SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

GULF CARBAMAZEPINE 200 (Tablets)

COMPOSITION:

Each tablet contains 200 mg of carbamazepine.

Inactive ingredients: Starch, sodium starch glycollate, gelatine, silicon dioxide, magnesium stearate

PHARMACOLOGICAL CLASSIFICATION:

A. 2.5 Anticonvulsant, including anti-epileptics

PHARMACOLOGICAL ACTION:

Carbamazepine possesses both anticonvulsant and psychotropic properties.

Pharmacokinetics:

Carbamazepine is absorbed slowly and erratically after oral administration.

Peak concentrations in plasma usually are observed 6 to 10 hours after a single oral dose, but may be delayed by as much as 24 hours.

Carbamazepine distributes rapidly into all tissues. Approximately 75 % of carbamazepine binds to plasma proteins and concentrations in the cerebrospinal fluid appear to correspond to the concentration of free medicine in plasma.

The predominant pathway of metabolism involves conversion to the 10,11-epoxide. This metabolite is as active as the parent compound, and its concentrations in plasma and brain may reach 50 % of those of carbamazepine. The 10,11-epoxide is metabolised further to inactive compounds, which are excreted in the urine principally as glucuronides.

Hepatic CYP3A4 is primarily responsible for biotransformation of carbamazepine. Carbamazepine induces CYP2C and CYP3A, thus enhancing the metabolism of medicines degraded by these enzymes.

Carbamazepine induces its own metabolism so that the plasma half- life may be considerably reduced after repeated dosage. The mean plasma half-life of carbamazepine on repeated dosage is about 12 to 24 hours; it appears to be considerably shorter in children than in adults. The pharmacokinetics of carbamazepine is affected by use with other antiepileptics (see "Interactions").

INDICATIONS:

Gulf Carbamazepine 200 is indicated for the treatment of:

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

Gulf Carbamazepine 200 is not effective in atypical or generalised absence seizures (petit mal) or myoclonic seizures.

CONTRA INDICATIONS:

- Known hypersensitivity to carbamazepine, tricyclic antidepressants or any of the inactive ingredients of **Gulf Carbamazepine 200.**
- 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 **Gulf Carbamazepine 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 low or decreases during treatment, the patient should be closely monitored and **Gulf Carbamazepine 200** should be discontinued if there is any evidence of significant bone-marrow depression.

Gulf Carbamazepine 200 should be withdrawn if signs and symptoms suggestive of severe skin reactions e.g. Stevens-Johnson syndrome or Lyell syndrome appears.

Gulf Carbamazepine 200 may trigger hypersensitivity reactions, including multi-organ hypersensitivity reactions, which can affect the skin, liver, haematopoietic organs and lymphatic system or other organs, either individually or together in the context of a systemic reaction. If signs and symptoms of hypersensitivity reactions occur, **Gulf Carbamazepine 200** should be withdrawn.

Gulf Carbamazepine 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, **Gulf Carbamazepine 200** should be withdrawn.

Complete urinanalysis 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 **Gulf Carbamazepine 200** plasma concentrations.

*Medicines that may have a resultant increase in **Gulf Carbamazepine 200** plasma levels and associated toxicity, when co-administered*:

Isoniazid, verapamil, diltiazem, viloxazine, fluoxetine, fluvoxamine, cimetidine, acetazolamide, danazol, desipramine, nicotinamide, nefazodone, macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin), azoles (e.g. itraconazole, miconazole, ketoconazole, fluconazole), loratadine

*Medicines that may have a resultant decrease in **Gulf Carbamazepine 200** plasma levels when co-administered:*

Phenobarbitone, phenytoin, primidone, theophylline, methsuximide, phensuximide, rifampicin, cisplatin, doxorubicin, clonazepam, St Johns Wort (hypericum perforation).

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

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

Isotretinoin – alters the bioavailability and/or clearance of **Gulf Carbamazepine 200** and its active metabolite carbamazepine-10, 11-epoxide.

Medicines that may have a resultant decrease in their plasma concentration when used concomitantly with **Gulf Carbamazepine 200**:

Clonazepam, ethosuximide, primidone, valproic acid, alprazolam, corticosteroids (e.g. prednisolone, dexamethasone), ciclosporin, doxycycline, felodipine, haloperidol, imipramine, methadone, oral contraceptives, theophylline, oral anticoagulants (warfarin), felbamate, lamotrigine, zonisamide, tiagabine, topiramate, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine), clozapine.

Plasma phenytoin levels have been reported both to be raised and to be lowered by **Gulf Carbamazepine 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 **Gulf Carbamazepine 200** and lithium, or metoclopramide, or neuroleptics (haloperidol, thioridazine) may lead to neurotoxicity (with latter combination even in the presence of "therapeutic plasma levels").

HIV-protease inhibitors (e.g. indinavir, saquinavir, ritonavir, nelfinavir, lopinavir) – reduced plasma concentration of HIV-protease inhibitors may result when given concomitantly with **Gulf Carbamazepine 200.** Ritonavir – plasma concentrations of **Gulf Carbamazepine 200** may be increased

Co-administration of **Gulf Carbamazepine 200** with efavirenz (a selective non-nucleoside reverse transcriptase inhibitor [NNRTI]) – decreased **Gulf Carbamazepine 200** AUC, Cmax and Cmin due to CYP3A4 induction.

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

Gulf Carbamazepine 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 **Gulf Carbamazepine 200**; it is therefore advisable to avoid alcohol during treatment.

PREGNANCY AND LACTATION:

Gulf Carbamazepine 200 is excreted into breast milk, 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's 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 **Gulf Carbamazepine 200**, or if the problem of initiating treatment with **Gulf Carbamazepine 200** arises during pregnancy, the medicines 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 **Gulf Carbamazepine 200** increases this risk has been reported, although conclusive evidence from controlled studies with **Gulf Carbamazepine 200** monotherapy is lacking. However there are rare reports of developmental disorders and malformations, including spina bifida in association with **Gulf Carbamazepine 200**.

Adequate folic acid supplementation is recommended before and during pregnancy to counteract the risk of neural tube defects in the offspring of women on **Gulf Carbamazepine 200**. 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 recommended. There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal **Gulf Carbamazepine 200** and other concomitant anticonvulsant medicine use. A few cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal **Gulf Carbamazepine 200** use. These reactions may represent a neonatal withdrawal syndrome.

