Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Verclob 10mg tablets

2. Qualitative and quantitative composition
Each tablet contains 10 mg clobazam.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Light Yellow coloured , elongated , biconvex , uniscored , uncoated Tablets

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.

4.2 Posology and method of administration

Treatment of anxiety

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 60 mg 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. 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 Treatment should always be withdrawn gradually.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.

Treatment of epilepcy in association with one or more other anticonvulsants.
In epilepcy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to maximum of 60 mg daily.

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.

Children

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 5 mg daily. A maintenance dose of 0.3 – 1 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.

Method of administration

Tablets should be swallowed without chewing with sufficient amount of liquid (1/2 glass).

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.

4.3 Contraindications

Clobazam 10mg Tablets must not be used:
- in patients with hypersensitivity to benzodiazepines or any of the excipients of Clobazam 10 mg Tablets - see 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).

4.4 Special warnings and precautions for use

Somnolence or Sedation

VERCLOB (Clobazam Tablet BP-10mg) causes somnolence and sedation. In clinical trials, somnolence or sedation were reported at all effective doses and were dose-related.

In general, somnolence and sedation begin within the first month of treatment and may diminish with continued treatment. Prescribers should monitor patients for somnolence and sedation, particularly with concomitant use of other central nervous system depressants. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of clobazam is known.

Potentiation of Sedation from Concomitant Use with Central Nervous System Depressants

Since clobazam has a central nervous system (CNS) depressant effect, patients or their caregivers should be cautioned against simultaneous use with other CNS depressant drugs or alcohol, and cautioned that the effects of other CNS depressant drugs or alcohol may be potentiated.

Withdrawal Symptoms

Abrupt discontinuation of clobazam should be avoided. Clobazam should be tapered by decreasing the dose every week by 5-10 mg/day until discontinuation [see Dosage and Administration].

Withdrawal symptoms occurred following abrupt discontinuation of clobazam; the risk of withdrawal symptoms is greater with higher doses. As with all antiepileptic drugs, clobazam should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus.

Serious Dermatological 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. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment initiation or when re-introducing therapy. Clobazam should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

Dependence

Use of benzodiazepines – including clobazam – may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse. Therefore the duration of treatment should be as short as possible.

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 mood changes, anxiety or sleep disturbances and restlessness.

A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (for example, Clobazam) to one with a short duration of action.

Suicidal ideation, suicide attempt, suicide and depression

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

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.

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.

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

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

Alcohol

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

4.5 Interaction with other medicinal products and other forms of interaction

Especially when clobazam is administered at higher doses, an enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anticonvulsant drugs, anaesthetics and sedative antihistamines. Special caution is also necessary when clobazam is administered in cases of intoxication with such substances or with lithium.

Alcohol

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

Anticonvulsants

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. Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels is recommended, prior to initiation of stiripentol, and then once new steady-state concentration has been reached, i.e. after 2 weeks approximately.

Narcotic analgesics

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

Muscle relaxants

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

CYP 2C19 inhibitors

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to Ndesmethylclobazam (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

CYP 2D6 substrates
Clobazam is a weak CYP2D6 inhibitor. Dose adjustment of drugs metabolized by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol may be necessary. 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

4.6 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 incidence of cleft lip and palate were observed in 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 to be continued, use clobazam 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 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 postnatal period is recommended.

Breast-feeding

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

Fertility

No clinical data on fertility are available. In a fertility study in male and female rats no effect on fertility was observed

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:

o The medicine has been prescribed to treat a medical or dental problem and
o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
o It was not affecting your ability to drive safely

4.8 Undesirable effects

Nervous system disorders

Clobazam may cause sedation, leading to fatigue and sleepiness, especially at the beginning of treatment and when higher doses are used. Side-effects such as slowing of reaction time, muscle weakness, ataxia, confusion, drowsiness, dizziness, numbed emotions and headaches, or a fine tremor of the fingers have been reported. These are more likely to occur at the beginning of treatment and often disappear with continued treatment or a reduction in dose. Disorders of articulation, unsteadiness of gait and other motor functions, or loss of libido may occur, particularly with high doses or in long-term treatment. These reactions are reversible. After prolonged use of benzodiazepines, impairment of consciousness, sometimes combined with respiratory disorders, has been reported in very rare cases, particularly in elderly patients: it sometimes persists for some length of time. These disorders have not been seen so far under clobazam treatment. Anterograde amnesia may occur, especially at higher dose levels. Amnesia effects may be associated with inappropriate behaviour

Psychiatric disorders

Paradoxical reactions, such as restlessness, irritability, difficulty in falling asleep or sleeping through, acute agitational states, , anxiety, aggressiveness , delusion, fits of rage, nightmare, hallucinations, psychotic reactions suicidal tendencies or frequent muscle spasms may occur, especially in elderly and in children. In the event of such reactions,

treatment with clobazam must be discontinued. Pre-existing depression may be unmasked during benzodiazepine use. Tolerance and physical and/or psychic dependence may develop, especially during prolonged use. Discontinuation of the therapy may result in withdrawal or rebound phenomena (see Warnings and Precautions). Abuse of benzodiazepines has been reported. When used as an adjuvant in the treatment of epilepsy, this preparation may in rare cases cause restlessness and muscle weakness. As with other benzodiazepines, the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use.

