1. Name of the medical product

Brand name: CARTOL

Product name: Carbamazepine Tablets 200mg

2. Qualitative and quantitative composition

Each tablet contains: Carbamazepine 200mg

For a full list of excipients, see section 6.1

3. Pharmaceutical form

White tablet

4. Clinical particulars

4.1 Therapeutic ¡ndications

CARTOL® is indicated for the control of secondarily generalized tonic-clonic seizures and partial seizures and in some primary generalized seizures. CARTOL ® is also used in the treatment of trigeminal neuralgia. It is also indicated in the prophylaxis of bipolar disorder unresponsive to lithium.

4.2 Posology/Dosage and method of administration

CARTOL® is given orally, usually in two or three divided doses. CARTOL® 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 (See information on genetic testings and cutaneous reactions in section 4.4).

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) (see warnings and precautions).

Adults: It is advised that with all formulations of CARTOL®, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient.

CARTOL® 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 CARTOL® should be selected with caution in elderly patients.
Children and adolescents: It is advised that with all formulations of CARTOL®, 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.

CARTOL® 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).

Maximum recommended dose
Up to 6 years of age: 35mg/kg/day
6 to15 years of age: 1000mg/day
>15 years of age: 1200mg/day.

Wherever possible, anti-epileptic agents should be prescribed as the sole anti-epileptic agent but if used in polytherapy the same incremental dosage pattern is advised.
When CARTOL® is added to existing antiepileptic therapy, this should be done gradually while maintaining or, if necessary, adapting the dosage of the other antiepileptic(s) (see 4.5 Interaction with other medicinal products and other forms of interaction).

Trigeminal neuralgia:
Slowly raise the initial dosage of 200-400mg daily until freedom from pain is achieved (normally at 200mg 3-4 times daily). In the majority of patients a dosage of 200mg 3 or 4 times a day is sufficient to maintain a pain free state. In some instances, doses of 1600mg CARTOL® daily may be needed. However, once the pain is in remission, the dosage should be gradually reduced to the

lowest possible maintenance level. Maximum recommended dose is 1200mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

Elderly population (65 years of age or above):
Due to drug interactions and different antiepileptic drug pharmacokinetics, the dosage of CARTOL® should be selected with caution in elderly patients.

Dosage in Trigeminal neuralgia
In elderly patients, an initial dose of 100mg twice daily is recommended. The initial dosage of 100mg twice daily should be slowly raised daily until freedom from pain is achieved (normally at 200mg 3 to 4 times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

For the prophylaxis of manic depressive psychosis in patients unresponsive to lithium therapy:
Initial starting dose of 400mg daily, in divided doses, increasing gradually until symptoms are controlled or a total of 1600mg given in divided doses is reached. The usual dosage range is 400-600mg daily, given in divided doses.

Special populations
Renal impairment / Hepatic impairment
No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

4.3 Contraindications

CARTOL® is contraindicated in;
Patients with AV (atrioventricular) conduction abnormalities.
Patients with a history of bone marrow depression,
Patients with Porphyria

4.4 Special warnings and precautions for use

CARTOL® should be given with caution to patients with a history of blood disorders or haematological reactions to other drugs, or patients with cardiac, hepatic or renal disease. Patients

or carers should be told how to recognize signs of blood, liver and skin toxicity and they should seek immediate attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising or bleeding develops.

CARTOL®should be withdrawn under the cover of a suitable alternative antiepi leptic, if leucopenia which is severe, progressive, or associated with clinical symptoms develops. Blood counts and hepatic and renal function test should be performed before starting CARTOL® therapy and periodically during treatment.

Caution is required when withdrawing CARTOL® therapy. Since CARTOL® has mild antimuscuranic properties; caution should be observed in patients with Glaucoma or raised intra-ocular pressure. CARTOL® should be used with caution in pregnancy and breast feeding.

4.5 Interaction with other drug products and other forms of interaction

The metabolism of CARTOL® is inhibited by some drugs reported to inhibit its metabolism by the cytochrome P1450 Isoenzyme CYP3A4, resulting in raised plasma concentrations and associated toxicity, such drugs are Erythromycin, clarithromycin, cimetidine, isoniazid, avoid concomitant administration.

Conversely, drugs that induce CYP3A4 may increase the metabolism of CARTOL® leading to reduced plasma concentrations and potentially a decrease in therapeutic effect. The dose of CARTOL® should be adjusted accordingly and/or the plasma concentration monitored.

Effects of other drugs on CARTOL®:

Alcohol: Alcohol may exacerbate the CNS side effects of CARTOL®.

Analgesics: Dextropropoxyphene enhances effect of CARTOL®, effect of methadone and tramadol deceased by CARTOL®.

Anticoagulants: reduction in anticoagulant effect, as metabolism of warfarin and acenocoumarol is accelerated.

Antidepressants: Antidepressant antagonizes the antiepileptic activity of CARTOL® by lowering the convulsive threshold.

Antiepileptics: Interaction between antiepileptics is complex and may enhance toxicity without a corresponding increase in antiepileptic effects. These interactions are highly variable and unpredictable; plasma monitoring is therefore advisable with combination therapy.

Phenobarbital often lowers the plasma concentration of CARTOL®. CARTOL® often lowers plasma concentration of phenytoin, clobazam, clonazepam, and valproate. Phenytoin has been reported to often lower the plasma concentration of CARTOL®.