DOSAGE AND DIRECTIONS FOR USE:

The tablets should be taken during or after meals with a little liquid. The tablets should not be chewed. When the patient is transferred from another anticonvulsant to **Gulf Carbamazepine 200**, the dosage of the first should be reduced gradually. Due to medicine interactions and different antiepileptic medicine pharmacokinetics, the dosage of **Gulf Carbamazepine 200** should be selected with caution in elderly patients.

Epilepsy:

When possible, **Gulf Carbamazepine 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 **Gulf Carbamazepine 200** is added to existing antiepileptic therapy, this should be added gradually while the dosage of the other antiepileptic medicine(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 1200 mg daily in divided doses. Doses up to 1600 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 1000 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 1600 mg daily in divided doses (three to four times a day) may be required. When pain relief has been achieved, the dosage should be gradually reduced to the minimum effective dose.

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

Mania and treatment of (bipolar) affective disorders:

An initial dose of 400 mg daily in divided doses is recommended which may be increased to a dose of up to 1600 mg daily, the usual maintenance dose range being 400 to 600 mg daily in divided doses. In

mania the dosage should be increased rather quickly, whereas small dosage increments are recommended for the treatment of bipolar disorders in order to provide optimal tolerability.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

At the initial stages of therapy with **Gulf Carbamazepine 200**, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reactions occur frequently e.g. central nervous system (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 dose 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 (see "Dosage and Directions for Use").

Adverse reactions are ranked under heading of frequency, as frequent or less frequent, the most frequent first,

Nervous system disorders:

Frequent: Dizziness, ataxia, drowsiness, fatigue, headache

Less frequent: Abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics) nystagmus, orofacial dyskinesia, eye movement disturbances, speech disorders (e.g. dysarthria or slurred speech). Choreoathetosis, peripheral neuropathy, paresthesia, muscle weakness and paresis, neuroleptic malignant syndrome (rare, but life-threatening, idiosyncratic reaction to a neuroleptic medication. The syndrome is characterized by fever, muscular rigidity, altered mental status, and autonomic dysfunction)

The causative role of **Gulf Carbamazepine 200** in inducing or contributing to the development of a neuromalignant syndrome, especially in conjunction with neuroleptics, is unclear.

Psychiatric disorders:

Less frequent: Hallucinations (visual or acoustic), depression, anorexia, restlessness, aggression, agitation, confusional state, activation of psychosis (particularly in elderly patients or if the initial dose is too high)

Skin and subcutaneous tissue disorders:

Frequent: Allergic dermatitis or skin reactions, urticaria which may be severe, exfoliative dermatitis and erythroderma

Less frequent: Systemic lupus erythematosus-like syndrome, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, hyperhydrosis (sweating), hair loss. Cases of hirsutism have been reported, but the causal relationship is not clear

Blood and Lymphatic system disorders:

Frequent: Leucopenia, thrombocytopenia, eosinophilia

Less frequent: Leucocytosis, lymphadenopathy, folic acid deficiency, agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, reticulocytosis, and possibly haemolytic anaemia

Hepatobiliary disorders:

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

Less frequent: Elevated transaminases, hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, jaundice, granulomatous hepatitis, hepatic failure

Gastrointestinal disorders:

Frequent: Nausea, vomiting, dryness of the mouth

Less frequent: Diarrhoea or constipation, abdominal pain, taste disturbances, glossitis, stomatitis, pancreatitis

Immune system disorders:

Less frequent: A delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, and lymphadenopathy, pseudo 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

Endocrine disorders:

Frequent: Oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological disorders

Less frequent: Increase in prolactin with or without clinical symptoms such as galactorrhoea, gynaecomastia. Abnormal thyroid function tests: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone. Bone metabolism disorders (decrease in plasma calcium and blood 25-OH-cholecalciferol), leading to osteomalacia/osteoporosis. Elevated levels of cholesterol, including HDL cholesterol and triglycerides

Eye disorders:

Frequent: diplopia, accommodation disorders (e.g. blurred vision)

Less frequent: Lenticular opacities, conjunctivitis, increased intraocular pressure

Ear and labyrinth disorders:

Less frequent: Hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception

Cardiac disorders:

Less frequent: Cardiac conduction disorders, hypertension or hypotension, bradycardia, dysrhythmia, atrioventricular block with syncope, circulatory collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thrombo-embolism (e.g. pulmonary embolism)

Respiratory, thoracic and mediastinal disorders:

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

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthralgia, muscle pain, muscle spasms

Renal and urinary disorders:

Less frequent: Interstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria and blood urea/azotaemia), urinary frequency, urinary retention, sexual disturbances/impotence

Reproductive system disorders:

Less frequent: Spermatogenesis abnormal (with decreased sperm count and/or motility)

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, and rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult his medical practitioner immediately.

Medical supervision during treatment is essential.

Abnormalities of liver function and jaundice have been associated with long-term treatment.

Mild skin reactions including isolated macular or maculopapular exanthema, are mostly transient and not hazardous. 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.

Gulf Carbamazepine 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, history of adverse haematological reactions to other medicines or to patients who have had interrupted courses of therapy with **Gulf Carbamazepine 200.**

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

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

As **Gulf Carbamazepine 200** has mild anticholinergic activity, care should be observed in patients with glaucoma or increased intra-ocular pressure.

Breakthrough bleeding has been reported in woman taking oral oestrogen-containing contraceptives, the reliability of oral contraceptives may be adversely affected by **Gulf Carbamazepine 200**. Women of childbearing age should be advised to consider using alternative birth control while taking **Gulf Carbamazepine 200.**

Tolerance may develop to some of the untoward effects of **Gulf Carbamazepine 200**. These effects can be minimised by gradual increase in dosage and adjustment to the lowest effective maintenance dosage.

Abrupt withdrawal of **Gulf Carbamazepine 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 antiepileptic.

Ability to drive or operate machinery:

Reaction time may be decreased by **Gulf Carbamazepine 200**. The patient's safety as a road user or operator of machines may be impaired in consequence.

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 and anuria, fluid retention, water intoxication due to ADH-like effect

Laboratory findings:

Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatinine phosphokinase

Treatment:

Measurement of the plasma level to confirm **Gulf Carbamazepine 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 dobutamine IV.

Disturbance of cardiac rhythm: to be handled on an individual basis.

Convulsions: administer a benzodiazepine (e.g. diazepam) or another antiepileptic e.g. phenobarbitone (with caution because of increased respiratory depression).

