produces bidirectional pharmacokinetic interactions. Data from a study ofhealthy volunteer subjects indicates that concurrent use with cannabidiol increases levels (3 to 4 times) of N-desmethylclobazam (an active metabolite of clobazam), probably as a result of CYP2C19 inhibition. Increased systemic levels of these active substances can lead to stronger pharmacological effects and an increase in undesirable drug effects. Concurrent use of cannabidiol and clobazam increases the incidence of drowsiness and sedation. A reduction of the clobazam dose should be considered if drowsiness or sedation occur when clobazam is used concomitantly with cannabidiol.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There is only a limited amount of data from the use of clobazam in pregnant women. Nevertheless, far-reaching experience documented in cohort studies has not yielded evidence of severe fetal malformations with the use of benzodiazepines in the first trimester of pregnancy, although some specific case control studies revealed cases of cleft lip and cleft palate.
Clobazam is not recommended during pregnancy or 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 about the benefits and risks of using clobazam during pregnancy and should be instructed to contact their doctor about discontinuing clobazam if they become pregnant or plan to become be pregnant. If treatment with clobazam is continued, the lowest effective dose should be used.
Cases of reduced fetal movement and variability in fetal heart rate have been described with the use of benzodiazepines during the second and third trimesters of pregnancy.If clobazam is administered during the later stages of pregnancy or during childbirth, effects may occur in the newborn, such as respiratory depression (including respiratory distress and apnoea), signs of sedation, hypothermia, hypotonia and feeding difficulties (floppy infant syndrome). Additionally, the children of mothers who used benzodiazepines long-term in the later stages of pregnancy may develop a physical dependency, thus creating a risk of withdrawal symptoms after birth. Appropriate monitoring of the newborn in the postnatal period is recommended.

Lactation:
Lactation Clocent 10 must not be taken during lactation because the active substance clobazam passes into breast milk. If treatment is absolutely essential, the infant should be weaned.

Fertility:
No disturbance of fertility was observed in fertility studies in animals (see section 5.3). However, exposure in animals was less than after the maximum recommended therapeutic dose.

4.7 Effects on ability to drive and use machines*:*
Even if used as instructed, this medicinal product may affect reactions to such an extent that the ability to drive or use machines is impaired. This applies particularly in combination with alcohol.
Therefore, patients should refrain from driving, using machines or undertaking any other hazardous activities entirely, and at least or the first few days of treatment. The decision in each individual case is made by the treating doctor, taking into account the response of the patient and the dose concerned.

4.8 Undesirable Effects (Side Effects)
Undesirable effects are ranked under headings of frequency, using the following convention:
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.

Psychatric disorders
*Common: i*rritability, aggression, restlessness, depression (in patients with a pre-existing depressive disorder, depressive moods may be aggravated), drug tolerance (especially during prolonged use), agitation.

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 (reversible; particularly with high doses or in long-term treatment), headache, tremor, ataxia.

Uncommon: emotional poverty, amnesia (may be associated with abnormal behavior), memory impairment, anterograde amnesia (in the normal dose range, but especially at higher dose levels). *Frequency 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 (reversible; particularly with high doses or in long-term treatment).

Eye disorders
Uncommon: diplopia (reversible; particularly with high doses or in long term treatment).

Respiratory, thoracic and mediastinal disorders
Frequency not known: respiratory depression, respiratory failure (may develop or worsen particularly in patients with pre-existing compromised respiratory function, e.g. in patients with bronchial asthma, or in patients with brain damage((see sections 4.3 and 4.4).

Gastrointestinal disorders
Common: dry mouth, constipation, nausea.

Skin and subcutaneous tissue disorders
Uncommon: rash. *Frequency not known:* urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome).

Musculoskeletal and connective tissue disorders
Frequency not known: muscle spasms, muscle weakness.

General disorders
Very common: fatigue (especially at the beginning of treatment and when higher doses are used). *Frequency not known*: slow response to stimuli, hypothermia

Investigations
Uncommon: weight increased (particularly with high doses or long-term treatment).

Injury
Uncommon: risk of fall (risk of severe injuries) (see section 4.4).