Antimalara: Chloroquine and mefloquine may antagonize the anti epileptic activity of CARTOL®

by lowering the convulsive threshold.
Metabolism of clozapine, haloperidol, olanzapine, and risperidone accelerated.
Calcium-channel blockers: diltiazem and verapramil enhance effect of CARTOL®. Effect of felodipine, isradipine, nifedipine reduced.
Ciclosporin: Metabolism accelerated (reduced plasma-ciclosporin concentration).
Lithium: Neurotoxicity may occur without increased plasma-lithium concentration.
Oestrogens and progestogens: CARTOL® accelerates metabolism or oral contraceptives.

4.6 Fertility, pregnancy and lactation

Fertility

There have been very rare reports.

Pregnancy

Carbamazepine crosses the placenta in humans. Carbamazepine should not be used during pregnancy unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risks of taking carbamazepine during pregnancy.

Lactation

Carbamazepine passes into the breast milk. The benefits of breast-l feeding should be weighed against the possibility of adverse effects occurring in the infant.

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. Patients should exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects

The fairly common effects of CARTOL® particularly at initial stage of therapy include dizziness, drowsiness, and ataxia. These effects may be minimized by starting therapy with a low dose.
Gastrointestinal symptoms are less common, this include dry mouth, abdominal pain, nausea and vomiting, anorexia, and diarrhoea and constipation.
Generalized erythematous rashes may be severe and may necessitate withdrawal of treatment.
Photosensitivity reactions, urticarial, alopecia, exfoliative dermatitis, toxic epidermal necrolysis,

erythema multifonne and stevens-johnson syndrome and systemic lupus erythematous has also been reported.

Occasional reports of blood disorders include: agranulocytosis, aplastic anaemia, eosiniphilis, persistent leucopenia, leucocytosis, thrombocytopenia and purpura. Lymphadenopathy, splenomegaly, pneumonitis, abnormalities of the liver and kidney functions, hepatitis and cholestatic jaundice have also been reported.

Other adverse effects are hyponatraemia, oedema, paraesthesia, headache, arrhythmias, heart block, heart failure, impotence, male infertility and gynaecomastia.

Congenital malformations have been reported in infants born to women who received carbamazepine during pregnancy.

4.9 Overdose

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (> 60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Treatment:

In the treatment of over dosage with CARTOL®, repeated doses of activated charcoal may be given by mouth to the patient. The aim is not only to prevent absorption but to also aid elimination. Gastric lavage may be considered if undertaken within 1 hour of ingestion. Supportive and symptomatic therapy alone may then suffice with particular attention to correcting hypoxia and hypotension; haemoperfusion has been suggested for severe poisoning.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen

5. Pharmacological properties

5.1 Pharmacodynamic properties

Therapeutic class: Anti-epileptic, neurotropic and psychotropic agent; Dibenzazepine derivative.
ATC Code: N03AF01.

As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation; generalised tonic-clonic seizures, as well as combinations of these types of seizures.

The mechanism of action of carbamazepine, the active substance of Curatil, 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 Pharmacokinetic 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. 4.5µ g/ml.

The bioavailability of It in various oral formulations has been shown to lie between 85-100%. Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of it.

Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

Distribution

Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma (20-30%). Concentrations in breast milk were found to be equivalent to 25-60% of the

corresponding 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. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.
Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.
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 (auto-induction 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.
The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.
After administration of a single oral dose of 400mg carbamazepine, 72% is excreted in the urine and 28% in the faces. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10, 11-epoxide metabolite.

5.3 Preclinical safety data

Preclinical data show no special hazard for humans based on conventional studies of single and repeated dose toxicity, local tolerance, genotoxicity and carcinogenic potential.
However, animal studies were insufficient to rule out the teratogenic effects of carbamazepine.
Carcinogenicity
In a 2-year carcinogenicity study in rats with carbamazepine, increased incidences of hepatocellular tumors in females and benign testicular tumors in males were observed. However, there is no evidence that these observations are relevant to therapeutic use in humans.

Genotoxicity

Various standard mutagenicity studies in bacteria and mammals revealed no evidence of carbamazepine genotoxicity.

Reproductive toxicity

The cumulative evidence from various animal studies in mice, rats and rabbits demonstrated that carbamazepine at doses 10 to 20 times higher than the recommended human dose during organ development resulted in increased embryonic lethality and growth retardation. Embryonic damage (mainly to the cerebral ventricles) was observed in mice. In reproduction studies in rats, the breastfed offspring demonstrated reduced weight gain at a maternal dosage level of 192mg/kg/day in the dam.

6. Pharmaceutical properties

6.1 List of excipients

Maize Starch, Dextrin, Sodium Starch Glycolate, Microcrystalline cellulose, 3% HPMC

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a cool dry place below 30°C and protect from light.

Keep medicines out of reach of children

6.5 Nature and contents of container

10 tablets per blister, 10 blister per box.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Name: VIXA PHARMACEUTICAL CO., LTD.

Name: 13B, Sunny Jigide Street, Off Celestial Way, Ogudu, Lagos, Nigeria

8. DRUG PRODUCT MANUFACTURER

Name: Jiangsu Shanfang Pharmaceutical Co., Ltd.

Address: Industrial concentration area, Xushe Town, Yixing, Jiangsu Province, China

9. NAFDAC REGISTRATION NUMBER(S)

A4-2318

10. Date of first of authorization / renewal of authorization

11. Date of revision of the text