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 ineffective.

Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption should be anticipated.

IDENTIFICATION:

White, round, flat tablet with a central break-line on one side

PRESENTATION:

Push through clear PVC/silver Al blister strips in a pack of 28, 30 or 100 tablets in a printed unit carton.

White HDPE containers of 30, 100, 500 or 1000 tablets

STORAGE INSTRUCTIONS:

Store at or below 25 °C in a cool, dry place. Do not remove blisters from unit carton until required for use.

Protect from light and moisture. Keep the HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

43/2.5/0840

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

Gulf Drug Company (Pty) Ltd

22 Burnside Drive

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

27/07/2012

NOVARTIS

SCHEDULING STATUS S3

PROPRIETARY NAME (AND DOSAGE FORM)

TEGRETOL 200® Tablets
TEGRETOL CR 200® Divitabs
TEGRETOL CR 400® Divitabs
TEGRETOL S® Suspension

COMPOSITION

Tablets: 200 mg carbamazepine.
Controlled release, film-coated divisible tablets: 200 mg and 400 mg carbamazepine.
Suspension: 100 mg/5 mL carbamazepine with methylparaben 0,12 % m/v, propylparaben 0,03 % m/v and 0,1 % m/v sorbic acid as preservatives. (See *warnings*).

PHARMACOLOGICAL CLASSIFICATION

A 2.5 Anticonvulsants, including anti-epileptics.

PHARMACOLOGICAL ACTION

Carbamazepine possesses both anticonvulsant and psychotropic properties.

Pharmacokinetics:

Carbamazepine is absorbed relatively slowly from the tablet. Peak plasma concentrations of the unchanged active substance are attained 4 to 24 hours after a single oral dose.
TEGRETOL CR 200 tablets yield a mean peak plasma concentration of the unchanged substance within 12 hours. With the suspension, mean peak plasma concentrations are attained within 2 hours.
There is no clinically relevant difference between the quantity of active substance absorbed from the various dosage forms.
The CR tablets provide more stable plasma concentrations throughout the day, thereby allowing twice daily dosage.
Carbamazepine becomes bound to plasma proteins to the extent of 70 to 80 %. The concentration of unchanged substance in the saliva reflects the non-protein-bound portion present in the plasma (20 to 30 %).
The elimination half-life of unchanged carbamazepine in the plasma averages approximately 36 hours following a single oral dose, whereas after repeated administration, which leads to auto-induction of hepatic enzymes, it averages only 16 to 24 hours, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing anti-epileptic agents, half-life values averaging 9 to 10 hours have been found.
Only 2 to 3 % of the dose, whether given singly or repeatedly, is excreted in the urine in unchanged form. The primary metabolite is the pharmacologically active 10,11-epoxide.
Carbamazepine is metabolized 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 P 450 has been identified as the major isoform responsible for the formation of carbamazepine-10,11 epoxide from carbamazepine. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. Other important biotransformation products are various monohydroxylated compounds, as well as the N-glucuronide of carbamazepine produced by uridine diphosphate glucuronosyl transferase 2B7.
The steady-state plasma concentrations of carbamazepine considered as 'therapeutic range' varies considerably interindividually: for the majority of patients a range between 4–12 µg/mL corresponding to 17–50 µmol/L has been reported.

INDICATIONS

Epilepsy with motor and psychic manifestations:
- psychomotor or temporal-lobe epilepsy
- generalized tonic-clonic seizure
- mixed forms of seizures
- complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalization.

Acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.
Idiopatic trigeminal neuralgia.
Idiopathic glossopharyngeal neuralgia
TEGRETOL is suitable for both monotherapy and combination therapy.
TEGRETOL is usually not effective in absences (petit mal) and myoclonic seizures. (See *precautions for use*).

CONTRA-INDICATIONS

- Known hypersensitivity to TEGRETOL, or structurally related drugs e.g.. tricyclic antidepressants, or any other component of the formulation.
- Patients with atrioventricular block,
- Patients with a history of bone-marrow depression,
- Patients with a history of porphyrias (e.g.. acute intermittent porphyria, variegate porphyria)
- The use of TEGRETOL is contra-indicated in combination with monoamine-oxidase inhibitors (MAOIs) (see *Interactions*)
- The active substance of TEGRETOL passes into the breast milk (about 25 – 60 % of plasma concentration). Mothers taking TEGRETOL should not breastfeed their infants.

WARNINGS

Pregnancy:

Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening. (See *Pregnancy and Lactation*)

Carcinogenicity:

In rats treated with TEGRETOL for two years, the incidence of tumours of the liver was found to be increased. There is, however, no evidence to indicate that this observation has any significance relative to the therapeutic use of the medicine.

Haematological effects:

Aplastic anaemia and agranulocytosis have been reported. Transient or persistent decreased platelet or white blood cell counts may occur; in the majority of cases these effects prove transient. Complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline and periodically thereafter. If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored. TEGRETOL should be discontinued if any evidence of significant bone-marrow depression appears.

Dermatological effects:

If signs and symptoms suggestive of severe skin reactions e.g.. Stevens-Johnson syndrome, or Lyell syndrome appear, TEGRETOL should be withdrawn at once.

Hypersensitivity:

TEGRETOL may trigger hypersensitivity reactions, including multi-organ hypersensitivity reactions, which can affect the skin, liver, haematopoietic organs and lymphatic system or other organs, either individually or together in the context of a systemic reaction. If signs and symptoms of hypersensitivity reactions occur, TEGRETOL should be withdrawn.

Seizures:

TEGRETOL should be used with caution in patients with mixed seizures, which includes absences, either typical or atypical. In all these conditions, TEGRETOL may exacerbate seizures. In the event of exacerbation of seizures, TEGRETOL should be discontinued.

Hepatic function:

Liver function tests should also be undertaken periodically. If allergic skin reactions occur, if the platelet count diminishes, if tests reveal deterioration in liver function, or if any serious adverse symptoms develop, TEGRETOL should be withdrawn.

Renal function:

Baseline and periodic complete urinalysis and blood urea determinations are recommended.

Others:

TEGRETOL S suspension contains parahydroxybenzoates which may cause allergic reactions (possibly delayed). It also contains sorbitol and, therefore, should not be administered to patients with rare hereditary problems of fructose intolerance.