4.9 Overdose

a) Symptoms of intoxication :
Overdose and intoxication with Clocent 10 and other benzodiazepines can cause depression of the central nervous system with the following symptoms: drowsiness, confusion and somnolence. The condition can progress to ataxia, respiratory depression, a drop in blood pressure and, in rare cases, coma. The symptoms of an overdose are more pronounced and may be life-threatening if other substances that affect the brain, including alcohol, are taken simultaneously.
Previous reports of overdose in the literature involving ingestion of up to ten times the recommended therapeutic daily dose did not result in any clinically significant damage. Symptoms included interruption of sleep by auditory stimuli or drowsiness and clouding of consciousness as well as weakness in the legs lasting a day.
Most cases of severe acute intoxication reported to the manufacturer have involved a combination of Clocent 10 and other psychotropic drugs or hypnotics.
Three cases of overdose have been caused largely by Clocent 10 itself. In two of these cases, the dose is unknown but serum levels of clobazam peaked at 2.8 and 1.5 mg/ml. In the third case, 880 mg was taken. These three cases all resulted in a sleep-like or comatose state lasting 8 to 24 days. One patient did not react to pain stimuli for the first 5 days. In all cases, spontaneous breathing was unaffected.

b) Treatment of intoxication :
In addition to monitoring respiration, pulse and blood pressure, gastric lavage, intravenous fluid replacement and general supportive measures are indicated. Facilities for dealing with complications such as obstruction of the airways or respiratory failure must be available.
Hypotension can be treated with plasma replacement and, if necessary, sympathomimetics.
Secondary elimination of the active substance (by means of forced diuresis or haemodialysis) is ineffective.
There is insufficient experience of additional administration of cholinergic physostigmine or the benzodiazepine antagonist flumazenil for an assessment of efficacy.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anxiolytic (tranquilizer) and anticonvulsant, 1.5-benzodiazepine ATC-Code: N05BA09
Tranquilising effect
Experimental models with various animal species have shown clobazam to have a clearly pronounced tranquilising, anxiolytic and aggression- reducing effect. At therapeutically relevant doses, the tranquilising effect occurs without impairing motor activity.

Effect on motor coordination
Like all benzodiazepines, clobazam influences muscle coordination. However, it differs from other substances, e.g. diazepam and chlordiazepoxide, in that the impairment is much less severe.

Anticonvulsant effect
Various animal models have shown clobazam to have a pronounced anticonvulsant effect exceeding that of chlordiazepoxide. *Potentiation of anaesthesia and analgesic effect*
Clobazam prolonged anaesthesia after administration of various barbiturates in mice. The narcotic effect of alcohol is also intensified by clobazam. Clobazam was also found to have an analgesic effect in three different pain tests.

Cardiovascular effect
The effect of clobazam on the cardiovascular system has been tested in various animal species. A minimal effect, largely in the form of a slight decrease in blood pressure, pulse and respiratory rate, was only evident after a dose 20 to 200 times higher than the corresponding human dose.

5.2 Pharmacokinetic properties
Clobazam is virtually insoluble in water (1:12,500) and its apparent coefficient of distribution is 9 (noctanol/phosphate buffer pH 7.4).
Absorption
After oral administration, clobazam is rapidly and extensively absorbed. Administration of clobazam as capsules, tablets or solution (in propylene glycol) had no significant effect on its relative bioavailability. Time to peak plasma concentrations (tmax) is achived from 0.5 – 4.0 hrs.
The administration of clobazam tablets with food or crushed in apple puree slows the rate of absorption by approximately 1 hour but does not affect the overall extent of absorption. Clobazam can be given without regard to meals.
Concurrent alcohol consumption can increase 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, whereas binding to cellular blood components is minimal.
Clobazam accumulates approximately 2-3 folds to steady-state while the active metabolite Ndesmethylclobazam (–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 desmethylclobazm (N-CLB) mediated by CYP3A4 and to a lesser extent by CYP2C19. –CLB is an active metabolite and the main circulating metabolite found in human plasma. NCLB undergoes further biotransformation in the liver to form 4-hydroxy—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.

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 feces.
Less than 1% of unchanged clobazam and less than 10% of unchanged N-CLB are excreted through the kidneys.
It crosses the placental barrier and can also be detected in breast milk. Active clobazam concentrations can be reached in foetal blood and breast milk.

6. Pharmaceutical Particulars

6.1 List of excipients Clocent 10:
Lactose monohydrate,Microcrystalline cellulose,Maize starch B,Purified water,Starch 1500 partially pregelatinized maize starch, Colloidal silicon dioxide, Magnesium stearate.

6.2 Incompatibilities :
Not applicable.

6.3 Shelf life :
36 months

6.4 Special precautions for storage:
Store below 30°C.
Keep out of the reach of children.

6.5 Nature and contents of container:
10 tablets packed in ALU-PVC blister and 12 such blisters packed in 1 carton.

Manufactured by:
CENTAUR PHARMACEUTICALS PVT. LTD.
Plot No. 4, International Biotech Park,
Hinjewadi Phase II, Pune- 411057, Maharashtra, INDIA.

Product Registration Holder and Imported by:-
Unimed Sdn Bhd.
No.53, Jalan Tembaga SD 5/2B,
Bandar Sri Damansara, 52200, Kuala Lumpur, Malaysia.

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