PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

PROPRIETARY NAME (and dosage form):

Partid-200 (tablets)

COMPOSITION:

Each tablet contains carbamazepine 200 mg.

Sugar free.

Excipients: Microcrystalline cellulose (pH 101), carmellose sodium, colloidal silicon dioxide, purified talc, magnesium stearate, sodium starch glycollate.

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Anticonvulsants, including anti-epileptics.

PHARMACOLOGICAL ACTION:

Carbamazepine possesses both anticonvulsant and psychotropic properties

Pharmacokinetic properties:

Absorption of carbamazepine is slow and variable following oral administration with peak plasma concentrations (9,3 µg/ml) being attained 4 to 8 hours after a single dose. The controlled release tablets yield a peak plasma concentration of about 12 hours following chronic administration.

Carbamazepine is metabolised by the liver and is extensively bound (about 75 %) to plasma proteins, with a bioavailability of > 70 %. The plasma elimination half-life of the unchanged carbamazepine averages approximately 36 hours following a single oral dose, whereas after repeated administration, it averages to about 16 to 24 hours. Up to 72 % of the metabolites is primarily excreted via the kidney with only about 3 % of carbamazepine appearing unchanged in the urine.

INDICATIONS:

PARTID-200 is indicated for the treatment of:

- Epilepsy:
    - psychomotor or temporal-lobe epilepsy
    - generalized tonic-clonic seizures (grand mal)
    - mixed forms of seizures
    - simple or complex partial seizures
- Mania, and treatment of bipolar affective disorders.
- Trigeminal neuralgia.

PARTID-200 is not effective in atypical or generalized absence seizures (petit mal) or myoclonic seizures.

CONTRA-INDICATIONS:

Known hypersensitivity to carbamazepine, or tricyclic antidepressants, or any of the ingredients.

Atrioventricular conduction abnormalities.

Patients with a history of bone marrow depression.

Porphyria.

Concurrent use with Monoamine Oxidase Inhibitors (MAOIs) or within 14 days of stopping such treatment.

Pregnancy and lactation (see “Pregnancy and Lactation”).

WARNINGS:

Patients who become pregnant while taking PARTID-200 should be counselled, regarding the risk of malformations and should be offered antenatal screening.

Aplastic anaemia and agranulocytosis have been reported. Transient thrombocytopenia or decreased white blood cell counts may occur. Complete blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained before treatment and periodically thereafter.

If the white blood counts or platelet count is definitely low or decreases during treatment, the patient should be closely monitored and PARTID-200 should be discontinued if there is any evidence of significant bone-marrow depression.

PARTID-200 should be withdrawn if signs and symptoms suggestive of severe skin reactions e.g. Stevens-Johnson syndrome, appear.

The previously known dangerous or even fatal skin reactions experienced by patients on carbamazepine therapy, i.e. Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), have now been found to be mostly associated with the presence of a particular human leucocyte antigen (HLA) allele, called HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including India. In many of

these countries the rate of SJS/TEN has been found to be considerably higher than in Caucasian populations.

Screening for HLA-B*1502 should be considered for patients with Asian ancestry before starting treatment with PARTID-200. For patients that test positive, PARTID-200 should not be started unless the expected benefit clearly outweighs the increased risk of these serious skin reactions. Tested patients who are negative* for the allele are thought to have a low risk of SJS/TEN. However, SJS/TEN can still rarely occur in these patients, so healthcare professionals should still watch for symptoms.

Genetic tests* for HLA-B*1502 are available in South African Laboratories.
Patients who have been taking PARTID-200 for more than a few months without developing SJS/TEN are at low risk of these events ever developing with PARTID-200. This information may be considered in deciding whether or not these patients need to be tested.

HLA-B*1502 is largely absent in individuals not of Asian ancestry including Caucasians, African-Americans, Hispanics and Native Americans.

The data suggest that the risk of these events is estimated to be about 1 to 6 per 10 000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. PARTID-200 to be discontinued at the first sign of a rash, unless the rash is clearly not Partid 200-related. If signs or symptoms suggest SJS/TEN, use of this medicine should not be resumed and alternative therapy should be considered.

Over 90 % of PARTID-200 treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on PARTID-200.

Application of HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management.
Many HLA-B*1502-positive Asian patients treated with PARTID-200 will not develop SJS/TEN, and these reactions may still occur infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Laboratory Tests

For genetically at-risk patients, high resolution 'HLA-B*1502 typing' is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.
PARTID-200 should be used with caution in patients with mixed seizures that include generalised absences or atypical absences as seizures may be exacerbated.