INTERACTIONS

Cytochrome P4503A (CYP3A4) is the main enzyme catalyzing formation of the active metabolite carbamazepine-10,11-epoxide. Co-administration of inhibitors of CYP 3A4 may result in increased plasma concentrations, which could induce adverse reactions.
Co-administration of CYP 3A4 inducers might increase the rate of TEGRETOL metabolism, thus leading to a potential decrease in carbamazepine serum level and potential decrease in the therapeutic effect.
TEGRETOL 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 metabolised by CYP3A4 by induction of their metabolism.
Agents that may raise carbamazepine and/or carbamazepine-10,11-epoxide plasma levels
Since raised plasma carbamazepine and/or carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g.. dizziness, drowsiness, ataxia, diplopia), the dosage of TEGRETOL should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below.
Analgesics, anti-inflammatory drugs: dextropropoxyphene, ibuprofen
Androgens: danazol
Antibiotics: macrolide antibiotics (e.g.. erythromycin, troleandomycin, josamycin, clarithromycin).
Antidepressants: possibly desipramine, fluoxetine, fluvoxamine, Nefazodone, viloxazine.
Antiepileptics: vigabatrin.
Antifungals: azoles (e.g.. itraconazole, ketoconazole, fluconazole, voriconazole).
Antihistamines: loratadine, terfenadine.
Antipsychotics: loxapine, olanzapine, quetiapine.
Antituberculosis: isoniazid.
Carbonic anhydrase inhibitors: acetazolamide.
Cardiovascular drugs: diltiazem, verapamil.
Gastrointestinal drugs: possibly cimetidine, omeprazole.
Muscle relaxants: oxybutynin, dantrolene.
Platelet aggregation inhibitors: ticlopidine.
Other interactions: nicotinamide (in adults, only in high dosage).
Loxapine, quetiapine, primidone, valproic acid and valpromide were reported to increase concentration of the active metabolite carbamazepine-10,11-epoxide.

Agents that may decrease carbamazepine and/or carbamazepine-10,11-epoxide plasma levels:

The dose of TEGRETOL may have to be adjusted when used concomitantly with the substances described below.
Antiepileptics: felbamate, methsuximide, oxcarbazepine, phenobarbitone, phensuximide, phenytoin, primidone, progabide, and, although the data are partly contradictory, possibly also clonazepam, valproic acid or valpromide.
Antineoplasics: cisplatin or doxorubicin.
Antituberculosis: rifampicin
Bronchodilatators or anti-asthma drugs: theophylline, aminophylline.
Dermatological drugs: isotretinoin.
Other interactions: herbal preparations containing St John's wort (*Hypericum perforatum*)

Effect of TEGRETOL on plasma levels of concomitant agents:

TEGRETOL may lower the plasma level, or diminish – or even abolish – the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirements:
Analgesics, anti-inflammatory agents: methadone, paracetamol, phenazone (antipyrine).
Antibiotics: doxycycline.
Anticoagulants: oral anticoagulants (e.g.. warfarin, phenprocoumon, dicoumarol and acenocoumarol).
Antidepressants: bupropion, citalopram, trazodone, tricyclic antidepressants (e.g.. imipramine, amitriptyline, nortriptyline, clomipramine). The use of TEGRETOL is contra-indicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering TEGRETOL MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits. (see *Contra-indications*)
Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, primidone, tiagabine, topiramate, valproic acid, zonisamide. Plasma phenytoin levels have been reported both to be raised and to be lowered by TEGRETOL, and there have been rare reports of an increase in plasma mephenytoin levels.
Antineoplasics: imatinib
Antipsychotics: clozapine, haloperidol and bromperidol, quetiapine.
Anxiolytics: alprazolam
Bronchodilatators or anti-asthma drugs: theophylline
Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered)
Cardiovascular drugs: calcium channel blockers (dihydropyridine group) e.g.. felodipine, digoxin
Corticosteroids: corticosteroids (e.g.. prednisolone, dexamethasone)
Immunosuppressants: ciclosporin, everolimus
The level of serum folic acid should be observed during anticonvulsant therapy since TEGRETOL may enhance the metabolism of folic acid.

Combinations to be taken into consideration:

Concomitant use of TEGRETOL and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.
Combined use of TEGRETOL and lithium, or metoclopramide on the one hand, and TEGRETOL and neuroleptics (haloperidol, thioridazine) on the other, may lead to increased neurological adverse reactions (with the latter combination even in the presence of 'therapeutic plasma levels').
Concomitant medication with TEGRETOL and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia.
TEGRETOL may antagonise the effects of non-depolarizing muscle relaxants (e.g.. pancuronium); their dosage may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.
TEGRETOL may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol during treatment.

PREGNANCY AND LACTATION

Pregnancy:

Safety of TEGRETOL in pregnancy has not been demonstrated conclusively.
Patients should consult their doctor for guidance on the use of TEGRETOL during pregnancy.
Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. The possibility that TEGRETOL increases this risk has been reported, although conclusive evidence from controlled studies with TEGRETOL monotherapy is lacking. However there are rare reports of developmental disorders and malformations, including spina bifida and hypospadias in association with TEGRETOL.
- If women receiving TEGRETOL become pregnant or plan to become pregnant, or if the problem of initiating treatment with TEGRETOL arises during pregnancy, the drug's potential benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy.
- In women of childbearing age TEGRETOL should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic drugs is greater than in those of mothers receiving the individual drugs as monotherapy.
- Minimum effective doses should be given and monitoring of plasma levels is recommended.
- During pregnancy, an effective antiepileptic treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus

Folic acid deficiency is known to occur in pregnancy. Anti-epileptic drugs have been reported to aggravate folic acid deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy.
In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K_1 be given to the mother during the last weeks of pregnancy as well as to the neonate.
There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal TEGRETOL 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 TEGRETOL 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.

Fertility:

There have been reports of impaired male fertility and/or abnormal spermatogenesis

Lactation:

Carbamazepine passes into breast milk.
Safety in breastfeeding has not been demonstrated. Excessive somnolence and allergic skin reactions has been reported in breastfed children.