Eye disorders
Visual disorders (e.g., double vision). Such reactions occur particularly with high doses or in long-term treatment, and are reversible.

Respiratory, thoracic and mediastinal disorders
Clobazam may cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (i.e., in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate.

Gastrointestinal disorders
Dryness of the mouth, constipation, loss of appetite, nausea

Skin and subcutaneous tissue disorders
Cutaneous reactions, such as rash or urticaria may develop in very rare cases. Stevens-Johnson syndrome, Toxic Epidermal Necrolysis

Metabolism and nutrition disorders
Weight gain, may occur particularly with high doses or in long-term treatment. This reaction is reversible.

General disorders
Fall

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

In the management of overdose, it is recommended that the possible involvement of multiple agents be taken into consideration.

Following overdose with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious, or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Secondary elimination of clobazam (by forced diuresis or haemodialysis) is ineffective.

Consideration should be given to the use of flumazenil as a benzodiazepine antagonist.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, Benzodiazepine derivatives.

ATC code: N05BA09.

Clobazam is a 1,5-benzodiazepine. In single doses up to 20 mg or in divided doses up to 30 mg, clobazam does not affect psychomotor function, skilled performance, memory or higher mental functions.

5.2 Pharmacokinetic properties

The peak plasma levels (Cmax) and the area under the curve (AUC) of clobazam are doseproportional over the dose range of 10-80 mg following single- or multiple-dose administration of clobazam. Based on a population pharmacokinetic analysis, the pharmacokinetics of clobazam are linear from 5-160 mg/day. Clobazam is converted to N-desmethylclobazam which has about 1/5 the activity of clobazam. The estimated mean elimination half-lives (t½) of clobazam and Ndesmethylclobazam were 36-42 hours and 71-82 hours, respectively.

Absorption

Clobazam is rapidly and extensively absorbed following oral administration. The time to peak concentrations (Tmax) range from 0.5 to 4 hours after single- or multipledose administrations. The relative bioavailability of clobazam tablets compared to an oral solution is approximately 100%. The administration of clobazam with food or when crushed in applesauce does not affect absorption.

Distribution

Clobazam is lipophilic and distributes rapidly throughout the body. The apparent volume of distribution at steady state was approximately 100 L. The in vitro plasma protein binding of clobazam and N-desmethylclobazam is approximately 80-90%

and 70%, respectively.

Metabolism

Clobazam is rapidly and extensively metabolized in the liver. Clobazam metabolism occurs primarily by hepatic demethylation to N-desmethylclobazam (N-CLB), mediated by CYP3A4 and to a lesser extent by CYP2C19. N-CLB is an active metabolite and the main circulating metabolite found in human plasma.

N-CLB undergoes further biotransformation in the liver to form 4-hydroxy-N desmethylclobazam, primarily mediated by CYP2C19.

CYP2C19 poor metabolizers exhibit a 5-fold higher plasma concentration of N-CLB compared to extensive metabolizers.

Clobazam is a weak CYP2D6 inhibitor. Co-administration with dextromethorphan led to increases of 90% in AUC and 59% in 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.

5.3 Preclinical safety data

Teratogenicity

Oral administration of clobazam to pregnant rats and rabbits throughout the period of organogenesis resulted in increased embryofetal mortality and increased incidences of fetal skeletal variations. In rabbits clobazam also decreased fetal body weights and increased the incidence of fetal malformations (visceral and skeletal). Additionally, oral administration of clobazam to rats throughout pregnancy and lactation resulted in decreased pup survival and alterations in offspring behaviour (locomotor activity). The observed embryo-fetal effects were associated with plasma exposures for clobazam and its major active metabolite N-desmethylclobazam less than those in humans at the maximum recommended dose.

Impairment of fertility

A study in rats in which clobazam was orally administered to male and female rats prior to and during mating and continuing in females to gestation day 6 had no effect on fertility and early embryonic development. The study was limited as the highest dose was associated with plasma exposures for clobazam and N-desmethylclobazam less than those in humans at the maximum recommended dose.

6 Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose BP, Sodium Starch glycolate BP, Starch BP, Dibasic Calcium Phosphate BP, Isopropyl alcohol BP, Methylene Di-Chloride BP, P.V.P.K-30 BP, Sodium Methyl Paraben BP, Sodium Propyl Paraben BP, Colloidal Silicon Dioxide BP, Magnesium Stearate BP, Talcum Powder, Lactose Monohydrate BP, Iron Oxide Yellow (HIS).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

36 Months.

6.4 Special Precautions for storage

The product must be stored at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and Content of container

Primary Packaging:

Printed Aluminium Blister Foil 148mm PVC Clear 160 mm

Secondary Packaging:

Printed Carton

Packing

10 tablets are packed in aluminium blister foil. 50 such foils are packed in a printed carton. This container closure system are suitable for storage, efficacy, transportation and use of the finished product.

6.6 Special precautions for disposal and other handling

None

7 Marketing Authorization Holder

Verve Human Care Laboratories
15-A, Pharmacity, Selaqui
Dehradun-248011
India

8 Marketing Authorization Number

CTD7799

9 Date of first authorization/renewal of the authorization

29/06/2023

10 Date of revision of the text

08/05/2025