1.17 SUMMARY OF PRODUCT CHARACTERISTICS

1.17.1 Product Information for Health Professionals

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

VERCLOB (Clobazam Tablets BP, 10mg)

2. Qualitative and Quantitative composition

Qualitative composition

Each uncoated tablet contains:

Clobazam BP

Excipients .

Colour: Iron Oxide Yellow

Quantitative composition

Each uncoated tablet contains:

Clobazam BP	10 mg
Excipients	q.s.
Colour: Iron Oxide Yellow	

3. Pharmaceutical form

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

4. Clinical particulars

4.1 Therapeutic indications

VERCLOB 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 illness. The use of **VERCLOB** 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 patient with anxiety associated with depression, **VERCLOB** must be used only in conjuction with adequate concomitant treatment. Use of benzodiazepine(such as **VERCLOB**) 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.

VERCLOB 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 60mg daily have been used in the treatment of adult in patients with severe anxiety.

The lowest dose that can control symptoms should be used. After improvement of the symptoms, the dose may be reduced.

It should not be used for longer than 4 weeks. 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 Treatment should always be withdrawn gradually.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 **VERCLOB** 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 5mg daily. A maintenance dose of 0.3 to 1mg/kg body weight daily in sufficient.

As there is no age appropriate formulation to enable safe and accurate dosing, no dosage recommendation can be made in children under 6 years of age.

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).

- In breast-feeding women.

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

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.

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 N-desmethylclobazam (N-CLB), the active metabolite of clobazam. Dosage adjustment of

clobazam may be necessary when co-administered with strong (e.g. fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors (please refer to Section 5.2).

• 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

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become pregnant or suspects that she is pregnant.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate such as hypothermia, hypotonia, moderate respiratory depression and difficulties in drinking (signs and symptoms of so-called “floppy infant syndrome”), can be expected due to the pharmacological action of the compound.

Moreover, infants born to mothers who took benzodiazepines during the latter stage of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

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

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

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.

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

ATC Code: N05BA09 (Nervous System, Psycholeptics, Anxiolytics, Benzodiazepine derivatives, Clobazam)

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

5.2 Pharmacokinetic properties

The peak plasma levels (C_{max}) and the area under the curve (AUC) of clobazam are dose-proportional 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 ($t_{½}$) of clobazam and N-desmethylclobazam were 36-42 hours and 71-82 hours, respectively.

Absorption

Clobazam is rapidly and extensively absorbed following oral administration. The time to peak concentrations (T_{max}) 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 and Excretion

Clobazam is extensively metabolized in the liver, with approximately 2% of the dose recovered in urine and 1% in feces as unchanged drug. The major metabolic pathway of clobazam involves N-demethylation, primarily by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. N-desmethylclobazam, an active metabolite, is the major circulating metabolite in humans, and at therapeutic doses, plasma concentrations are 3-5 times higher than those of the parent compound. Based on animal and *in vitro* receptor binding data, estimates of the relative potency of N-desmethylclobazam compared to parent compound range from 1/5 to equal potency. N-desmethylclobazam is extensively metabolized, mainly by CYP2C19. N-desmethylclobazam and its metabolites comprise ~94% of the total drug-related components in urine. Following a single oral dose of radiolabeled drug, approximately 11% of the dose was excreted in the feces and approximately 82% was excreted in the urine.

5.3 Preclinical safety data

None applicable

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 contents of container

Packing Details

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. Registrant

Generics Africa Limited
Aqua Office Suites,
5th Floor, Murang'a Road, Nairobi,
Kenya.

8. Manufacturer

Verve Human Care Laboratories

15-A, Pharmacity, Selaqui,

Dehradun-248011

India

9. Date of revision of the text

Not applicable

10. Dosimetry (If Applicable)

Not applicable

11. Instructions for preparations of Radiopharmaceuticals (if Applicable)

Not applicable

1.17.2 Patient Information Leaflet

Not Applicable as this Product is subjected to medical prescription:

o Controlled Drug Substance
o Prescription Only Medicine, POM