DOSAGE AND DIRECTIONS FOR USE

The tablets and the suspension (to be shaken before use) may be taken during, after, or between meals. The TEGRETOL CR DIVITABS should be swallowed unchewed with a little liquid.
TEGRETOL S (one measure=5 mL=100 mg) is particularly suitable for infants and small children and for elderly patients as the liquid form affords easier and more flexible dosage.
As a result of slow, controlled release of the active substance from the CR tablets these are designed to be taken in a twice daily dosage regimen.
Since a given dose of TEGRETOL S suspension produces higher peak levels than the same dose in tablet form, therapy should be started with low doses and should be increased slowly to avoid adverse reactions.
Dosage should be as low as is consistent with a satisfactory effect. Blood plasma levels can be used to help establish the optimum dose. Usually the optimum therapeutic plasma levels range between 4 and 12 µg / mL (16 to 50 µmol / L). When the patient is transferred from another anticonvulsant drug to TEGRETOL, the dosage of the first should be reduced gradually.
In switching patients from TEGRETOL tablets to suspension, the same daily dose should be given in smaller, more frequent doses. Switching patients form conventional tablets to CR tablets: clinical experience shows that in some patients the dosage in the form of CR tablets may need to be increased.
Due to drug interactions and different anti-epileptic drug pharmacokinetics, the dosage of TEGRETOL should be selected with caution in elderly patients.

Dosage:
When possible, TEGRETOL should be prescribed as monotherapy.
Treatment should be initiated with a low daily dosage, to be slowly increased until an optimal effect is obtained.
Determination of plasma levels may help in establishing the optimum dosage.
When TEGRETOL is added to existing anti-epileptic therapy, this should be done gradually while maintaining, or if necessary adapting, the dosage of the other anti-epileptic(s). (*See interactions*)

Usual dosage for adults:
Initially, 100 mg to 200 mg once or twice a day, followed by a slow increase until usually at a level of 400 mg twice or three times a day, the best response is obtained. In some instances 1 600 mg in 3 to 4 divided doses may be necessary.

Usual dosage for children:
For children aged 4 years or less, a starting dose of 20 – 60 mg/day, increasing by 20 – 60 mg every second day, has been recommended. For children over the age of 4 years, therapy may begin with 100 mg/day, increasing at weekly intervals by 100 mg.

Maintenance dosage:
10 – 20 mg/kg body weight daily in divided doses, e.g..
Age up to 1 year: 100 – 200 mg daily (=1–2 measures of suspension)
1 to 5 years: 200 – 400 mg daily (=2 x 1–2 measures of suspension)
6 to 10 years: 400 – 600 mg daily (=2–3 x 2 measures of suspension)
11 to 15 years: 600 – 1000 mg daily (=3–3½ x 2–3 measures of suspension)

Trigeminal Neuralgia:
The initial dosage of 200 – 400 mg should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 – 4 times daily, in some instances it may necessitate 1 600 mg daily). The dosage should then be gradually reduced to the lowest possible maintenance level. In elderly and particularly sensitive patients (see *Side-effects and special precautions*) an initial dosage of 100 mg twice a day is recommended.

Acute mania and maintenance treatment of (bipolar) affective disorders:
Dosage range:
Approximately 400 – 1 600 mg daily, the usual dosage being 400 – 600 mg daily given in 2 – 3 divided doses. In acute mania, the dosage should be increased rather quickly, whereas small dosage increments are recommended for maintenance therapy of bipolar disorders in order to ensure optimal tolerability.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS
Particularly at the start of treatment with TEGRETOL, 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.
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 the plasma levels.
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10)); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000), including isolated reports.

Table 1

	Blood and lymphatic system disorders
Very common:	leukopenia.
Common:	thrombocytopenia, eosinophilia.
Rare:	leukocytosis, lymphadenopathy, folic acid deficiency.
Very rare:	agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, reticulocytosis, and possibly haemolytic anaemia.
	Immune system disorders
Rare:	a delayed multiorgan hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, 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).
Very rare:	aseptic meningitis, with myoclonus and peripheral eosinophilia; anaphylactic reaction, angioneurotic oedema.
	Endocrine disorders
Common:	oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusion, neurological disorders.
Very rare:	Blood prolactin increased with or without clinical manifestations such as galactorrhoea, gynecomastia, abnormal thyroid function tests: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol), leading to osteomalacia/ osteoporosis, increased blood cholesterol, including HDL cholesterol, and triglycerides.
	Psychiatric disorders
Rare:	hallucinations (visual or auditory), depression, anorexia, restlessness, aggression, agitation, confusional state.
Very rare:	activation of psychosis (particularly in elderly patients or if initial dosage is too high).
	Nervous system disorders
Very common:	dizziness, ataxia, drowsiness, fatigue.
Common:	headache, diplopia, accommodation disorders (e.g.. blurred vision).
Uncommon:	abnormal involuntary movements (e.g.. tremor, asterixis, dystonia, tics); nystagmus.
Rare:	orofacial dyskinesia, eye movement disturbances, speech disorders (e.g.. dysarthria, slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, and paresis.
Very rare:	taste disturbances, neuroleptic malignant syndrome.
	Eye disorders
Very rare:	Lenticular opacities, conjunctivitis, intraocular pressure increased.
	Ear and labyrinth disorders
Very rare:	hearing disorders, e.g.. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
	Cardiac disorders
Rare:	cardiac conduction disorders; hypertension or hypotension.
Very rare:	bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thromboembolism (e.g.. pulmonary embolism).
	Respiratory, thoracic and mediastinal disorders
Very rare:	pulmonary hypersensitivity characterized e.g.. by fever, dyspnoea, pneumonitis or pneumonia.
	Gastrointestinal disorders
Very common:	nausea, vomiting.
Common:	Dry mouth.
Uncommon:	diarrhoea, constipation.
Rare:	abdominal pain.
Very rare:	glossitis, stomatitis, pancreatitis.
	Hepatobiliary disorders
Very common:	increased gamma-GT (due to hepatic enzyme induction), usually not clinically relevant.
Common:	increased blood alkaline phosphatase.
Uncommon:	increased transaminases.
Rare:	hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type jaundice.
Very rare:	granulomatous hepatitis.
	Skin and subcutaneous tissue disorders
Very common:	dermatitis allergic, urticaria which may be severe.
Uncommon:	exfoliative dermatitis and erythroderma.
Rare:	systemic lupus erythematosus, pruritus.
Very rare:	Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, hyperhydrosis, hair loss.
	Musculoskeletal, connective tissue and bone disorders
Very rare:	arthralgia, muscle pain, muscle spasms.
	Renal and urinary disorders
Very rare:	interstitial nephritis, renal failure, renal impairment (e.g.. albuminuria, haematuria, oliguria, and blood urea increased/azotemia), urinary frequency, urinary retention.
	Reproductive system
Very rare:	sexual dysfunction/impotence, spermatogenesis abnormal (with decreased sperm count and/or motility).

