1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the Medicinal Product

BFIFCY CARBAMAZEPINE TABLETS

Carbamazepine Tablets USP 200 mg

1.2 Strength

Each uncoated tablet contains:
Carbamazepine USP 200 mg
Excipients Q.S.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Ingredients	Specification	Qty. in mg/tab	Qty. in kg/tab	Reason on inclusion
MIXING					
1.	Carbamazepine	USP	200.00	20.00	Active
2.	Maize Starch	BP	36.00	3.600	Binder
3.	Microcrystalline Cellulose	BP	25.00	2.500	Diluent
WET GRANULATION					
4.	Maize Starch	BP	12.0	1.200	Binder
5.	Povidone K-30	BP	6.00	0.600	Binder
LUBRICATION					
6.	Magnesium stearate	BP	4.00	0.400	Lubricant
7.	Purified Talc	BP	8.00	0.800	Glidant
8.	Colloidal Anhydrous Silica	BP	3.00	0.300	Glidant
9.	Croscarmellose Sodium	BP	6.00	0.600	Disintegrant
	Total weight of tablet		**300.00 mg**	**30.00 kg**	

where, USP= United States Pharmacopoeia
BP=British Pharmacopoeia

3. PHARMACEUTICAL FORM

Tablets

4. Clinical particulars

4.1 Therapeutic indications

Epilepsy - generalised tonic-clonic and partial seizures.
Note: Carbamazepine is not usually effective in absences (petitmal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences. The paroxysmal pain of trigeminal neuralgia.
For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy

4.2 Posology and method of administration

Carbamazepine is given orally, usually in two or three divided doses. Carbamazepine may be taken during, after or between meals, with a little liquid e.g. a glass of water.
Before deciding to initiate treatment, patients of Han Chinese and Thai origin should whenever possible be screened for HLA-B*1502 as this allele strongly predicts the risk of severe carbamazepine-associated Stevens-Johnson syndrome
Epilepsy:
The dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Determination of plasma levels may help in establishing the optimum dosage. In the treatment of epilepsy, the dose of carbamazepine usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre).
Adults: It is advised that with all formulations of Carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient.
Carbamazepine should be taken in a number of divided doses although initially 100-200mg once or twice daily is recommended.
This may be followed by a slow increase until the best response is obtained, often 800-1200mg daily. In some instances, 1600mg or even 2000mg daily may be necessary.

Elderly population (65 years or above): Due to the potential for drug interactions, the dosage of Carbamazepine should be selected with caution in elderly patients.
Children and adolescents: It is advised that with all formulations of Carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. Usual dosage 10-20mg/kg bodyweight daily taken in several divided doses.
Carbamazepine tablets are not recommended for very young children.
5-10 years: 400 to 600 mg daily (2-3 x 200mg tablets per day, to be taken in divided doses).
10-15 years: 600 to 1000mg daily (3-5 x 200mg tablets per day, to be taken in several divided doses).
>15 years of age: 800 to 1200mg daily (same as adult dose).

4.3 Contraindications

Known hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any other component of the formulation.
Patients with atrioventricular block, a history of bone marrow depression or a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda).
The use of Carbamazepine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs)
Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Warnings

Agranulocytosis and aplastic anaemia have been associated with Carbamazepine; however, due to the very low incidence of these conditions, meaningful risk estimates for Carbamazepine are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anaemia.

Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Carbamazepine. Nonetheless, complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline, and periodically thereafter.

Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult the physician immediately.

4.5 Interaction with other medicinal products and other forms of Interactions:

Cytochrome P450 3A4 (CYP 3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine 10, 11-epoxide. Co-administration of inhibitors of CYP 3A4 may result in increased carbamazepine plasma concentrations which could induce adverse reactions. Co-administration of CYP 3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to potential decreases in the carbamazepine serum level and therapeutic effect. Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels. Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism.

Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11- transdiol derivative from carbamazepine-10,11 epoxide. Coadministration of inhibitors of human microsomal epoxidehydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Risk summary

Offspring of epileptic mothers with untreated epilepsy are known to be more prone to developmental disorders, including malformations. Developmental disorders and malformations, including spina bifida, and also other congenital anomalies

e.g. craniofacial defects such as clept lip/palate, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with the use of Carbamazepine. Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

Lactation:

Carbamazepine passes into the breast milk (about 25-60% of the plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers taking Carbamazepine may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction). There have been some reports of cholestatic hepatitis in neonates exposed to carbamazepine during antenatal and or during breast feeding.

4.7 Effects on ability to drive and use machines

The patient's ability to react may be impaired by the medical condition resulting in seizures and adverse reactions including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision have been reported with Carbamazepine, especially at the start of treatment or in connection with dose adjustments. Patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects:

Summary of the safety profile

Particularly at the start of treatment with Carbamazepine, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia), gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions. The dose-related adverse reactions usually abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels and divide the daily dosage into smaller (i.e. 3-4) fractional doses.

4.9 Overdose

Signs and symptoms

The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, respiratory systems

Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyper-reflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

Respiratory system: Respiratory depression, pulmonary oedema.

Cardiovascular system: Tachycardia, hypotension and at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest.

Gastro-intestinal system: Vomiting, delayed gastric emptying, reduced bowel motility.

Musculoskeletal system: There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity.

Renal function: Retention of urine, oliguria or anuria; fluid retention, water intoxication due to ADH-like effect of carbamazepine.

Laboratory findings: Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatine phosphokinase.

Management

There is no specific antidote.

Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm carbamazepine poisoning and to ascertain the size of the overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonists, plain,

ATC Code: C09CA07

Mechanism of action:

Therapeutic class: Anti-epileptic, neurotropic and psychotropic agent; (ATC Code: N03 AF01). Dibenzazepine derivative. As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation; generalised tonicclonic seizures, as well as combinations of these types of seizures.
The mechanism of action of carbamazepine, the active substance of Carbamazepine, has only been partially elucidated. Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. It is conceivable that prevention of repetitive firing of sodium-dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action. Whereas reduction of glutamate release and stabilisation of neuronal membranes may account for the antiepileptic effects, the depressant effect on dopamine and noradrenaline turnover could be responsible for the antimanic properties of carbamazepine.

5.2 Pharmacokinetics Properties

Absorption

Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours (chewable tablets 6 hours; syrup 2 hours) following single oral doses. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approx. 4.5µg/ml.
The bioavailability of Carbamazepine in various oral formulations has been shown to lie between 85-100%.

Distribution

Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration ofunchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion inplasma (20-30%). Concentrations in breast milk were found to be equivalent to 25-60% of thecorresponding plasma levels. Carbamazepine crosses the placental barrier. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.

Biotransformation

Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10, 11- epoxide from carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide.

Elimination

The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours (autoinduction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9-10 hours have been found.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, local tolerance, genotoxicity and carcinogenic potential. Reproductive toxicity studies in animals were insufficientto rule out a teratogenic effect of carbamazepine in humans.

Carcinogenicity

In rats treated with carbamazepine for two years, there was an increased incidence of hepatocellular tumours in females and benign testicular tumours in males. However, there is no evidence to date that these observations are of any relevance to the therapeutic use of carbamazepine in humans.

Fertility

In chronic toxicity studies dose related testicular atrophy and a spermatogenesis occurred in rats receiving carbamazepine. The safety margin for this effect is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch BP
Microcrystalline Cellulose BP
Povidone BP
Magnesium stearate BP
Purified Talc BP
Colloidal Anhydrous Silica BP
Croscarmellose Sodium BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life:

24 months

6.4 Special precautions for storage:

Do not store above 30°C. in the original package in order to protect from moisture.

6.5 Nature and contents of container

10 Tablets are packed in an Alu-PVC blister pack. Such 10 Alu-PVC blisters are packed in a printed carton along with pack insert.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

M/S. Bfificy Pharmaceutials Limited.,
26-27, France Road, Sabon Gari, Kano,
Kano State, Nigeria

8 MARKETING AUTHORISATION NUMBER

C4-0935