Liver function tests are recommended before treatment and periodically during treatment.
If allergic skin reactions occur or platelet count diminishes or tests reveal deterioration in liver function, or any serious adverse symptoms develop, PARTID-200 should be withdrawn.
Complete urinalysis and blood urea determinations prior to initiation of therapy and periodically during treatment are recommended.

INTERACTIONS:

Co-administration with agents that inhibit or induce CYP3A4 may alter PARTID-200 plasma concentrations.

Agents that may have a resultant increase in PARTID-200 *plasma levels and associated toxicity, when co-administered:* isoniazid, verapamil, diltiazem, dextropropoxyphene, viloxazine, fluoxetine, fluvoxamine, cimetidine, acetazolamide, danazol, desipramine, nicotinamide, nefazodone, macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin), azoles (e.g. itraconazole, miconazole, ketoconazole, fluconazole), terfenadine, loratadine.

Agents that may have a resultant decrease in PARTID-200 *plasma levels when co-administered:* phenobarbitone, phenytoin, primidone, theophylline, methosuximide, phensuximide, rifampicin, cisplatin, doxorubicin, clonazepam, St John's Wort (hypericum perforation).

Valproic acid, valpromide, clobazam have been reported to increase the plasma concentrations of the pharmacologically active carbamazepine-10,11-epoxide metabolite.

Felbamate – may decrease the PARTID-200 serum concentration associated with an increase in carbamazepine-10,11-epoxide concentration.

Isotretinoin – alters the availability and/or clearance of PARTID-200 and its active metabolite carbamazepine-10,11-epoxide.

Agents that may have resultant decrease in their plasma concentration when used concomitantly with PARTID-200: clonazepam, ethosuximide, primidone, valproic acid, alprazolam, corticosteroids (e.g. prednisolone, dexamethasone), cyclosporine, doxycycline, felodipine, haloperidol, imipramine, methadone, oral contraceptives, theophylline, oral anticoagulants (warfarin, phenprocoumon, dicoumarol), felbamate, lamotrigine, zonisamide, tiagabine, topiramate, tricyclic antidepressants (e.g. imipramine, amitryptiline, nortriptyline, clomipramine), clozapine.

Plasma phenytoin levels have been reported both to be raised and to be lowered by PARTID-200 and plasma mephenytoin levels have been reported in rare instances to increase.

Folic acid – metabolism may be enhanced hence requirement for folic acid increased.

Paracetamol – bioavailability and hence therapeutic effect of paracetamol may be reduced.

Isoniazid – may lead to isoniazid-induced hepatotoxicity.

Combined use of PARTID-200 and lithium, or metoclopramide, or neuroleptics (haloperidol, thioridazine) may lead to neurotoxicity (with latter combination even in the presence of "therapeutic plasma levels").

Symptomatic hyponatraemia has been reported when PARTID-200 was co-administered with a diuretic e.g. hydrochlorothiazide or furosemide.

PARTID-200 antagonises the effects of non-depolarising muscle relaxants (e.g. pancuronium), patients should be monitored closely for more rapid recovery from neuromuscular blockage than expected.

Alcohol may exacerbate the CNS side-effects of PARTID-200, it is therefore advisable to avoid alcohol during treatment.

PREGNANCY AND LACTATION:

PARTID-200 is excreted into breastmilk which exposes the nursing infant to a possibility of adverse reactions.

Epileptic patients who wish to become pregnant should consult their doctor for advice. Anticonvulsant agents should, wherever possible, be prescribed as monotherapy, because the *incidence of congenital abnormalities* in the offspring treated with a combination of anti-epileptic medicines is greater than in those of mothers receiving the individual medicines as monotherapy. The lowest possible effective dose should be given and monitoring of plasma levels is recommended.

If pregnancy occurs in a woman receiving PARTID-200, or if the problem of initiating treatment with PARTID-200 arises during pregnancy, the medicine's potential benefit must be weighed against its possible hazards, particularly in the first 3 months of pregnancy.

Infants born to epileptic mothers are known to be more prone to developmental disorders, including malformations. The possibility that PARTID-200 increases this risk has been reported, although conclusive evidence from controlled studies with PARTID-200 monotherapy is lacking. However there are rare reports of developmental disorders and malformations, including spina bifida in association with PARTID-200.

Adequate folic acid supplementation is recommended before and during pregnancy to counteract the risk of neutral tube defects in the offspring of women on anti-epileptics. Administration of Vitamin K_1 to the mother during the last weeks of pregnancy as well as to the newborn to prevent neonatal bleeding disorders, is also been recommended.
There have been few cases of neonatal seizures and/or respiratory depression associated with maternal PARTID-200 and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal PARTID-200 use. These reactions may represent a neonatal withdrawal syndrome.

Women with manic depressive (bipolar) disorders have an increased risk to relapse during pregnancy and/or the post partum period.

DOSAGE AND DIRECTIONS FOR USE:

The tablets should be taken during or after meals with a little liquid. The tablets should not be chewed.

The controlled release of the active substance from the tablets allows an effective twice, daily administration.

When the patient is transferred from another anticonvulsant to PARTID-200, the dosage of the first should be reduced gradually.

Due to medicine interactions and different anti-epileptic medicine pharmacokinetics, the dosage of PARTID-200 should be selected with caution in elderly patients.

Epilepsy:

When possible, PARTID-200 should be prescribed as a monotherapy. A low initial dose is recommended, which should be adjusted until optimum dosage to achieve adequate control of seizures. Plasma levels may be helpful in establishing the optimum dose. When PARTID-200 is added to existing anti-epileptic therapy, this should be added gradually while the dosage of the other anti-epileptic agent(s) is maintained or adapted (see “Interactions”).

Adults: An initial dose of 100 mg to 200 mg once or twice daily is recommended which may be gradually increased to a usual maintenance dose of 800 mg to 1 200 mg daily in divided doses. Doses up to 1 600 mg daily in divided doses may occasionally be necessary.

Children 5 years and older: Therapy may begin with 100 mg daily, increasing at weekly intervals by 100 mg. A maintenance dosage of 10 to 20 mg/kg bodyweight daily in divided doses is recommended e.g.

Children aged 5 years:	200 to 400 mg daily
Children 6 to 10 years:	400 to 600 mg daily
Children 11 to 15 years:	600 to 1 000 mg daily

Trigeminal neuralgia:

An initial dose of 200 to 400 mg which is gradually increased as necessary until pain is relieved. Doses up to 1 600 mg daily in divided doses may be required. When pain relief has been achieved, then dosage should be gradually reduced to the minimum effective dose.

Elderly and particularly sensitive patients: Initial dosage of 100 mg twice daily is recommended.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

At the initial stages of therapy with PARTID-200, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reactions may occur frequently. Dose related adverse reactions may 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 plasma levels.

Central Nervous System

Neurological:

Frequent: Dizziness, ataxia, drowsiness, fatigue, headache, diplopia, accommodation disorders (e.g. blurred vision).

Less frequent: Abnormal involuntary movements (e.g. tremor, asterixis, dystonias, tics), nystagmus. Orofacial dyskinesia, oculomotor disturbances, speech disorders (e.g. dysarthria, slurred speech), choreo-athetotic disorders, peripheral neuritis, paraesthesia, muscle weakness, and paretic symptoms. The causative role of carbamazepine in inducing or contributing to the development of a neuromalignant syndrome, especially in conjunction with neuroleptics, is unclear.

Psychiatric:

Less frequent: Hallucinations (visual or acoustic), depression, loss of appetite, restlessness, aggressive behaviour, agitation, confusion. Activation of psychosis (particularly in elderly patients or if initial dosage is too high).

Skin and appendages:

Frequent: Allergic skin reactions, urticaria which may be severe.

Less frequent: Exfoliative dermatitis and erythroderma. Systemic lupus erythermatosus-like syndrome, pruritus. Stevens-Johnson syndrome, toxic epidermal necrolysis (See WARNINGS) photosensitivity, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, sweating, hair loss. Hirsutism has been reported, but the casual relationship is not clear.

Haematological:

Frequent: Leucopenia.

Less frequent: Thrombocytopenia, eosinophilia. Leucocytosis, lymphadenopathy, folic acid deficiency. Agranulocytosis, aplastic anaemia, pure red cell aplasia, megaloblastic anaemia, acute intermittent porphyria, reticulocytosis, and possibly haemolytic anaemia.

Liver:

Frequent: Elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant. Elevated alkaline phosphatase.

Less frequent: Elevated transaminases. Hepatitis of cholestatic, parechymal (hepatocellular) or mixed type, jaundice. Granulomatous hepatitis.

Gastro-intestinal:

Frequent: Nausea, vomiting. Dryness of the mouth.

Less frequent: Diarrhoea or constipation. Abdominal pain. Glossitis, stomatitis, pancreatitis.

Hypersensitivity reactions:

Less frequent: A delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests, occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon). Aseptic meningitis, with myoclonus and peripheral eosinophilia; anaphylactic reaction, angioedema. Treatment should be discontinued when such hypersensitivity reactions occur.

Cardiovascular:

Less frequent: Disturbances of cardiac conduction, hypertension or hypotension. Bradycardia, dysryhthmias, AV block with syncope, collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thrombo-embolism.

Endocrine/Metabolic:

Frequent: Oedema, fluid retention, weight increase, hyponatraemia and reduced plasma osmolality due to an antidueretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities.

Less frequent: Increase in prolactin with or without clinical manifestations such as galactorrhoea, gynaecomastia. Abnormal thyroid function tests: decreased L-Thyroxin (FT4, T4, T3) and increased TSH, usually without clinical manifestations.
Disturbances of bone metabolism (decrease in plasma calcium and 25-OH-cholecalciferol), leading to osteomalacia, elevated levels of cholesterol, including HDL cholesterol, and triglycerides.

Genito-urinary:

Less frequent: Interstitial nephritis, renal failure, renal dysfunction (e.g. albuminuria, haematuria, oliguria, and elevated BUN/azotemia), urinary frequency, urinary retention, sexual disturbances/impotence.

Special senses:

Less frequent: Taste disturbances, lens opacities (see SPECIAL PRECAUTIONS), conjunctivitis, hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.

Musculoskeletal:

Less frequent: Arthralgia, muscle pain or cramp.

Respiratory:

Less frequent: Pulmonary hypersensitivity characterized e.g. by fever, dyspnoea, pneumonitis or pneumonia.

Special precautions:

Patients should be aware of early toxic signs and symptoms 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 his physician immediately.

Medical supervision during treatment is essential.
Abnormalities of liver function and jaundice have been associated with long-term treatment.
Reaction time may be decreased by PARTID-200. The patient's safety as a road user or operator of machines may be impaired in consequence, particularly in the presence of lens opacities. Mild skin reactions including isolated macular or maculopapular exanthema, are mostly transient and not hazardous, and they usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage; however, the patient should be kept under surveillance.

PARTID-200 should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with cardiac damage, hepatic or renal function impairment, or history of adverse haematological reactions to other drugs, or to patients who have had interrupted courses of therapy with PARTID-200.

The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

Isolated reports of impaired male fertility and/or abnormal spermatogenesis are on file.
A causal relationship has not been established.

As PARTID-200 has mild anticholinergic activity, care should be observed in patients with

glaucoma or increased intra-ocular pressure.

Breakthrough bleeding has been reported in women taking oral oestrogen-containing contraceptives; the reliability of oral contraceptives may be adversely affected by PARTID-200, and women of childbearing age should be advised to consider using alternative birth control while taking PARTID-200.

Tolerance may develop to some of the untoward effects of PARTID-200. These effects can be minimized by gradual increase in dosage and adjustment to the lowest effective maintenance dosage.

Abrupt withdrawal of PARTID-200 may precipitate seizures. If treatment has to be withdrawn abruptly in a patient with epilepsy, withdrawal should be made under cover of a suitable alternative anti-epileptic.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

Central nervous system: CNS depression, disorientation, 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 or hypertension, conduction disturbance with widening of QRS complex, syncope in association with cardiac arrest.
Gastrointestinal system: Vomiting, delayed gastric emptying, reduced bowel motility.
Renal function: Retention of urine, oliguria or anuria, fluid retention, water intoxication due to an ADH-like effect.
Laboratory findings: Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatinine phosphokinase.

Treatment:

Measurement of the plasma level to confirm PARTID-200 poisoning and to ascertain the size of the overdose.
Evacuation of the stomach, gastric lavage undertaken within 1 hour after ingestion, and oral administration of repeated doses of activated charcoal.
Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations:
Hypotension: administer dopamine or dobutamine iv.
Disturbance of cardiac rhythm: to be handled on an individual basis.
Convulsions: administer a benzodiazepine (e.g. diazepam) or another anti-epileptic, e.g. phenobarbitone (with caution because of increased respiratory depression), or paraldehyde.

Hyponatraemia (water intoxication): fluid restriction and slow and careful NaCl 0,9 % infusion iv. These measures may be useful in preventing brain damage. Charcoal haemoperfusion has been recommended. Forced diuresis, haemodialysis, and peritoneal dialysis have been reported to be not effective. Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

IDENTIFICATION:

White to off white, biconvex, circular, uncoated tablet.

PRESENTATION:

Partid comes in 15 or 84 tablets in silver bioxilary oriented polypropylene patient ready packs.

28, 50, 56, 84 or 100 tablets in clear transparent PVC/aluminium foil blister strips.

100 tablets in milky-white high-density polyethylene containers.

STORAGE INSTRUCTIONS:

Store below 25 ^{o}C, in well-closed containers. Keep out of reach of children.

REGISTRATION NUMBER:

37/2.5/0482

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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