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 TEGRETOL. The patient's safety as a road-user or operator of machines may be impaired in consequence.
Mild skin reactions, e.g.. 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.
TEGRETOL should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic, or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with TEGRETOL. The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.
TEGRETOL has shown mild anti-cholinergic activity; patients with increased intra-ocular pressure should therefore be closely observed during therapy.
Breakthrough bleeding has been reported in women taking hormonal contraceptives; the reliability of hormonal contraceptives may be adversely affected by TEGRETOL, and women of childbearing age should be advised to consider using alternative forms of birth control while taking TEGRETOL.
Tolerance may develop to some of the untoward effects of TEGRETOL. These effects can be minimized by gradual increase in dosage and adjustment to the lowest effective maintenance dosage.
Abrupt withdrawal of TEGRETOL may precipitate seizures. If treatment with TEGRETOL has to be withdrawn abruptly in a patient with epilepsy, the change-over to the new anti-epileptic compound should be made under cover of a suitable drug (e.g.. diazepam or phenytoin).

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, at times 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 creatine phosphokinase.

Treatment:
No specific antidote. Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm TEGRETOL poisoning and to ascertain the size of the overdose.
Evacuation of the stomach, gastric lavage, and administration of activated charcoal. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations:
Hypotension: administer dopamine or dobutamine i.v.
Disturbances 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 i.v. 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
TEGRETOL 200®
White, round tablet, flat on both sides, with slightly bevelled edges. Imprinted "CG" on one side, and "G/K" with a score on the other. Diameter approximately 9,0 mm. Thickness approximately 3,7 mm.
TEGRETOL CR 200®
Beige-orange, ovaloid-shaped, convex, film-coated tablets, scored on both sides. Imprinted "C/G" on one side and "H/C" on the other. Approximately 12,2 x 5,6 mm and approximately 5,0 mm thick.
TEGRETOL CR 400®
Brownish-orange, ovaloid-shaped, convex, film-coated tablets, scored on both sides. Imprinted "CG/CG" on one side and "ENE/ENE" on the other. Approximately 16,7 x 6,7 mm and approximately 6,0 mm thick.
TEGRETOL S®
A milky white, viscous suspension with the odour and taste of caramel.

PRESENTATION
TEGRETOL 200® is supplied as tablets in packs of 100.
TEGRETOL CR 200® and TEGRETOL CR 400® are supplied in packs of 30.
TEGRETOL S® is supplied in bottles of 250 mL.

STORAGE INSTRUCTIONS
TEGRETOL 200
Store below 30 °C and protect from moisture.
TEGRETOL CR 200 and TEGRETOL CR 400
Store below 25 °C and protect from moisture.
TEGRETOL S
Store below 30 °C and protect from light.
KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS
TEGRETOL 200® B1530 (Act 101/1965)
TEGRETOL CR 200® V/2.5/321
TEGRETOL CR 400® V/2.5/322
TEGRETOL S® D/2.5/204

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
NOVARTIS SOUTH AFRICA (PTY) LTD
72 Steel Road
Spartan
Kempton Park
1619

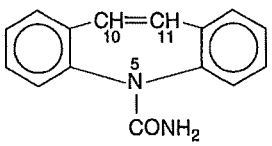
DATE OF PUBLICATION OF THIS PACKAGE INSERT
26 June 2009

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Product proprietary name: Gulf Carbamazepine 200
Dosage form and strength: Tablet – Carbamazepine 200 mg

zure agent in 1974. It has been employed since the 1960s for the treatment of trigeminal neuralgia. It is now considered to be a primary drug for the treatment of partial and tonic-clonic seizures.

Chemistry. Carbamazepine is related chemically to the tricyclic antidepressants. It is a derivative of iminostilbene with a carbamyl group at the 5 position; this moiety is essential for potent antiseizure activity. The structural formula of carbamazepine is:



CARBAMAZEPINE

Pharmacological Effects. Although the effects of carbamazepine in animals and humans resemble those of phenytoin in many ways, the two drugs exhibit important differences. Carbamazepine has been found to produce therapeutic responses in manic-depressive patients, including some in whom lithium carbonate is not effective. Further, carbamazepine has antidiuretic effects that are sometimes associated with reduced concentrations of antidiuretic hormone (ADH) in plasma. The mechanisms responsible for these effects of carbamazepine are not clearly understood.

Mechanism of Action. Like phenytoin, carbamazepine limits the repetitive firing of action potentials evoked by a sustained depolarization of mouse spinal cord or cortical neurons maintained *in vitro* (McLean and Macdonald, 1986b). This appears to be mediated by a slowing of the rate of recovery of voltage-activated Na^+ channels from inactivation. These effects of carbamazepine are evident at concentrations in the range of therapeutic drug levels in CSF in humans. The effects of carbamazepine are selective at these concentrations, in that there are no effects on spontaneous activity or on responses to iontophoretically applied GABA or glutamate. The carbamazepine metabolite, 10,11-epoxycarbamazepine, also limits sustained repetitive firing at therapeutically relevant concentrations, suggesting that this metabolite may contribute to the antiseizure efficacy of carbamazepine.

Pharmacokinetic Properties. The pharmacokinetics of carbamazepine are complex. They are influenced by its limited aqueous solubility and by the ability of many antiseizure drugs, including carbamazepine itself, to increase their conversion to active metabolites by hepatic oxidative enzymes.

Carbamazepine is absorbed slowly and erratically after oral administration. Peak concentrations in plasma usually are observed 4 to 8 hours after oral ingestion, but may be delayed by as much as 24 hours, especially following the administration of a large dose. The drug distributes rapidly into all tissues. Approximately 75% of carbamazepine binds to plasma proteins and concentrations in the CSF appear to correspond to the concentration of free drug in plasma.

The predominant pathway of metabolism in humans involves conversion to the 10,11-epoxide. This metabolite is as active as the parent compound in various animals, and its concentrations in plasma and brain may reach 50% of those of carbamazepine, especially during the concurrent administration of phenytoin or phenobarbital. The 10,11-epoxide is metabolized further to inactive compounds, which are excreted in the urine principally as glucuronides. Carbamazepine also is inactivated by conjugation and hydroxylation. Hepatic CYP3A4 is primarily responsible for biotransformation of carbamazepine. Carbamazepine induces CYP2C, CYP3A, and UGT, thus enhancing the metabolism of drugs degraded by these enzymes. Of particular importance in this regard are oral contraceptives, which are also metabolized by CYP3A4.

Toxicity. Acute intoxication with carbamazepine can result in stupor or coma, hyperirritability, convulsions, and respiratory depression. During long-term therapy, the more frequent untoward effects of the drug include drowsiness, vertigo, ataxia, diplopia, and blurred vision. The frequency of seizures may increase, especially with overdosage. Other adverse effects include nausea, vomiting, serious hematological toxicity (aplastic anemia, agranulocytosis), and hypersensitivity reactions (dermatitis, eosinophilia, lymphadenopathy, splenomegaly). A late complication of therapy with carbamazepine is retention of water, with decreased osmolality and concentration of Na^+ in plasma, especially in elderly patients with cardiac disease.

Some tolerance develops to the neurotoxic effects of carbamazepine, and they can be minimized by gradual increase in dosage or adjustment of maintenance dosage. Various hepatic or pancreatic abnormalities have been reported during therapy with carbamazepine, most commonly a transient elevation of hepatic transaminases in plasma in 5% to 10% of patients. A transient, mild leukopenia occurs in about 10% of patients during initiation of therapy and usually resolves within the first 4 months of continued treatment; transient thrombocytopenia also has been noted. In about 2% of patients, a persistent leukopenia may develop that requires withdrawal of the drug. The initial concern that aplastic anemia might be a frequent complication of long-term therapy with carbamazepine has not materialized. In most cases, the administration of multiple drugs or the presence of another underlying disease has made it difficult to establish a causal relationship. In any event, the prevalence of aplastic anemia appears to be about 1 in 200,000 patients who are treated with the drug. It is not clear whether

.8 Undesirable effects

Particularly at the start of treatment with Tegretol, 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.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10) common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports.

Blood and lymphatic system disorders	
Very common :	Leucopenia
Common	Thrombocytopenia, eosinophilia.
Rare	Leucocytosis, lymphadenopathy, folic acid deficiency.
Very rare	Agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, reticulocytosis, and possibly haemolytic anaemia.
Immune system disorders	
Rare:	A delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests, occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, colon).
Very rare:	Aseptic meningitis, with myoclonus and peripheral eosinophilia; anaphylactic reaction, angioneurotic oedema.
Endocrine disorders	
Common :	Oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders.
Very rare:	Blood prolactin increased with or without clinical symptoms such as galactorrhoea, gynaecomastia, abnormal thyroid function tests; decreased l-thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased

	blood thyroid stimulating hormone, usually without clinical manifestations, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol), leading to osteomalacia /osteoporosis, increased blood cholesterol, including HDL cholesterol and triglycerides.
Psychiatric disorders	
Rare:	Hallucinations (visual or auditory), depression, anorexia, restlessness, aggression, agitation, confusional state.
Very rare:	Activation of psychosis.
Nervous system disorders	
Very common:	Dizziness, ataxia, drowsiness, fatigue.
Common:	Headache, diplopia, accommodation disorders (e.g. blurred vision).
Uncommon:	Abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics); nystagmus.
Rare:	Orofacial dyskinesia, eye movement disturbances, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, muscle weakness, and paresis
Very rare:	Taste disturbances, neuroleptic malignant syndrome
Eye disorders	
Very rare:	lenticular opacities, conjunctivitis, intraocular pressure increased
Ear and labyrinth disorders	
Very rare:	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
Cardiac disorders	
Rare:	Cardiac conduction disorders, hypertension or hypotension.
Very rare:	Bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thrombo-embolism (e.g. pulmonary embolism).
Respiratory , thoracic and mediastinal disorders	
Very rare:	Pulmonary hypersensitivity characterised e.g. by fever, dyspnoea, pneumonitis or pneumonia.
Gastro-intestinal disorders	
Very common:	Nausea, vomiting.
Common:	Dry mouth, with suppositories rectal irritation may occur.
Uncommon:	Diarrhoea, constipation.
Rare:	Abdominal pain

Very rare:	Glossitis, stomatitis, pancreatitis.
Hepatobiliary disorders	
Very common:	Increased-gamma-GT (due to hepatic enzyme induction), usually not clinically relevant.
Common:	Increased blood alkaline phosphatase.
Uncommon:	Increased transaminases.
Rare:	Hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, jaundice.
Very rare:	Granulomatous hepatitis. Hepatic failure.
Skin and subcutaneous tissue disorders:	
Very common:	Dermatitus allergic, urticaria, which may be severe.
Uncommon:	Exfoliative dermatitis and erythroderma.
Rare:	Systemic lupus erythematosus, pruritus.
Very rare:	Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, hyperhydrosis, hair loss. Very rare cases of hirsutism have been reported, but the causal relationship is not clear.
Musculoskeletal, connective tissue and bone disorders	
Very rare:	Arthralgia, muscle pain, muscle spasms.
Renal and urinary disorders	
Very rare:	Interstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria and blood urea/ azotaemia), urinary frequency, urinary retention, sexual disturbances/impotence.
Reproductive System	
Very rare:	Spermatogenesis abnormal (with decreased sperm count and/or motility).

STANDARDISED PACKAGE INSERT FOR CARBAMAZAPINE.

(Based on the controlled release tablet formulation, each tablet containing 200 mg or 400 mg of carbamazepine.)

This is the minimum information required. It is the applicant's responsibility to add new safety information as soon as it becomes available and make any other necessary amendments, with supporting references.

DATE OF COUNCIL APPROVAL: 07 APRIL 2006

SCHEDULING STATUS:

S3

PROPRIETARY NAMES AND DOSAGE FORMS:

(MRF 1: First page of dossier)

COMPOSITION:

(Regulation 9 of Act 101 of 1965, as amended)

PHARMACOLOGICAL CLASSIFICATION:

A. 2.5 Anticonvulsants, including anti-epileptics

Pharmacological Action:

Carbamazepine possesses both anticonvulsant and psychotropic properties.

Pharmacokinetics:

Absorption of carbamazepine is slow and variable following oral administration with peak plasma concentrations (9.3μg/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:

(TRADE NAME) 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.

(TRADE NAME) 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 **(TRADE NAME)** should be counselled, regarding the risk of malformations and should be offered antenatal screening.

Aplastic anaemia and agranulocytosis have been reported. Transient thrombocytopaenia 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 **(TRADE NAME)** should be discontinued if there is any evidence of significant bone-marrow depression.

(TRADE NAME) should be withdrawn if signs and symptoms suggestive of severe skin reactions eg. Stevens-Jonson syndrome appear.

(TRADE NAME) 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, **(TRADE NAME)** 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 **(TRADE NAME)** plasma concentrations.

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

Agents that may have a resultant decrease in **(TRADE NAME)** *plasma levels when co-administered:*

Phenobarbitone, phenytoin, primidone, theophylline, methsuximide, 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 **(TRADE NAME)** serum concentration associated with an increase in carbamazepine-10, 11-epoxide concentration.

Isotretinoin – alters the bioavailability and/or clearance of **(TRADE NAME)** and its active metabolite carbamazepine-10, 11-epoxide.

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

Plasma phenytoin levels have been reported both to be raised and to be lowered by **(TRADE NAME)** 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 **(TRADE NAME)** 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 **(TRADE NAME)** was co-administered with a diuretic eg. hydrochlorothiazide or furosemide.

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

Alcohol may exacerbate the CNS side effects of **(TRADE NAME)**, it is therefore advisable to avoid alcohol during treatment.

PREGNANCY AND LACTATION:

(TRADE NAME) is excreted into breast milk 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 offsprings 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 **(TRADE NAME)**, or if the problem of initiating treatment with **(TRADE NAME)** 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 **(TRADE NAME)** increases this risk has been reported, although conclusive evidence from controlled studies with **(TRADE NAME)** monotherapy is lacking. However there are rare reports of developmental disorders and malformations, including spina bifida in association with **(TRADE NAME)**.

Adequate folic acid supplementation is recommended before and during pregnancy to counteract the risk of neural tube defects in the offspring of women on antiepileptics.

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 a few cases of neonatal seizures and/or respiratory depression associated with maternal **(TRADE NAME)** 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 **(TRADE NAME)** 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 **(TRADE NAME)**, the dosage of the first should be reduced gradually.

Due to medicine interactions and different anti-epileptic medicine pharmacokinetics, the dosage of **(TRADE NAME)** should be selected with caution in elderly patients.

Epilepsy:

When possible, **(TRADE NAME)** 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 **(TRADE NAME)** is added to existing anti-epileptic therapy, this should be added gradually while the dosage of the other antiepileptic agent(s) is maintained or adapted (see **"Interactions"**).

***Adults*:** An initial dose of 100mg to 200mg 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 600mg daily in divided doses may occasionally be necessary.

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

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

Trigeminal neuralgia:

An initial dose of 200 to 400mg 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.

Mania, and treatment of (bipolar) affective disorders:

An initial dose of 400 mg daily in divided doses is recommended which may be increased to a dose of up to 1 600 mg daily, the usual maintenance dose range being 400 to 600 mg daily in divided doses. In mania the dosage should be increased rather quickly, whereas small dosage increments are recommended for treatment of bipolar disorders in order to provide optimal tolerability.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side Effects:

The side effects should be formatted according to system organ class and CIOMS frequency categories. If frequency data are not available, "frequent" and "less frequent" may be used. The applicant should indicate the references consulted for frequency categories and where frequencies are unknown the applicant should indicate references consulted and use the following wording, "the following side effects have been reported and frequencies are unknown", under each system organ class (Refer to WHOART or MeDra).

At the initial stages of therapy with **(TRADE NAME)**, 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:

Dizziness, ataxia, drowsiness, fatigue. Headache, diplopia, accommodation disorders (e.g. blurred vision). Abnormal involuntary movements (e.g. tremor, asterixis, dystonia, 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:

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:

Allergic skin reactions, urticaria which may be severe. Exfoliative dermatitis and erythroderma. Systemic lupus erythematosus-like syndrome, pruritus. Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, sweating, hair loss. Hirsutism have been reported, but the causal relationship is not clear.

Haematological:

Leucopaenia, thrombocytopaenia, eosinophilia. leucocytosis, lymphadenopathy, folic acid deficiency. agranulocytosis, aplastic anaemia, pure red cell aplasia, megaloblastic anaemia, acute intermittent porphyria, reticulocytosis, and possibly haemolytic anaemia.

Liver:

Elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant. Elevated alkaline phosphatase, elevated transaminases hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, jaundice. granulomatous hepatitis.

Gastrointestinal:

Nausea, vomiting, dryness of the mouth, diarrhoea or constipation, abdominal pain, glossitis, stomatitis, pancreatitis.

Hypersensitivity reactions:

A delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leucopaenia, 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:

Disturbances of cardiac conduction, hypertension or hypotension. bradycardia, arrhythmias, AV block with syncope, collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thrombo-embolism.

Endocrine/Metabolic:

Oedema, fluid retention, weight increase, hyponatraemia and reduced plasma osmolality due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities, increase in prolactin with or without clinical manifestations such as galactorrhea, 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.

Genitourinary:

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

Special senses:

Taste disturbances, lens opacities, conjunctivitis, hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.

Musculoskeletal:

Arthralgia, muscle pain or cramp.

Respiratory:

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 **(TRADE NAME)**. The patient's safety as a road user or operator of machines may be impaired in consequence.

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.

(TRADE NAME) 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 **(TRADE NAME)**.

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 **(TRADE NAME)** 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 **(TRADE NAME)**, and women of childbearing age should be advised to consider using alternative birth control while taking **(TRADE NAME)**.

Tolerance may develop to some of the untoward effects of **(TRADE NAME)**. These effects can be minimized by gradual increase in dosage and adjustment to the lowest effective maintenance dosage.

Abrupt withdrawal of **(TRADE NAME)** 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 **(TRADE NAME)** 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 i.v.

Disturbance of cardiac rhythm: to be handled on an individual basis.

Convulsions: administer a benzodiazepine (eg. diazepam) or another anti-epileptic, eg. phenobarbitone (with caution because of increased respiratory depression), or paraldehyde.

Hyponatraemia (water intoxication): fluid restriction and slow and careful NaCl 0,9 % infusion i.v. 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:

(MRF 1: Part 3F of dossier)

PRESENTATION:

(MRF 1: Part 3D of dossier)

STORAGE INSTRUCTIONS:

(MRF 1: Part 3G of dossier)

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

(Regulation 9 Act 101 of 1965 as amended)

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

(Regulation 9 Act 101 of 1965 as amended)

DATE OF PUBLICATION OF THIS PACKAGE INSERT: