AE PKG

TEGRETOL®-XR

(carbamazepine extended release tablets)

NDA 20-234

Anticonvulsant

Category 3S

Volume 1 of 1

NDA 20-234

MAR 25 1996

Ciba Pharmaceuticals
Ciba-Geigy Corporation
Attention: Adrian L. Birch
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Birch:

Please refer to your new drug application of October 31, 1991, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tegretol®-XR (carbamazepine extended release tablets) 100 mg, 200 mg, and 400 mg tablets.

We acknowledge receipt of the following amendments:

December 28, 1995	January 29, 1996	January 20, 1996
February 6, 1996	February 8, 1996	February 9, 1996
March 15, 1996		

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on February 6, 1996. Accordingly, the application is approved effective on the date of this letter.

As you were notified in the telephone conversation of February 21, 1996, between Steven D. Hardeman, of this Division and Ms. Mara Stiles of your firm, the Office of Clinical Pharmacology and Biopharmaceutics has established revised Q values for the interim dissolution specifications. The revised values are:

3 hours
6 hours
12 hours
24 hours

Please note that we have incorporated the wider ranges that you have requested with the exception of the lower limit of the 12-hour point and the upper limit of the 6-hour point. We believe that it is necessary to maintain the lower limit of the 12-hour point at 65% to ensure that patients receive the expected total dose. (If the tablet is not sufficiently dissolved at 12 hours, it is possible that it could be eliminated before the full dose is released). It should be noted that with these revised specifications, none of the 20 production batches and none of the 11 developmental lots for which you have submitted data would potentially fail based on having

mean values outside of the proposed specifications. In addition, only six of the production batches would require testing to the S2 or S3 level.

Once you have generated the requested data on 12 tablets of each strength from three consecutive production batches, please forward the result to the Agency so that final specifications can be established.

We note that you have committed to conduct and complete a revalidation for each of the three strengths of Tegretol®-XR, processed at target conditions, including granulation, compression, coating, laser drilling and drying operations.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. We note your commitment to continued cooperation in this matter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Regulatory Management Officer, at (301) 594-2777.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Tegretol®

C96-9 (Rev. 2/96)
665400

carbamazepine USP

Chewable Tablets of 100 mg - red-speckled, pink
Tablets of 200 mg - pink
Suspension of 100 mg/5mL

Tegretol®-XR

(carbamazepine extended-release tablets)
100 mg, 200 mg, 400 mg

Prescribing Information

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

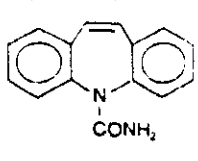
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, XR tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5mL (teaspoon). Its chemical name is 5*H*-dibenz[b,f]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Tablets: Colloidal silicon dioxide, D&C Red No. 30 Aluminum Lake (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, *and sucrose (chewable tablets only).* Suspension: *Citric acid,* FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum. Tegretol-XR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200-mg tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Tegretol has demonstrated anticonvulsant properties *in rats and mice with electrically and* chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of Tegretol, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several in vivo animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of Tegretol has not been established.

Pharmacokinetics

In clinical studies, Tegretol suspension, conventional tablets, and XR tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the XR tablet slightly slower, than the conventional tablet. The bioavailability of the XR tablet was 89% compared to suspension. Following a b.i.d. dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Following a b.i.d. dosage regimen, Tegretol-XR tablets afford steady-state plasma levels comparable to conventional Tegretol tablets given q.i.d., when administered at the same total mg daily dose. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 µg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 µg/mL. In polytherapy, the concentration of Tegretol and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see PRECAUTIONS, Drug Interactions). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4-5 hours after administration of conventional Tegretol tablets and 3-12 hours after administration of Tegretol-XR tablets. The CSF/serum ratio is 0.22, similar to the 75% unbound Tegretol in serum. Because Tegretol induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, decreasing to 12-17 hours on repeated doses. Tegretol is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from Tegretol. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol.

The pharmacokinetic parameters of Tegretol disposition are similar in children and in adults. However, there is a poor correlation between plasma concentrations of carbamazepine and Tegretol dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an anticonvulsant in animal screens) in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10-15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

Epilepsy

Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (*psychomotor, temporal lobe*). *Patients with* these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal)
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia

Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical *grounds its use with monoamine oxidase inhibitors is not recommended. Before administration* of Tegretol, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular *pressure should be closely observed during therapy.*

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General

Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with Tegretol.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Interference with some pregnancy tests has been reported.

Drug Interactions

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to, the following:

Agents That May Affect Tegretol Plasma Levels

CYP 3A4 inhibitors inhibit Tegretol metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include

cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clanthromycin, fluoxetine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketaconazole, itraconazole, verapamil, valproate.*

CYP 3A4 inducers can increase the rate of Tegretol metabolism. Drugs that have been shown, or that would be expected, to decrease plasma carbamazepine levels include

cisplatin, doxorubicin HCl, felbamate, rifampin, phenobarbital, phenytoin, primidone, theophylline.

*increased levels of the active 10,11-epoxide

†decreased levels of carbamazepine and increased levels of the 10,11-epoxide

Effect of Tegretol on Plasma Levels of Concomitant Agents

Increased levels: clomipramine HCl, phenytoin, primidone

Tegretol induces hepatic CYP activity. Tegretol causes, or would be expected to cause, decreased levels of the following:

acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, valproate, warfarin.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at dose of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C

Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

In humans, transplacental passage of Tegretol is rapid (30-60 minutes), and the drug accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lung.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery

The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers

Tegretol and its epoxide metabolite are transferred to breast milk. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for Tegretol and about 0.5 for the epoxide. The estimated doses given to the newborn during breast feeding are in the range of 2-5 mg daily for Tegretol and 1-2 mg daily for the epoxide.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Substantial evidence of Tegretol's effectiveness for use in the management of children with epilepsy (see Indications for specific seizure types) is derived from clinical investigations performed in adults and from studies in several in vitro systems which support the conclusion that (1) the pathogenetic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports the conclusion that the generally accepted therapeutic range of total carbamazepine in plasma (4-12 mcg/mL) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No long-term data from clinical trials is available.

Geriatric Use

No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, *erythema multiforme and nodosum*, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Tegretol® carbamazepine USP
Tegretol®-XR (carbamazepine extended-release tablets)

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, > 60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

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

Respiration: Irregular breathing, respiratory depression.

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

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

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taappropriate steps to diminish absorption. If these measures cannot be implemented without on the spot, the patient should be transferred at once to a hospital, while ensuring that functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the the stomach should be repeatedly irrigated, especially if the patient has also consumed alco

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacem transfusion is indicated in severe poisoning in small children.

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

Hypotension, Shock: Keep the patient s legs raised and administer a plasma expander. If b pressure fails to rise despite measures taken to increase plasma volume, use of vasoac substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especiall children), hypotension, and coma. However, barbiturates should not be used if drugs that in monoamine oxidase have also been taken by the patient either in overdosage or in re therapy (within 1 week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temp ture, pupillary reflexes, and kidney and bladder function should be monitored for several d

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depres develops, the following recommendations are suggested: (1) stop the drug, (2) perform c CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine bio immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibod (2) ^{59}Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on mar and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemogl electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and ther for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the indivi patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate co is achieved, the dosage may be reduced very gradually to the minimum effective le Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same d given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teasp q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients shoul converted by administering the same number of mg per day in smaller, more frequent doses b.i.d. tablets to t.i.d. suspension).

Tegretol-XR is an extended-release formulation for twice-a-day administration. When verting patients from Tegretol conventional tablets to Tegretol-XR, the same total daily mg o of Tegretol-XR should be administered. **Tegretol-XR tablets must be swallowed whole never crushed or chewed.** Tegretol-XR tablets should be inspected for chips or cra Damaged tablets should not be consumed.

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age — Initial: Either 200 mg b.i.d. for tablets and tablets, or 1 teaspoon q.i.d. for suspension (400 mg/day). Increase at weekly intervals by ad up to 200 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the d formulations until the optimal response is obtained. Dosage generally should not exceed mg daily in children 12-15 years of age, and 1200 mg daily in patients above 15 years of Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** A dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age — Initial: Either 100 mg b.i.d. for tablets or XR tablets, o teaspoon q.i.d. for suspension (200 mg/day). Increase at weekly intervals by adding up to mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formula until the optimal response is obtained. Dosage generally should not exceed 1000 mg d ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Children under 6 years of age — Initial: 10-20 mg/kg/day b.i.d. or t.i.d. as tablets, or q.i suspension. Increase weekly to achieve optimal clinical response administered t.i.d. or ***Maintenance:*** Ordinarily, optimal clinical response is achieved at daily doses below 35 m If satisfactory clinical response has not been achieved, plasma levels should be measur determine whether or not they are in the therapeutic range. No recommendation regardin safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When a to existing anticonvulsant therapy, the drug should be added gradually while the other ant vulsants are maintained or gradually decreased, except phenytoin, which may have t increased (see PRECAUTIONS, Drug Interactions, and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, either 100 mg b.i.d. for tablets or XR tablets, or 1/2 teaspoon q.i.d. for suspension, for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours for tablets or XR tablets, or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg daily. *Maintenance:* Control of pain can be maintained in most patients with 400-800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg — round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100 ..... NDC 58887-052-30
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 58887-052-32

Do not store above 86°F (30°C). *Protect from light and moisture. Dispense in tight, light-resistant container (USP).*

Tablets 200 mg — capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

Bottles of 100 ..... NDC 58887-027-30
Bottles of 1000 ..... NDC 58887-027-40
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 58887-027-32

Do not store above 86°F (30°C). *Protect from moisture. Dispense in tight container (USP).*

XR Tablets 100 mg — round, yellow, coated (imprinted T on one side and 100 mg on the other), release portal on one side

Bottles of 100 ..... NDC 0083-0061-30
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0083-0061-32

XR Tablets 200 mg — round, pink, coated (imprinted T on one side and 200 mg on the other) release portal on one side

Bottles of 100 ..... NDC 0083-0062-30
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0083-0062-32

XR Tablets 400 mg — round, brown, coated (imprinted T on one side and 400 mg on the other) release portal on one side

Bottles of 100 ..... NDC 0083-0060-30
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0083-0060-32

Store at controlled room temperature 15°-30°C (59°-86°F). *Protect from moisture. Dispense in tight container (USP).*

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Suspension 100 mg/5 mL (teaspoon) — yellow-orange, citrus-vanilla flavored

Bottles of 450 mL ..... NDC 58887-019-76

Shake well before using.

Do not store above 86°F (30°C). *Dispense in tight, light-resistant container (USP).*

Dosage Information

Indication	Initial Dose			Subsequent Dose			Maximum Daily Dose		
	Tablet*	XR†	Suspension	Tablet*	XR†	Suspension	Tablet*	XR†	Suspension
Epilepsy									
Under 6 yr	10-20 mg/kg/day b.i.d. or t.i.d.		10-20 mg/kg/day q.i.d.	Increase weekly to achieve optimal clinical response, t.i.d. or q.i.d.		Increase weekly to achieve optimal clinical response, t.i.d. or q.i.d.	35 mg/kg/24 hr (see Dosage and Administration section above)		35 mg/kg/24 hr (see Dosage and Administration section above)
6-12 yr	100 mg b.i.d. (200 mg/day)	100 mg q.i.d. (200 mg/day)	1/2 tsp q.i.d. (200 mg/day)	Add up to 100 mg/day at weekly intervals, t.i.d. or q.i.d.	Add 100 mg/day at weekly intervals, b.i.d.	Add up to 1 tsp (100 mg)/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hr		
Over 12 yr	200 mg b.i.d. (400 mg/day)	200 mg b.i.d. (400 mg/day)	1 tsp q.i.d. (400 mg/day)	Add up to 200 mg/day at weekly intervals, t.i.d. or q.i.d.	Add up to 200 mg/day at weekly intervals, b.i.d.	Add up to 2 tsp (200 mg)/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hr (12-15 yr) 1200 mg/24 hr (>15 yr) 1600 mg/24 hr (adults, in rare instances)		
Trigeminal Neuralgia	100 mg b.i.d. (200 mg/day)	100 mg b.i.d. (200 mg/day)	1/2 tsp q.i.d. (200 mg/day)	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 2 tsp (200 mg)/day in increments of 50 mg (1/2 tsp) q.i.d.	1200 mg/24 hr		

*Tablet = Chewable or conventional tablets

†XR = Tegretol®-XR extended-release tablets

P000000 665400

C96-9 (Rev. 2/9

Tegretol Suspension Manufactured by
Ciba-Geigy Canada, Ltd.
Dorval, Quebec, Canada

CIBA

Ciba-Geigy Corporation
Pharmaceuticals Division
Summit, NJ 07901

Labeling: N(AF)
NDA No: [illegible] Rc'd. [illegible]
Reviewed by: Steve Hardman
2/21/96

Tegretol®

carbamazepine USP

C96-9 (Rev. 2/96)
665400

Chewable Tablets of 100 mg - red-speckled, pink
Tablets of 200 mg - pink
Suspension of 100 mg/5mL

Tegretol®-XR

(carbamazepine extended-release tablets)
100 mg, 200 mg, 400 mg

Prescribing Information

WARNING
APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO *PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.*

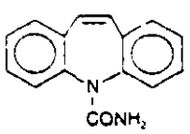
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine *USP*, is an *anticonvulsant and specific analgesic for trigeminal* neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, XR tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5mL (teaspoon). Its chemical name is 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Tablets: Colloidal silicon dioxide, D&C Red No. 30 Aluminum Lake (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum. Tegretol-XR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200-mg tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Tegretol has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and

(Note to Sponsor: Changes are in REDLINE, requests for information in *italics*)

Chewable Tablets of 100 mg - red-speckled, pink
Tablets of 200 mg - pink
Suspension of 100 mg/5mL

Tegretol®-XR
(carbamazepine extended-release tablets)
100 mg, 200 mg, 400 mg

Prescribing Information

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(figure)

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Mechanism of Action

Tegretol has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of Tegretol, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several in vivo animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of Tegretol has not been established.

Pharmacokinetics

In clinical studies, Tegretol suspension, conventional tablets, and XR tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the XR tablet slightly slower, than the conventional tablet. The bioavailability of the XR tablet was 89% compared to suspension. Following a b.i.d. dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Following a b.i.d. dosage regimen, Tegretol-XR tablets afford steady-state plasma levels comparable to conventional Tegretol tablets given q.i.d., when administered at the same total mg daily dose. Tegretol in blood is 76%

bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/mL. In polytherapy, the concentration of Tegretol and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see **PRECAUTIONS, Drug Interactions**). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4-5 hours after administration of conventional Tegretol tablets, and 3-12 hours after administration of Tegretol-XR tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound Tegretol in serum. Because Tegretol induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from Tegretol. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol.

The pharmacokinetic parameters of Tegretol disposition are similar in children to those in adults. However, there is poor correlation between plasma concentrations of carbamazepine and Tegretol dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10-15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

Epilepsy

Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.

2. Generalized tonic-clonic seizures (grand mal).

3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia

Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia. Beneficial results have also been reported in glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General

Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see **INDICATIONS AND USAGE**).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with Tegretol.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see **DOSAGE AND ADMINISTRATION**).

Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see **CLINICAL PHARMACOLOGY**) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Interference with some pregnancy tests has been reported.

Drug Interactions:

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to, the following:

Agents That May Affect Tegretol Plasma Levels

CYP 3A4 inhibitors inhibit Tegretol metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or that would be expected, to increase plasma carbamazepine levels include:

> cimetidine, danazol, diltiazem, macrolides (erythromycin, troleandomycin, clarithromycin), fluoxetine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, verapamil, ketoconazole, itraconazole, valproate*
>
> *{Note to sponsor: Please provide justification for the inclusion of niacinamide and nicotinamide in the preceeding section, i.e. literature references.}*

CYP3A4 inducers can increase the rate of Tegretol metabolism. Drugs that have been shown for that would be expected , to decrease plasma carbamazepine levels include:

cisplatin, doxorubicin HCl, felbamate,† phenobarbital, rifampin, phenytoin, primidone, theophylline

*increased levels of the active 10,11-epoxide
†decreased levels of carbamazepine and increased levels of the 10,11-epoxide

{Note to sponsor: Please provide justification for the inclusion of cisplatin, doxorubicin HCl, and theophylline in the preceeding section, i.e. literature references.}

Effect of Tegretol on Plasma Levels of Concomitant Agents

Increased Levels: *clomipramine HCl, phenytoin, primidone*

Tegretol induces hepatic CYP activity. Tegretol causes, or would be expected to cause, decreased levels of the following:

acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phensuximide, phenytoin, *theophylline, valproate, warfarin*

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C

Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). *In reproduction studies in rats, nursing offspring* demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

In humans, transplacental passage of Tegretol is rapid (30-60 minutes), and the drug is accumulated in

fetal tissues, with higher levels found in liver and kidney than in brain and lung.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery

The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers

[Note to sponsor: Please supply the evidence that supports the following italicized statement]

Tegretol and its epoxide metabolite are transferred to breast milk. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for Tegretol and about 0.5 for the epoxide. The estimated doses given to the newborn during breast feeding are in the range of 2-5 mg daily for Tegretol and 1-2 mg daily for the epoxide.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Substantial evidence of Tegretol's effectiveness for use in the management of children with epilepsy (see Indications for specific seizure types) is derived from clinical investigations performed in adults and from studies in several in vitro systems which support the conclusion that (1) the pathogenetic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports a conclusion that the generally accepted therapeutic range of total carbamazepine in plasma (i.e., 4-12 mcg/mL) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No longer-term data from clinical trials is available.

Geriatric Use

No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see **boxed WARNING**), the skin, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue,

blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

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

Respiration: Irregular breathing, respiratory depression.

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

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

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

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

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within 1 week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe - ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Tegretol-XR is an extended-release formulation for twice-a-day administration. When converting patients from Tegretol conventional tablets to Tegretol-XR, the same total daily mg dose of Tegretol-XR should be administered. **Tegretol-XR tablets must be swallowed whole and never crushed or chewed.** Tegretol-XR tablets should be inspected for chips or cracks. Damaged tablets should not be consumed.

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age - Initial: Either 200 mg b.i.d. for tablets and XR tablets, or 1 teaspoon q.i.d. for suspension (400 mg/day). Increase at weekly intervals by adding up to 200 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily. ***Children 6-12 years of age - Initial:*** Either 100 mg b.i.d. for tablets or XR tablets, or 1/2 teaspoon q.i.d. for suspension (200 mg/day). Increase at weekly intervals by adding up to 100 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Children under 6 years of age - Initial: 10-20 mg/kg/day b.i.d. or t.i.d. as chewable tablets, or q.i.d. as suspension. Increase weekly to achieve optimal clinical response administered t.i.d. or q.i.d. ***Maintenance:*** Ordinarily optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see **PRECAUTIONS, Drug Interactions, and Pregnancy Category C**).

Trigeminal Neuralgia (see **INDICATIONS AND USAGE**)

Initial: On the first day, either 100 mg b.i.d. for tablets or XR tablets, or 1/2 teaspoon q.i.d. for suspension, for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours for tablets or XR tablets, or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400-800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg - round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 58887-052-30
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 58887-052-32

Do not store above 86°F (30°C). *Protect from light and moisture. Dispense in tight, light-resistant container (USP).*

Tablets 200 mg - capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

Bottles of 100	NDC 58887-027-30
Bottles of 1000	NDC 58887-027-40
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 58887-027-32

Do not store above 86°F (30°C). *Protect from moisture. Dispense in tight container (USP).*

XR Tablets 100 mg - round, yellow, coated (imprinted T on one side and 100 mg on the other), release portal on one side

Bottles of 100	NDC 0083-0061-30
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0083-0061-32

XR Tablets 200 mg - round, pink, coated (imprinted T on one side and 200 mg on the other), release portal on one side

Bottles of 100..... NDC 0083-0062-30
Unit Dose (blister pack)
Box of 100 (strips of 10)..... NDC 0083-0062-32

XR Tablets 400 mg - round, brown, coated (imprinted T on one side and 400 mg on the other), release portal on one side
Bottles of 100..... NDC 0083-0060-30
Unit Dose (blister pack)
Box of 100 (strips of 10)..... NDC 0083-0060-32

Store at controlled room temperature 15°-30°C (59°-86°F). *Protect from moisture. Dispense in tight container (USP).*

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Suspension 100 mg/5 mL (teaspoon) - yellow-orange, citrus-vanilla flavored
Bottles of 450 mL..... NDC 58887-019-76

Shake well before using.

Do not store above 86°F (30°C). *Dispense in tight, light-resistant container (USP).*

dcc: c:\docs\...\tol\labeling.fda

Hardman

JAN 2 2 1996

NDA 20-234

Ciba-Geigy Corporation
Attention: Adrian L. Birch
556 Morris Avenue
Summit, NJ 07901-1398

Dear Mr. Birch:

Please refer to your October 31, 1991 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tegretol®-XR (carbamazepine extended release tablets) 100 mg, 200 mg, and 400 mg tablets.

We acknowledge receipt of your amendments dated:

February 20, 1992	February 27, 1992	March 27, 1992
May 11, 1992	June 10, 1992	August 3, 1992
August 25, 1992	September, 9, 1992	November 5, 1992
November 17, 1992	January 19, 1993	February 23, 1993
March 3, 1993	June 10, 1993	June 23, 1993
August 16, 1993	October 18, 1993	November 15, 1993
December 14, 1993	March 9, 1994	March 29, 1994
June 3, 1994	June 8, 1994	August 16, 1994
July 18, 1995	October 4, 1995	October 6, 1995
October 16, 1995	October 17, 1995	October 24, 1995
November 21, 1995	November 22, 1995	December 11, 1995

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following requests and comments:

1. Please submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft labeling. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

2. As you are aware, our inspection revealed that, contrary to your assertion in the NDA, not all plasma samples in Protocol 91012 were analyzed in some plasma samples were analyzed at the We request that you provide documentation

of the site(s) of analysis of all plasma samples for all patients in the study, or at least documentation (if true) that all plasma samples from a given patient were analyzed at a single site.

3. Our Division of Biopharmaceutics has established interim dissolution specifications for testing dissolution properties of Tegretol®-XR 100, 200, and 400 mg tablets. The dissolution specifications are as follows:

Apparatus:
Medium:
Volume:
Sampling time:

Q values: 3 hours
6 hours
12 hours
24 hours

We request that you submit dissolution profiles of 12 tablets each from three consecutive production lots, upon approval, to set the final dissolution specifications for this product.

4. The report (Ref 24 and 25) on the correlation between *in vivo* absorption rate and *in vitro* dissolution rate is very interesting and encouraging. The use of plasma concentration-time data from protocol 32 should be analyzed further before the correlations may be used to allow minor changes in formulations, manufacturing processes and site changes.

5. Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

6. Please note that the establishment inspections have not yet been completed. We cannot approve this application until satisfactory Establishment Inspection Reports have been received for all facilities involved in the manufacture and packaging of the bulk drug and the drug product.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit sixteen copies of the printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Steven D. Hardeman, R.Ph.
Regulatory Management Officer
Telephone: (301) 594-2777

Sincerely yours,

Robert Temple, 1/15/96

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

D. Summary Basis of Approval - NONE

Revised 4/29/96

EXCLUSIVITY SUMMARY for NDA # 20-234 SUPPL # _____

Trade Name Tegretol-XR **Generic Name** Carbazepine
Applicant Name Ciba-Geigy **HFD-** 120

Approval Date 3/25/96

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /✓/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /__/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /__/ NO /✓/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   NDA consists of 5 bioavailability studies and a single efficacy study performed in non-human primates.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 16-608 Tegretol

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__/ NO /✓/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # ____ YES /___/ ! NO /___/ Explain: _____

! _____

Investigation #2 !

IND # ____ YES /___/ ! NO /___/ Explain: _____

! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Steven D. Hardman 4/29/96
Signature Date
Title: RPM

4/29/96
Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

G. Pediatric Checklist - N/A since not NME

NDA 20-234
TEGRETOL-XR
(carbamazepine, USP)

Basel Pharmaceuticals
Division of CIBA-GEIGY Corporation

ITEM 13 - SUPPLEMENTAL PATENT INFORMATION

1. Active Ingredient	carbamazepine
2. Strengths	100 mg, 200 mg & 400 mg
3. Trade Name	Tegretol-XR
4. Dosage Form, Route of Administration	Oral tablet, sustained release
5. Applicant Firm Name	Division of CIBA-GEIGY Corporation
6. NDA Number	20-234
7. Approval Date	Pending
8. Exclusivity- Date First ANDA Could Be Approved and Length of Exclusivity	New Dosage Form, New Strength Three years from effective approval
9. Applicable Patent Numbers and Expiration Date of Each	1. US 5,284,662, expiring Feb. 8, 2011

[Note to Sponsor: Changes are in RED LINE]

Chewable Tablets of 100 mg - red-speckled, pink
Tablets of 200 mg - pink
Suspension of 100 mg/5mL

Tegretol®-XR
(carbamazepine extended-release tablets)
100 mg, 200 mg, 400 mg

Prescribing Information

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, XR tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5mL (teaspoon). Its chemical name is 5*H*-dibenz[b,f]azepine-5-carboxamide, and its structural formula is

(figure)

Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Tablets: Colloidal silicon dioxide, D&C Red No. 30 Aluminum Lake (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum. Tegretol-XR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200-mg tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Tegretol has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of Tegretol, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of Tegretol has not been established.

Pharmacokinetics

In clinical studies, Tegretol suspension, conventional tablets, and XR tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the XR tablet slightly slower, than the conventional tablet. The bioavailability of the XR tablet was 89% compared to suspension. Following a b.i.d. dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Following a b.i.d. dosage regimen, Tegretol-XR tablets afford steady-state plasma levels comparable to conventional Tegretol tablets given t.i.d. when administered at the same total mg daily doses. Tegretol in blood is 76%

bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/mL. In polytherapy, the concentration of Tegretol and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see **PRECAUTIONS, Drug Interactions**). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4-5 hours after administration of conventional Tegretol tablets, and 3-12 hours after administration of Tegretol-XR tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound Tegretol in serum. Because Tegretol induces its own metabolism, the half-life is also variable. The time course of autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from Tegretol. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol.

The pharmacokinetic parameters of Tegretol disposition are similar in children to those in adults. However, there is poor correlation between plasma concentrations of carbamazepine and Tegretol dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10-15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated

INDICATIONS AND USAGE

Epilepsy

Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.

2. Generalized tonic-clonic seizures (grand mal).

3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia

Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia. Beneficial results have also been reported in glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General

Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see **INDICATIONS AND USAGE**).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with Tegretol.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see **DOSAGE AND ADMINISTRATION**).

Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see **CLINICAL PHARMACOLOGY**) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Interference with some pregnancy tests has been reported.

Drug Interactions:

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to, the following:

Agents That May Affect Tegretol Plasma Levels

CYP3A4 inhibitors inhibit Tegretol metabolism and can thus increase plasma carbamazepine levels. [illegible] include:

cimetidine, danazol, diltiazem, macrolides (erythromycin, troleandomycin, clarithromycin), fluoxetine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, verapamil, ketoconazole, valproate*

[redacted]

cisplatin, doxorubicin HCl, felbamate,[1] phenobarbital, [redacted], phenytoin, primidone, theophylline

*increased levels of the active 10,11-epoxide
[1]decreased levels of carbamazepine and increased levels of the 10,11-epoxide

Effect of Tegretol on Plasma Levels of Concomitant Agents

Increased Levels: clomipramine HCl, phenytoin, primidone

Tegretol induces hepatic CYP activity. As a result, Tegretol causes, or would be expected to cause, decreased levels of the following:

acetaminophen, alprazolam, clonazepam, dicumarol, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, valproate, warfarin

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C

Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

In humans, transplacental passage of Tegretol is rapid (30-60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lung.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that

there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery

The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers

[Note to sponsor: Please supply the evidence that supports the following italicized statement]

Tegretol and its epoxide metabolite are transferred to breast milk. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for Tegretol and about 0.5 for the epoxide. The estimated doses given to the newborn during breast feeding are in the range of 2-5 mg daily for Tegretol and 1-2 mg daily for the epoxide.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Substantial evidence of Tegretol's effectiveness for use in the management of children with epilepsy (see Indications for specific seizure types) is derived from clinical investigations performed in adults and from studies in several in vitro systems which support the conclusion that (1) the pathogenetic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports a conclusion that the generally accepted therapeutic range of total carbamazepine in plasma (i.e., 4-12 mcg/mL) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No longer-term data from clinical trials is available.

Geriatric Use

No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see **boxed WARNING**), the skin, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium have been reported.

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

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

Respiration: Irregular breathing, respiratory depression.

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

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

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

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

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should <u>not</u> be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within 1 week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe - ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Tegretol-XR is an extended-release formulation for twice-a-day administration. When converting patients from Tegretol conventional tablets to Tegretol-XR, the same total daily mg dose of Tegretol-XR should be administered. **Tegretol-XR tablets must be swallowed whole and never crushed or chewed.** Tegretol-XR tablets should be inspected for chips or cracks. Damaged tablets should not be consumed.

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age - Initial: Either 200 mg b.i.d. for tablets and XR tablets, or 1 teaspoon q.i.d. for suspension (400 mg/day). Increase at weekly intervals by adding up to 200 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily. ***Children 6-12 years of age - Initial:*** Either 100 mg b.i.d. for tablets or XR tablets, or 1/2 teaspoon q.i.d. for suspension (200 mg/day). Increase at weekly intervals by adding up to 100 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Children under 6 years of age - Initial: 10-20 mg/kg/day b.i.d. or t.i.d. as chewable tablets, or q.i.d. as suspension. Increase weekly to achieve optimal clinical response administered t.i.d. or q.i.d. ***Maintenance:*** Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine

whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see **PRECAUTIONS, Drug Interactions, and Pregnancy Category C**).

Trigeminal Neuralgia (see **INDICATIONS AND USAGE**)

Initial: On the first day, either 100 mg b.i.d. for tablets or XR tablets, or 1/2 teaspoon q.i.d. for suspension, for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours for tablets or XR tablets, or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400-800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg - round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100.....	NDC 58887-052-30
Unit Dose (blister pack)	
Box of 100 (strips of 10).....	NDC 58887-052-32

Do not store above 86°F (30°C). *Protect from light and moisture. Dispense in tight, light-resistant container (USP).*

Tablets 200 mg - capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

Bottles of 100.....	NDC 58887-027-30
Bottles of 1000.....	NDC 58887-027-40
Unit Dose (blister pack)	
Box of 100 (strips of 10).....	NDC 58887-027-32

Do not store above 86°F (30°C). *Protect from moisture. Dispense in tight container (USP).*

XR Tablets 100 mg - round, yellow, coated (imprinted T on one side and 100 mg on the other), release portal on one side

Bottles of 100.....	NDC 0083-0061-30
Unit Dose (blister pack)	
Box of 100 (strips of 10).....	NDC 0083-0061-32

XR Tablets 200 mg - round, pink, coated (imprinted T on one side and 200 mg on the other), release portal on one side

Bottles of 100.....	NDC 0083-0062-30
Unit Dose (blister pack)	
Box of 100 (strips of 10).....	NDC 0083-0062-32

XR Tablets 400 mg - round, brown, coated (imprinted T on one side and 400 mg on the other), release portal on one side

Bottles of 100..... NDC 0083-0060-30
Unit Dose (blister pack)
Box of 100 (strips of 10)..... NDC 0083-0060-32

Store at controlled room temperature 15°-30°C (59°-86°F). *Protect from moisture. Dispense in tight container (USP).*

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Suspension 100 mg/5 mL (teaspoon) - yellow-orange, citrus-vanilla flavored
Bottles of 450 mL..... NDC 58887-019-76

Shake well before using.

Do not store above 86°F (30°C). *Dispense in tight, light-resistant container (USP).*

doc: c:\docs\nda\tegretol\labeling.fda

NDA 20-234
JUN 18 1990

REVIEW AND EVALUATION OF CLINICAL DATA

IND

Sponsor:	Ciba-Geigy
Drug:	Tegretol OROS (carbamazepine, USP)
Indication:	Epilepsy, Trigeminal Neuralgia
Date of Submission:	May 16, 1990
Date Received:	May 21, 1990

The purpose of this study is to generate data which demonstrates that the rate of Tegretol absorption does not effect efficacy.

1.0 New Protocol: Effects Of Rate Of Oral Drug Input On Efficacy And Toxicity Of Carbamazepine In Monkey Model.

Fourteen (N-12 and 2-spares) male monkeys (Macaca fasicularis) will be made experimentally epileptic by the intracortical injection of aluminum hydroxide in the left pre- and postcentral gyrus during a sterile craniotomy. After the animals have developed a stable seizure frequency, the 12 study monkeys will be instrumented with a stomach catheter for drug delivery and dural electrodes for EEG interictal spike analysis.

After their epileptic foci are fully developed (4 months) the animals will be assigned to one of six dosing sequences.

Baseline	- 2 weeks
Induction	- 1 week
Treatment	- 6 weeks
Washout	- 2 weeks

Regimen/Dosage:
Drug administration will be via an implanted gastric catheter 4, 6, 12 times a day (q6h, q4h, q2h) in a randomized sequence. The doses will be 18 mg/kg(q6h), 12 mg/kg(q4h), or 6 mg/kg(q2h) such that all animals receive the same daily dose of 72 mg/kg. In addition, the catheters will be flushed with varying volumes of water so that the total daily volume of suspension plus water will be the same for all animals.

Study Design:
The study will use a randomized, crossover design, balanced for residual effects with 5 sequential phases.

Phase 1 (Week 1-2) - No-Drug Baseline Week
Phase 2 (Week 3) - Auto-Induction Phase 12mg/kg(q4h)

Starting Week 4, all animals will be randomly assigned to one of the following 6 dosing sequences (2 animals per sequence) in accord with a fully counterbalanced Latin Square Design.

Dosing Sequence	Week 5-4	Week 6-7	Week 8-9
(A-B-C)	12mg/kg q4h	6mg/kg q2h	18mg/kg q6h
(A-C-D)	12mg/kg q4h	18mg/kg q6h	6mg/kg q2h
(B-C-A)	6mg/kg q2h	18mg/kg q6h	12mg/kg q4h
(B-A-C)	6mg/kg q2h	12mg/kg q4h	18mg/kg q6h
(C-B-A)	18mg/kg q6h	6mg/kg q2h	12mg/kg q4h
(C-A-B)	18mg/kg q6h	12mg/kg q6h	6mg/kg q2h

Note: (1) Because of the auto-induction behavior of carbamazepine, a one week "induction week" will be allowed initially before the first active treatment. Subsequently, the initial four days at each new dose will be considered an adjustment period.
(2) Although seizures will be monitored continuously, only the last 10 days of each phase will be utilized for seizure and EEG quantification.

Treatment Phase:
Blood samples will be taken during the drug period for plasma drug level determinations. The samples will be obtained before the 8:00am dose(min) and 1h after each dose (approximate maximum on Monday, Wednesday, Friday of each week.

Elimination Phase: (Day 14 of each treatment period, half-life determinations)
Day 14 - 8:00am to 8:00pm q1h samples
Stop drug at 8:00pm
8:00pm to 12:00pm q1h samples
Drug resumes at 12:00pm(or 2h later for the q6h group)

Note: The "off drug" schedule will be such that the q2h animals miss 2 doses (8:00pm and 10:00pm) while the q4h and q6h animals miss only the 8:00pm dose.

EEG Samples:
EEG recordings (30min in duration) will be scheduled twice a week for each animal such that feeding periods are avoided and every animal is recorded on the same day and at the same time. These recordings will be utilized to quantify interictal spikes (Thursday and Friday of each week).

Seizure Monitoring:
Each animal will be monitored 24h a day via a polygraph recording "Slow Speed" EEG and motor activity via a cage accelerometer. This allows the quantification of seizure frequency, duration, severity, and time of occurrence.

2.0 Comment

I understand that this model was used for the NDA. My only comment is that the protocol is extremely sketchy, particularly regarding the identification of primary outcome measures and statistical analysis. I recommend obtaining a Biopharm consult on this one.

Janeth Rouzer-Kammeyer, M.D.

HFD-120
HFD-120/RKatz
JRouzer-K
cso/SDeCorte
ft/mb/6/13/90
DOC 1621n

Agree - also, sperm should be repeated to:
① consider no phase
② monitor 17,11 steroid levels.
Sperm should be called c the experts and
feel that biopharm consult is indicated.
6/11/90

Pharmaceuticals Division
CIBA-GEIGY Corporation
Summit, New Jersey 07901

CIBA-GEIGY

COPY 1

May 16, 1990

Submission #025

IND
Tegretol OROS

Center for Drug Evaluation and Research (HFN-120)
Document Control Room #10B-20
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products

Dear Dr. Leber:

Reference is made to our IND for Tegretol OROS and to our May 12, 1989 end-of-Phase II Meeting. For ease of reference, a copy of the minutes of the meeting, previously submitted to the Division on June 19, 1989 is provided in Attachment A.

The end-of-Phase II Meeting discussion focused primarily upon the pharmacokinetic program proposed for Tegretol OROS. A concern raised by the Division during this discussion was the existence of data which clearly demonstrates that the rate of Tegretol absorption does not affect efficacy. CIBA-GEIGY agreed to explore the feasibility of conducting a study which would adequately address this issue. Pursuant to this agreement, Attachment B of this submission provides a protocol by entitled "Effects of Rate of Oral Drug Input on Efficacy and Toxicity of Carbamazepine in Monkey Model."

Unless notified otherwise by the Division, implementation of this protocol is anticipated for mid-June 1990.

Please direct any questions or comments you may have concerning this submission to Ms. Nancy Martin, Assistant Director, CNS/Drug Regulatory Affairs, at (201) 277-5988.

Very truly yours,

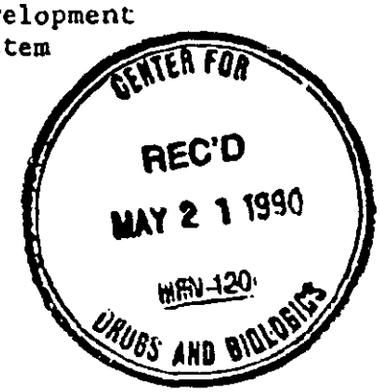
PHARMACEUTICALS DIVISION
CIBA-GEIGY Corporation

Nancy Martin

Ronald Kartzinel, M.D., Ph.D.
Vice President, Development
Central Nervous System

RK/NM:mmp
a:inc

Desk Copies to:
Ms. Susan DeCorte - HFN-120, Room #10B-45
Dr. Paul Leber - HFN-120, Room #10B-45
Dr. Protapa Prosad - HFD-426, Room #13B-03



ATTACHMENT A

Tegretol OROS
IND
End of Phase II Meeting
Neuropharm Division
May 12, 1989

FDA	CIBA-GEIGY
Dr. Joseph Contrera	Dr. H. Faleck
Ms. Susan DeCorte	Ms. M. Fertally
Dr. Russell Katz	Dr. H. Hakkarainen
Dr. Paul Leber	Dr. R. Kartzinel
Dr. Karen Oseekey	Dr. L. Leeson
Dr. Janeth Rouzer	Dr. M. Powell
Mr. Robert Shultz	Dr. E. Redalieu
Dr. Andrew Sostek	Dr. E. Snowhill

After introductions, the proposed revision to the indication section of the Tegretol package insert, based on successful outcome of the Tegretol OROS program, was shown: "Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available as chewable tablets of 100 mg, tablets of 200 mg and OROS controlled release tablets of 100, 200 and 400 mg. (Underscore is future addition to insert upon approval of OROS.)

Dr. Elliott Redalieu then presented an overview of the pharmacokinetic program we plan to conduct for Tegretol OROS.

Dr. Leber asked if we were seeking approval of the Tegretol OROS formulation with a different input rate as long as the same plasma levels are achieved. We confirmed this.

Dr. Leber emphasized that the controlled release guidance we were referring to is only that - a guidance, and does not necessarily reflect the position of the reviewing division on all matters.

Dr. Leber discussed his main concern: ascertaining that rate of absorption does not affect efficacy. He said that the sponsor should provide evidence, though not necessarily obtained in man, that rate of absorption is not important to efficacy. He mentioned that the same question had come up with respect to another anticonvulsant and that it had been answered with a pump study in a primate model.

Dr. Leeson mentioned that had done a study along those lines with carbamazepine using I.V. infusions.

We agreed to attempt such a study, if it is determined that data does not already exist that addresses the concern.

Concerning our overall pharmacokinetic program, Dr. Leber said we are probably doing more than necessary. We said that we need the studies to write labeling and characterize the formulation for marketing.

Accordingly, we understand from FDA that our pharmacokinetic program is more than sufficient to support approval of Tegretol OROS provided we show equivalence of AUC and fluctuation.

Regarding the pharmacokinetic program, Dr. Karen Oseekey said it is probably not necessary to do a study in patients on polytherapy. We explained that we felt this was important to study because the half-life may be shorter in polytherapy. Dr. Karen Oseekey noted we did not use the 400 mg in the food effect study, and if there is a food effect demonstrated she would need additional data using the higher strength.

Dr. Karen Oseekey said the most important comparison is between the conventional QID and BID OROS and that we should be sure to have enough patients to show this comparison, in terms of confidence levels.

It was clarified that what we meant by the term dose proportionality was actually formulation proportionality. Dr. Oseekey said the most critical aspect is seeing results with the highest daily dosage recommended in the labeling, i.e. 2000 mg per day. Dr. Oseekey agreed, however, that results up to 1600 mg/day would be sufficient. (In fact, 1600 mg is the highest daily dosage recommended in the package insert.)

We mentioned that in order to obtain more patient experience, we were we were planning on doing a study comparing Tegretol OROS and Tegretol Tablets. This study (Protocol 36) is in addition to the pharmacokinetic program.

There being no further discussion on Tegretol OROS, general topics on anticonvulsants were discussed.

Dr. Kartzinel asked what has to be done to include women in Phase III trials of anticonvulsants. Dr. Leber said an add-on trial can demonstrate whether the drug has anticonvulsant efficacy. Dr. Leber said that for Phase III he could rely upon expert(s) from the advisory committee who would become involved at the end-of-Phase II meeting stage. He also said that active-active design studies are viewed as safety studies (unless, of course, one drug shows superiority).

Dr. Leber said that the add-on trial could provide enough evidence for the drug to be labeled as an anticonvulsant. The labeling would probably also say that that had been determined in an add-on design (thus showing it had not been studied in monotherapy). Dr. Leber said demonstration of effectiveness in monotherapy could be handled later.

Mara Fertally 6/19/89
Mara Fertally

MF:aeh
4mf5.19

ATTACHMENT B

EFFECTS OF RATE OF ORAL DRUG INPUT ON EFFICACY AND TOXICITY OF CARBAMAZEPINE IN MONKEY MODEL

Research Protocol

DESIGN

Fourteen (N-12 and 2 spares) male monkeys (Macaca fascicularis) will be made experimentally epileptic (surgical procedure). After their epileptic foci are fully developed (4 months) the animals will be assigned to one of six dosing sequences.

Purchase & Quarantine	/ Epileptic Preparation	/ Baseline	/ Induction	/ Treatment	/ Wash-out	/ Post-baseline
4 mo.	/ 4 mo.	/ 2 wk.	/ 1 wk.	/ 6 wk.	/ 1 wk.	/ 2 wk.

Note: The purchase and quarantine period will be utilized to prepare the laboratory and purchase equipment and supplies.

ANIMAL PREPARATION

Fourteen adolescent male monkeys (3-5 kg) will be made chronically epileptic by the intracortical injection of aluminum hydroxide in the left pre- and postcentral gyrus during a sterile craniotomy. After the animals have developed a stable seizure frequency, the 12 study monkeys will be instrumented with:

1) A stomach catheter for drug delivery;
2) Dural electrodes for EEG interictal spike analysis.

REGIMEN/DOSAGE

Drug administration will be via an implanted gastric catheter 4, 6, or 12 times a day (q6h, q4h, or q2h) in a randomized sequence. The doses will be 18 mg/kg (q6h), 12 mg/kg (q4h), or 6 mg/kg (q2h) such that all animals receive the same daily dose of 72 mg/kg. In addition, the catheters will be flushed with varying volumes of water so that the total daily volume of suspension plus water will be the same for all animals.

STUDY DESIGN

The study will use a randomized, crossover design, balanced for residual effects with 5 sequential phases.

Phase 1 (Week 1-2): No-Drug Baseline Week
Phase 2 (Week 3): Auto-induction Phase 12 mg/kg, q4h

Starting Week 4, all animals will be randomly assigned to one of the following 6 dosing sequences (2 animals per sequence) in accord with a fully counterbalanced Latin Square Design:

Dosing Sequence	Week 4-5	Week 6-7	Week 8-9
(A-B-C)	12 mg/kg, q4h	6 mg/kg, q2h	18 mg/kg, q6h
(A-C-B)	12 mg/kg, q4h	18 mg/kg, q6h	6 mg/kg, q2h
(B-C-A)	6 mg/kg, q2h	18 mg/kg, q6h	12 mg/kg, q4h
(B-A-C)	6 mg/kg, q2h	12 mg/kg, q4h	18 mg/kg, q6h
(C-B-A)	18 mg/kg, q6h	6 mg/kg, q2h	12 mg/kg, q4h
(C-A-B)	18 mg/kg, q6h	12 mg/kg, q6h	6 mg/kg, q2h

Note: 1) Because of the auto-induction behavior of carbamazepine, a one week "induction week" will be allowed initially before the first active treatment. Subsequently, the initial 4 days at each new dose will be considered an adjustment period.

2) Although seizures will be monitored continuously, only the last 10 days of each phase will be utilized for seizure and EEG quantification.

EXPERIMENTAL SCHEME

3 Months	Monkey Acquisition & Quarantine
6 Months	Aluminum Hydroxide Injection
	EEG Electrodes
	Stomach Catheterization
Weeks 1-2	Baseline EEG Recording
	Baseline Seizure Recording
	Laboratory Tests
Week 3	Auto-Induction Phase (12 mg/kg, q4h)
	Blood Sampling
	Toxicity Monitoring
	Laboratory Tests
Weeks 4-9 (done weekly)	
	Adjustment Period (first 4 days)
	Drug Study Period (last 10 days)
	Blood Sampling
	EEG Recording
	Seizure Recording
	Toxicity Monitoring
	Laboratory Tests
Week 10	Drug clearance
	EEG Recording
	Seizure Recording
	Withdrawal Monitoring
Weeks 11-12	Post-Baseline EEG Recording
	Post-Baseline Seizure Recording
	Withdrawal Monitoring (if needed)

HEALTH MONITORING

1) Visual clinical assessments of animals will be made 3 times daily.
2) Food, fruit and water intake, as well as the feces and urine excreted, will be monitored.
3) Blood counts will be taken during baseline and then only if the health of the animal is in question.

4) Blood chemistry screens will be conducted on all animals upon their initial arrival (to insure their health) and then once per week during the study protocol.

5) Cultures will be necessary in the event of illness to insure appropriate therapy.

PLASMA SAMPLES

Each sample (1 ml of blood) will be placed in a tube containing an appropriate anticoagulant (EDTA), spun for 10 minutes and the plasma drawn off. Plasma storage will be at or below 0°C until assayed.

1) "Auto-induction phase"; plasma sampling schedule:

Day 1:	0 (pre-dose),	8 pm
Day 2:	8 am	8 pm
Day 3	8 am	8 pm
Day 4	8 am	8 pm
Day 5	8 am	
Day 6	8 am	
Day 7	8 am	

Note: All samples are taken before the dose (minimums).

2) "Treatment phase"; schedule as follows:

Blood samples will be taken during the drug period for plasma drug level determinations. The samples will be obtained before the 8 am dose (min) and 1 hour after each dose (approximate maximum) on Mondays, Wednesdays and Fridays of each week.

3) "Elimination phase" (day 14 of each treatment period, half-life determinations); schedule as follows:

Day 14 - 8am to 8pm q1h samples
Stop drug at 8pm
8pm to 12pm q1h samples
Drug resumes at 12 pm (or 2 hrs. later for the q6h group)

Note: The "off drug" schedule will be such that the q2h animals miss 2 doses (8pm and 10pm) while the q4h and q6h animals miss only the 8pm dose.

EEG SAMPLES

EEG recordings (30 minutes in duration) will be scheduled twice a week for each animal such that feeding periods are avoided and every animal is recorded on the same day and at the same time. These recordings will be utilized to quantify interictal spikes (Thursday and Friday of each week).

SEIZURE MONITORING

Each animal will be monitored 24 hrs. a day via a polygraph recording "slow speed" EEG and motor activity via a cage accelerometer. This allows the quantification of seizure frequency, duration, severity, and time of occurrence.

Chem.

PHARMACOLOGIST REVIEW OF GLP EIR
(CP 7348.808)

FIRM NAME

CITY, STATE:

CFN: 30-------

DISTRICT OFFICE:

QUARTER/FISCAL YEAR ASSIGNED: 2/93

EI DATE(S): 2/22-24/93

INVESTIGATOR(S):
1. William G. Zuber, HFR-PA350
2. Charles A. Snipes, HFD-345
3.

INSPECTION TYPE:	____ ROUTINE SURV.	_X_ DIRECTED
FDA-483 ISSUED:	_X_ NO	____ YES
LETTER TO ISSUE:	_X_ NONE	____ PI LETTER
	____ WARNING LETTER	____ REJECTION OF STUDY

DATE EIR REC'D DSI: 4/09/93

DATE EIR REC'D BY REVIEWER: 4/15/93

DATE REVIEW COMPLETED: 4/26/93

FINAL HQ CLASSIFICATION: NAI

Study #: none
Completed: report undated, submitted 10/31/91
Protocol Title: Anticonvulsant and Pharmacokinetic Effects of Different Carbamazepine Dosing Regimens in a Monkey Model
Test Article: Tegretol OROS (a sustained release version of carbamazepine)
Type of Study: subchronic (9 weeks)
Testing Facility: this Department
Sponsor: Pharmaceuticals Division
Ciba-Geigy Corporation
556 Morris Avenue
Summit, New Jersey 07901
IND:
NDA: 20-234

An audit of the above study was requested by the Division of Neuropharmacological Drug Products, HFD-120. That Division was interested especially in whether all records and data had been available to the Agency.

This was the first inspection for this department. Another laboratory at this . was given a GLP surveillance inspection January 11, 1982 for CBER with a resulting VAI-2 classification.

The EIR consists of a summary of findings, a discussion of persons interviewed/study staff, a summary of the background of the study, twenty three appended exhibits, and reviews of:

facilities
test drug receiving records (and care of test article)
study dose selection
animal receiving and screening
pre-study medications
on-study medications
on-study animal health observations
animal dosing
food, water & excretion records
on-study clinical laboratory testing
EEG data
seizure data
animal disposition
drug chemistry laboratory
study report
historical controls
protocol deviations
incidental observations

Computer usage is discussed at appropriate places in the above sections.

Mr. Zuber and I elected not to request minutes of the . Proceeding on, we found that the group doing the study had attempted to make all records and data available to the sponsor. Further, all records and data requested during this audit were supplied (or directions for obtaining were given, in the case of the animal receiving unit and

We found that the work was typical of that done at most academic institutions; reliable work, but not complying or intended to comply, with the Good Laboratory Practice regulations. The most important GLP deficit was the failure of the facility to provide Quality assurance for the study in question. However, no FDA-483 was issued, because:

1) the facility had and has no intention to perform studies that must comply with the GLP regulations.

2) There is some question that the audited study, because of its objectives, was subject to the GLP regulations.

DISCUSSION:

I was a member of the investigational team, and will not recapitulate the EIR here. More than is the case in most audits, I expect that in this instance persons interested in our findings will read the EIR itself.

The audited work appeared good to me when judged by its own standards, those common to the academic laboratory.

told us she never intended the study to be an efficacy study. She said she would have designed it differently had she so intended, going so far as to not even use the Latin square design. She also said that, until we told her, she had not known of the existence of a revised report dated April 1, 1992 of the audited study. This report, entitled "Anticonvulsant and Pharmacokinetic Effects of Different Carbamazepine Dosing Regimens in a Monkey Model" was submitted to FDA by Ciba Geigy She was unaware of this even though her name is listed on the report as a collaborator and even though the report is described as being "rewritten" in a letter dated February 20, 1992 to the Agency from Dr. Irene Chow of Ciba-Geigy.

RECOMMENDATIONS:

1> Classify NAI - No Action Indicated

2> Reinspect only on further assignment.

Charles A. Snipes, Ph.D.
Pharmacologist

NDA 20-234

NOV - 8 1991

Geigy Pharmaceuticals
Division of Ciba-Geigy Corporation
Attention: Nancy Martin
556 Morris Avenue
Summit, New Jersey 07901

Dear: Ms. Martin:

We have received your new drug application submitted pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product: Tegretol® OROS® Tablets

Date of Application: October 31, 1991

Date of Receipt: November 5, 1991

Our Reference Number: 20-234

Unless we find the application not acceptable for filing, the filing date will be January 4, 1992.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning this NDA, please contact Ms. Susan M. DeCorte, Project Manager, at (301)443-3504.

Sincerely yours,

John S. Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacological
Drug Products
Office for Drug Evaluation I
Center for Drug Evaluation and Research

NDA 20-234 TEGRETOL® OROS® (CR) TABLETS 100, 200 AND 400 MG

REVISED CHEMISTRY LETTER

We have identified the following major chemistry and manufacturing control deficiencies in your application:

1. The manufacturing information for the drug product ~~specifications~~ lacks a detailed description of the used for the Tegretol CR tablets. This description should include a diagram, explanation on how the tablets are moved into the how the tablets are how many

2. The Master Production Batch Formula lacks a specific value for the weight gain which should be achieved in the coating process.

3. The large variation in the amount of coating which may be applied to the tablet cores requires validation due to the controlled release designation of this drug product. The validation should include detailed comparisons of dissolution and stability using tablets at the extremes of this range.

4. The sampling plans for the drug product manufacturing are not acceptable. Each sub-divided batch, pan or laser unit should be treated as an individual sample set. Although it is preferred not to perform any composite sampling, we will permit samples collected within a sub-group to be combined. Samples obtained from separate sub-divided manufacturing operations should not be combined into composite samples. Samples should be collected throughout the manufacturing process to ensure complete randomization. The sampling plan used for the drug product in the final container/closure system should be defined. The sampling of the packaged drug product should be uniform throughout the packaging run and testing should include all regulatory specifications. Contingencies and requirements for retesting if either an In-process or final release Specification fail an analytical test should be submitted in detail. If retesting is to be performed, standard operating procedures should be included which describe how the original failed sample will be included in the batch evaluation. Out-of-specification samples should not be simply discarded without explaination or accounting.

5. The stability data submitted for the drug product does not support your proposed (24 months) expiration date. The studies are inadequate by design and the data submitted is not sufficient to fully evaluate the present manufacturing process. Our primary concern is the lack of data on full-scale production batches as well as the

limited data (3 months) submitted for the pilot batches. The information submitted for the clinical batches can only be considered supportive information due to the changes in formulation and manufacturing upon scale-up. In addition, no stability data has been submitted for the 100 and 200 mg tablets in blister packaging.

6. The Specifications for the drug product are not acceptable. A Specification for the amount of residual water should be added
The Specification for residual water content should also be included in the stability protocol. We also believe that the specification for residua
should be reduced to avoid the possibility of reaching unacceptable doses when administering multiple daily doses.

7. The manufacturing process has not been adequately validated. The possibility that impurities will be produced through the degradation of drug substance during the coating or drilling processes has not been examined.

The following items, while not considered as significant as the preceding comments, should also be addressed:

8.

10. A page was missing from your submission in the 100 mg Master Batch Formulation which describes t
the target weight, thickness, hardness and friability.

11.

12. Considering your lack of experience with the manufacturing process at full scale production, we are concerned with the comment that the granulation tends to "gum up" easily. Please submit contingencies or reprocessing procedures which would be used in the event this problem manifests itself in the full scale manufacturing process.

13. Please consider the use of pharmaceutical coil in your HDPE packaging to protect the tablets from possible damage which may lead to dose dumping. Have studies been performed to demonstrate that the tablets are not easily damage with normal handling?

14. The controlled release nature of this drug product requires additional labeling to ensure the proper administration. The bottle and/or box labeling should contain a warning to swallow tablets whole and avoid biting or chewing. The package insert should contain a statement to inspect the tablets for chips or cracks and not to consume tablets which are damaged.

15. The tablet drying process described in the NDA should be specified as mandatory and the option not to perform this operation should be withdrawn. Please submit a more detailed discussion on the drying operation and the effects of the appropriate variables (i.e. temperature, time, pressure, etc.) on the release Specifications and stability of the drug product.

16. Please clarify the allowable storage periods for the bulk granulation, bulk tablet cores and coated tablets prior . Provide evidence of stability and suitability of these materials after storage for extended periods.

6 Lg

NEW CORRESPONDENCE

Pharmaceuticals Division
CIBA-GEIGY Corporation
Summit, New Jersey 07901

CIBA - GEIGY

February 20, 1992

NDA 20-234
Tegretol-SR ™
(carbamazepine, USP)

Center for Drug Evaluation and Research (HFN-120)
Document Control Room #10B-20
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products

NAI
KY 2/25/92

Dear Dr. Leber:

Reference is made to the Tegretol-SR NDA 20-234 submitted on October 31, 1991, the February 3, 1992 teleconference between the Division and CIBA-GEIGY, and subsequent telephone communications with Dr. Katz on February 12 and Nancy Chamberlin on February 20, 1992.

In accordance with 21 CFR 314.60, CIBA-GEIGY is preparing an amendment to NDA 20-234 consisting of the final medical report for Protocol 36, and a rewritten Monkey Model Study Report which will address the Division's questions of February 3, 1992. This amendment will be submitted to NDA 20-234 on or before April 7, 1992.

To accommodate the Division's review of this forthcoming amendment and in accordance with 21 CFR 314.100 (c), this correspondence documents the agreement between CIBA-GEIGY and the Division that the review period for NDA 20-234 will be extended 180 days from the filing date of this amendment in early April 1992.

Please direct any questions or comments regarding the contents of this submission, to Ms. Nancy Martin, Associate Director, CNS/Drug Regulatory Affairs at (908) 277-5988.

Very truly yours,

BASEL Pharmaceuticals
Division of CIBA-GEIGY Corporation

Nancy Martin
for
Irene Chow, Ph.D.
Senior Vice President, Development

IC/NM:mmp
a:srrvwper.ext

NDA ORIG AMENDMENT

Pharmaceuticals Division
CIBA-GEIGY Corporation
Summit, New Jersey 07901

CIBA - GEIGY

February 27, 1992

N (BB)

NDA 20-234
Tegretol-SR ™
(carbamazepine, USP)

Center for Drug Evaluation and Research (HFN-120)
Document Control Room #10B-20
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products

Dear Dr. Leber:

Reference is made to the Tegretol-SR NDA 20-234 submitted on October 31, 1991, and to the February 19 and 24, 1992 telephone requests of Dr. Rahman.

In response to Dr. Rahman's request for additional information on NDA 20-234, CIBA-GEIGY has enclosed the following documentation.

1) **Expiration Dates:** The Division of Biopharmaceutics requested the expiration dates for all of the Tegretol OROS lots used in Protocols 32, 33, 34, 36, 37, and 42. Provided in Tab A is an explanation of CIBA-GEIGY's policy for the expiration dating of clinical supplies and supporting stability data for Tegretol OROS (SR) Tablets.

2) **Chromatograms:** The Division of Biopharmaceutics requested sample patient chromatograms (1 per patient), and a QC sample chromatogram for Protocols 32 and 42. Provided in Tab B is a coy of one representative chromatogram for each subject after each formulation, and one representative chromatogram for a QC sample for Protocols 32 and 42. A legend is enclosed for each protocol to facilitate the identification of the samples.

3) **Statistical Analysis:** The Division of Biopharmaceutics requested a log transformation data analysis of the data generated from Protocols 32, 33, 37, and 42. CIBA-GEIGY anticipates that this information will be available and immediately forwarded to the [illegible] the third week of March 1992.

CENTER FOR DRUG
REC'D
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EVALUATION

Please direct any questions or comments regarding the contents of this submission to Ms. Nancy Martin, Associate Director, CNS/Drug Regulatory Affairs, at (908) 277-5988.

Very truly yours,

PHARMACEUTICALS DIVISION
CIBA-GEIGY Corporation

Nancy Martin
for

Irene Chow, Ph.D.
Senior Vice President, Development

IC/NM:mmp
a:tgsrbiop.rqs

EFFECTS OF RATE OF [illegible] ON EFFICACY AND TOXICITY
OF CA[illegible] MONKEY MODEL

DESIGN

Fourteen (N-12 and 2 spares) male monkeys (Macaca fascicularis) will be made experimentally epileptic (surgical procedure). After their epileptic foci are fully developed (4 months) the animals will be assigned to one of six dosing sequences.

Purchase & Quarantine	Epileptic Preparation	Baseline	Induction	Treatment	Wash-out	Post-baseline
4 mo.	4 mo.	2 wk.	1 wk.	6 wk.	1 wk.	2 wk.

Note: The purchase and quarantine period will be utilized to prepare the laboratory and purchase equipment and supplies.

ANIMAL PREPARATION

Fourteen adolescent male monkeys (3-5 kg) will be made chronically epileptic by the intracortical injection of aluminum hydroxide in the left pre- and postcentral gyrus during a sterile craniotomy. After the animals have developed a stable seizure frequency, the 12 study monkeys will be instrumented with:

1) A stomach catheter for drug delivery;
2) Dural electrodes for EEG interictal spike analysis.

REGIMEN/DOSAGE

Drug administration will be via an implanted gastric catheter 4, 6, or 12 times a day (q6h, q4h, or q2h) in a randomized sequence. The doses will be 18 mg/kg (q6h), 12 mg/kg (q4h), or 6 mg/kg (q2h) such that all animals receive the same daily dose of 72 mg/kg. In addition, the catheters will be flushed with varying volumes of water so that the total daily volume of suspension plus water will be the same for all animals.

STUDY DESIGN

The study will use a randomized, crossover design, balanced for residual effects with 5 sequential phases.

Phase 1 (Week 1-2): No-Drug Baseline Week
Phase 2 (Week 3): Auto-induction Phase 12 mg/kg, q4h

Starting Week 4, all animals will be randomly assigned to one of the following 6 dosing sequences (2 animals per sequence) in accord with a fully counterbalanced Latin Square Design:

Dosing Sequence	Week 4-5	Week 6-7	Week 8-9
(A-B-C)	12 mg/kg, q4h	6 mg/kg, q2h	18 mg/kg, q6h
(A-C-B)	12 mg/kg, q4h	18 mg/kg, q6h	6 mg/kg, q2h
(B-C-A)	6 mg/kg, q2h	18 mg/kg, q6h	12 mg/kg, q4h
(B-A-C)	6 mg/kg, q2h	12 mg/kg, q4h	18 mg/kg, q6h
(C-B-A)	18 mg/kg, q6h	6 mg/kg, q2h	12 mg/kg, q4h
(C-A-B)	18 mg/kg, q6h	12 mg/kg, q6h	6 mg/kg, q2h

Note: 1) Because of the auto-induction behavior of carbamazepine, a one week "induction week" will be allowed initially before the first active treatment. Subsequently, the initial 4 days at each new dose will be considered an adjustment period.

2) Although seizures will be monitored continuously, only the last 10 days of each phase will be utilized for seizure and EEG quantification.

EXPERIMENTAL SCHEME

3 Months	Monkey Acquisition & Quarantine
6 Months	Aluminum Hydroxide Injection
	EEG Electrodes
	Stomach Catheterization
Weeks 1-2	Baseline EEG Recording
	Baseline Seizure Recording
	Laboratory Tests
Week 3	Auto-Induction Phase (12 mg/kg, q4h)
	Blood Sampling
	Toxicity Monitoring
	Laboratory Tests
Weeks 4-9 (done weekly)	
	Adjustment Period (first 4 days)
	Drug Study Period (last 10 days)
	Blood Sampling
	EEG Recording
	Seizure Recording
	Toxicity Monitoring
	Laboratory Tests
Week 10	Drug clearance
	EEG Recording
	Seizure Recording
	Withdrawal Monitoring
Weeks 11-12	Post-Baseline EEG Recording
	Post-Baseline Seizure Recording
	Withdrawal Monitoring (if needed)

PLASMA SAMPLES

Each sample (1 ml of blood) will be placed in a tube containing an appropriate anticoagulant (EDTA), spun for 10 minutes and the plasma drawn off. Plasma storage will be at or below 0°C until assayed.

1) "Auto-induction phase"; plasma sampling schedule:

Day 1:	0 (pre-dose),	8 pm
Day 2:	8 am	8 pm
Day 3	8 am	8 pm
Day 4	8 am	8 pm
Day 5	8 am	
Day 6	8 am	
Day 7	8 am	

Note: All samples are taken before the dose (minimums).

2) "Treatment phase"; schedule as follows:

Blood samples will be taken during the drug period for plasma drug level determinations. The samples will be obtained before the 8 am dose (min) and 1 hour after each dose (approximate maximum) on Mondays, Wednesdays and Fridays of each week.

3) "Elimination phase" (day 14 of each treatment period, half-life determinations); schedule as follows:

Day 14 - 8am to 8pm q1h samples
Stop drug at 8pm
8pm to 12pm q1h samples
Drug resumes at 12 pm (or 2 hrs. later for the q6h group)

Note: The "off drug" schedule will be such that the q2h animals miss 2 doses (8pm and 10pm) while the q4h and q6h animals miss only the 8pm dose.

EEG SAMPLES

EEG recordings (30 minutes in duration) will be scheduled twice a week for each animal such that feeding periods are avoided and every animal is recorded on the same day and at the same time. These recordings will be utilized to quantify interictal spikes (Thursday and Friday of each week).

SEIZURE MONITORING

Each animal will be monitored 24 hrs. a day via a polygraph recording "slow speed" EEG and motor activity via a cage accelerometer. This allows the quantification of seizure frequency, duration, severity, and time of occurrence.

HEALTH MONITORING

1) Visual clinical assessments of animals will be made 3 times daily.
2) Food, fruit and water intake, as well as the feces and urine excreted, will be monitored.
3) Blood counts will be taken during baseline and then only if the health of the animal is in question.

4) Blood chemistry screens will be conducted on all animals upon their initial arrival (to insure their health) and then once per week during the study protocol.

5) Cultures will be necessary in the event of illness to insure appropriate therapy.

TABLE 1

SUPPLEMENTS FOR APPROVAL

Date Submitted	NDA 16-608 SNDA #	NDA 18-281 SNDA#	NDA 18-927 SNDA#	Description
3/4/87	059	010		Pediatric indication (Under six)

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Clinical Review of NDA

NDA	20-234
Sponsor:	Ciba-Geigy
Brand Name	Tegretol XR®
Indication	Epilepsy
NDA Classification	~~2C~~ 3S
Original Receipt Date	October 31,1991
Review Competed	August 2, 1995
Clinical Reviewer	Cynthia G. McCormick, M.D.

1.0 BACKGROUND

OVERVIEW OF TEGRETOL XR® NDA SUBMISSION

This NDA was submitted with the intent of demonstrating bioequivalency between Tegretol XR® delivered twice daily to approved dosing regimens for commercial Tegretol tablets. The NDA consists of 5 clinical biopharmaceutics studies, which include both single and multiple-dose clinical pharmacology studies and a single "efficacy" study performed in non-human primates.

Data or support from the literature illustrating the importance or lack of importance of rate of delivery of a drug was requested of the firm, or, alternatively, completion of a study that would establish that the rate of absorption is not important for clinical efficacy. To this end, the firm undertook a study in monkeys which was intended to demonstrate that the rate of Tegretol absorption does not effect efficacy, that is, that the rate of input does not affect the rate of plasma concentration. The FDA review of the protocol for this study (6/11/90) recommended a placebo phase to the study as well as attention to epoxide levels with monitoring. The study was completed on June 27, 1991 and submitted as evidence for efficacy as part of this NDA.

In the above study, experimentally epileptic monkeys were treated via an implanted gastric catheter with carbamazepine suspension 4,6,and 12 times a day (q2h, q4h, and q6h) according to a balanced Latin square design. The doses were 54 mg every 2 hr, 36 mg every 4 hr, and 18 mg, every 2 hr such that the daily dose of 216 mg was provided by all 3 regimens. Seizure frequency data and blood level data were collected. This study was reviewed in section 7.0 of this NDA review. The study is considered a failed study by this reviewer and in consultation with the statistical reviewer and biopharm reviewer. In addition it is acknowledged to have been a failed study by the firm as well, (telecon 7/28/93)

In addition to the monkey model study an attempt is made based on simulation data from study 36 (Submitted 5/1992) to demonstrate that there is bioequivalence between the BID Tegretol XR® formulation and the commercial Tegretol given TID or QID. This data is obtained form the analysis of actual plasma level data obtained in patients on chronic treatment as well as simulations of the repetitive dosing regimens. The validity of the assumptions relied upon in developing these simulations was reviewed by biopharm consultants and this reviewer will defer to their expertise and careful analysis.

Finally, a single short term human clinical safety study involving patients with epilepsy was submitted as the 4 month safety update.

PROPOSED INDICATIONS, DOSAGE FORM, AND STRENGTH, ROUTE OF ADMINISTRATION AND DIRECTIONS FOR USE.

Tegretol is currently indicated for use as an anticonvulsant drug and for the treatment of trigeminal neuralgia. Both indications are sought for this new formulation.

Tegretol XR® will be available in the following dosage forms: 100, 200 and 400 mg tablets to be given BID orally. According to the sponsor, Tegretol XR® tablets given BID afford steady-state plasma levels comparable to conventional Tegretol tablets given qid when administered orally at the same total mg daily dose.

2.0 MATERIAL REVIEWED

- NDA (1.1-1.20)
- ISS (1.20)
- Proposed Labelling (1.6)
- CLINICAL TRIALS SUBMITTED IN SUPPORT OF NDA

    - Clinical Trial Report: Protocol 32 (Vol 1.15) Relative Bioavailability and Effects of Food on Plasma Levels of Carbamazepine and its Epoxide Metabolite following a singe dose of Tegretol Oros Drug Delivery System
    - Clinical Trial Report: Protocol 33 (Vol 1.16) Comparative Pharmacokinetic Study in Epileptic Patients Receiving Tegretol in the Form of Commercial and OROS dosage forms
    - Clinical Trial Report: Protocol 37 (Vol. 1.19) Comparative Pharmacokinetic Study in Epileptic Patients Receiving Tegretol in the form of Commercial and OROS dosage forms
    - CDP Report 90039 (Vol 1.17) A Pilot Dosage Form Proportionality Study Comparing one 200-MG and two 100-MG Tegretol OROS Tablets in Healthy Subjects

- Clinical Summary : Protocol 42 (Vol 1.18) Dosage Form Proportionality Study of four 100-MG, two 200-MG and one 400-MG Tegretol OROS Tablets in healthy volunteers

- *Safety Update (Vol. 2.1-2.5, and 6.1)*
  - Clinical Trial Report: Protocol 36 Crossover comparison of Tegretol OROS Tablets and Commercial Tegretol with regard to seizure control, serum therapeutic drug levels, safety and tolerability

3.0 CHEMISTRY

There are no outstanding chemistry or manufacturing issues of clinical importance. Tegretol XR® is a new formulation of a known chemical entity.

4.0 PHARMACOLOGY

No new toxicology is submitted with this NDA because the assumption was that of bioequivalence with a marketed formulation.

5.0 CLINICAL DATA SOURCES

The development program for Tegretol XR® included clinical pharmacology studies involving normal healthy subjects and clinical pharmacology studies involving patients. The clinical database consists of information from 36 healthy subjects, and the studies involving patients consisted of information from 155 epilepsy patients. Totalling 192 patients and subjects. The demographic breakdown of these 192 are found on the next page and the summary of exposure data are found in Section 7.0 of this review.

DEMOGRAPHICS

The demographic distributions of subjects and patients in this NDA are found in Sponsor's Table 2, appendix D in the supplementary submission to the "Safety Update" (below).

DEMOGRAPHIC, MEDICAL HISTORY AND BASELINE VARIABLES
(CUMULATIVE BY SUBJECTS AND BY PATIENTS)

	N	%
NUMBER OF SUBJECTS		
MALE	34	94.4
FEMALE	2	5.6
TOTAL	36	100.0
NUMBER OF PATIENTS		
MALE	84	55.6
FEMALE	67	44.4
TOTAL	151	100.0
AGE (YEARS)		
>=6 <10	4	2.1
10 <20	21	11.2
20 <30	63	33.7
30 <40	53	28.3
40 <50	31	16.6
50 <60	11	5.9
>=60	4	2.1
ORIGIN		
WHITE	169	90.4
BLACK	15	8.0
OTHER	3	1.6

6.0 HUMAN PHARMACOLOGY

A brief summary of human biopharmaceutics is presented here, as a formal and lengthy review by the Division of Biopharmaceutics is provided.

Summary: *The sponsor has studied single and multiple dose pharmacokinetics and relative* bioavailability of Tegretol XR®, dose-proportionality linking the 100, 200 and 400 mg tablets, and performance of the XR® formulation compared to the conventional tablets in both the adult and pediatric populations. While the studies confirm bioequivalence between Tegretol XR® and existing formulations with respect to the parent compound, in some of the bioequivalence studies[1], the active metabolite, the 10,11-epoxide of tegretol did not meet the current standards for bioequivalence.

Bioequivalence and Bioavailability

The relative bioavailability of Tegretol XR®(fasting conditions) relative to a 2% Tegretol suspension (200 mg doses) averaged about 88%. (Sponsor's Study Report 91035)

Carbamazepine was more rapidly absorbed when administered postprandially compared to the fasted state in a comparison of 200 mg OROS tablet (Study 32), however the AUC was similar in fed and fasted conditions. For the epoxide metabolite, the rate and extent of absorption were affected by the presence of food.

Pharmacokinetics

Single dose: Following single dose administration of Tegretol XR® and commercial Tegretol tablet in the fasted state the AUC and Cmax for the active metabolite were not equivalent, although equivalence was demonstrated for the parent compound for both parameters.

Multiple dose: Steady state plasma concentration-time profiles of both CBZ and CBZE were characterized for peak and trough levels and fluctuation indices. The CBZE failed again to pass 90% confidence interval for C_{max}. However, for C_{ave}, C_{min}, fluctation index the parent and the CBZE did pass.

7.0 EFFICACY FINDINGS

Monkey Model Study

One study is submitted in support of efficacy of this new formulation of Tegretol. The background information presented above verify that there was agreement on the part of the Division that proof that efficacy was dependent on AUC and not means of delivery, that further efficacy studies would not be needed. Tegretol has been a marketed antiepileptic for nearly 20 years and its efficacy and safety are not in question here. That the new formulation will alter the behavior of the product such that either the safety or efficacy are changed is the question. The following study was chosen in an effort to provide an answer to the question of the relationship between delivery and efficacy of this compound. The FDA suggested that if the results of this study were sufficiently robust further efficacy studies might not be needed.

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[1]See Biopharm Review, signed February 8, 1994

The model that was selected was the epilepsy in the fascicularis monkey.

TITLE:
Effects of Rate of Oral Drug Input on Efficacy and Toxicity of Carbamazepine in Monkey Model

OBJECTIVE:
While no objective was stated in the protocol, it was understood, and later stated that the objective was

STUDY POPULATION:
Fourteen adult male monkeys (N=12 and 2 spares) (Macaca fasciularis: 3-5 kg weight) rendered experimentally epileptic by intracortical injection of aluminum hydroxide in the left postcentral gyrus during a sterile craniotomy.

STUDY DESIGN: Randomized crossover, balanced Latin square design with three treatments :

Treatment A: 36mg/kg CBZ given q4hr (Q4)
Treatment B: 18 mg/kg CBZ given q2hr (Q2)
Treatment C: 54 mg/kg CBZ given q6hr (Q6)

The total daily dose for each group in each treatment period would be 216 mg/kg/day and the study would consist of 6 dosing sequences within 5 sequential phases.

STUDY SCHEDULE Fourteen male monkeys were to be made experimentally epileptic. After their epileptic foci were fully developed the animals would be assigned to one of six dosing sequences. Each treatment would last for two weeks during which time monkeys would be monitored for seizure frequency, Tegretol concentrations, seizure free days, discharge amplitude.

PERIOD 1:
Purchase and Quarantine:
4 months
Preparation of lab and purchase of equipment and supplies

PERIOD 2:
Epileptic Preparation 4 months
Fourteen adolescent male monkeys (3-5 kg) would be made chronically epileptic by the intracortical injection of aluminum hydroxide in the left pre-and postcentral gyrus during a sterile craniotomy. After the animals developed a stable seizure frequency, the 12 study monkeys would be instrumented with a stomach catheter for drug delivery and dural electrodes for EEG interictal spike analysis.

PERIOD 3 : WEEKS 1-2
Baseline (2 weeks)

PERIOD 4: WEEK 3

Autoinduction (1 week)
18 mg/kg, q2h
Plasma sampling on days 1-7 (sample taken prior to dose)

PERIOD 5: **WEEKS 4-9**
Treatment (6 weeks)
Starting week 4 all animals were randomly assigned to one of the following 6 dosage sequences (2 animals per sequence)

	Week 4-5	Week 6-7	Week 8-9	ID
SEQUENCE A-B-C	36 mg/kg q4h	18 mg/kg q2h	54 mg/kg q6h	346, 843
SEQUENCE A-C-B	36 mg/kg q4h	54 mg/kg q6h	18 mg/kg q2h	405, 579
SEQUENCE B-C-A	18 mg/kg q2h	54 mg/kg q6h	36 mg/kg q4h	428, 882
SEQUENCE B-A-C	18 mg/kg q2h	36 mg/kg q4h	54 mg/kg q6h	516, 776
SEQUENCE C-B-A	54 mg/kg q6h	18 mg/kg q2h	36 mg/kg q4h	83
SEQUENCE C-A-B	54 mg/kg q6h	36 mg/kg q4h	18 mg/kg q2h	775,881

PERIOD 6:
Wash-out 1 week

PERIOD 7:
Post-baseline 2 weeks

REGIMEN/DOSAGE:
Drug administration would be via an implanted gastric catheter 4,6, or 12 times a day (q6h, q4h, or q2h) in a randomized sequence. The doses will be 18 mg/kg (q6h), 12 mg/kg q4h, or 6 mg/kg q2h such that all animals receive the same total daily dose of 72 mg/kg. In addition, the catheters would be flushed with varying volumes of water so that the total daily volume of suspension plus water will be the same for all animals.

18-MG/kg q2H = 216-MG/kg/day

Animals received the same TDD in one of three regimens allocated to a treatment sequence (one of 6) determined by randomization.

Data Collection: Information on seizure frequency, duration , seizure free days, carbamazepine levels was obtained.

Statistical Analysis: No statistical analysis was described.

CONDUCT OF THE TRIAL
Protocol Deviations
The alumina gel injection was completed while the monkeys were in the quarantine period. This resulted in a 6 month baseline period rather than a 4 month baseline period as specified in the protocol.

RESULTS:

MEAN SEIZURE COUNTS FOR EACH TREATMENT PERIOD

Baseline	I	II	III	stBaseline	ID
BL	q4h	q2h	q6h	PBL	
10.6	10	10.4	9.7	9.6	346
1.5	0.5	0.3	0.8	0.5	843
BL	q6h	q4h	q2h	PBL	
0.5	0.4	0.5	0.3	0.1	777
2.7	4.1	2.2	2.7	1.4	881
BL	q2h	q6h	q4h	PBL	
1.6	1.6	0.8	0.4	0	428
1.7	1.7	1.3	0.9	0.7	882
BL	q2h	q4h	q6h	PBL	
2.6	0.7	0.2	0.4	0.5	516
21.4	11.8	9.1	12.9	17.4	776
BL	q4h	q6h	q2h	PBL	
13.2	6.7	8.3	7.6	9.8	405
12.6	9.8	5.2	7.2	5.4	579
BL	q6h	q2h	q4h	PBL	
0.4	euthanized				835

STATISTICAL ANALYSIS(FIRM):
Comparisons between regimens were made by analysis of variance with multiple comparisons (Systat, Inc). significance level was set at p=1.017 (Bonferroni's correction for three comparisons).
The firm did not, however, submit these analyses for independent review.

In the August 16, 1993 submission, the sponsor wrote the following in response to one of numerous attempts on the part of the FDA to obtain the data and analysis from the Monkey Model study, "Ciba-Geigy has been unable to retrieve this material fron The circumstances surrounding the Monkey Model Study were discussed with the Division during a July 27, 1993 teleconference during which it was agreed that even if Ciba could retrieve the data, the value of the analysis would be extremely limited. "

FDA COMMENTS:

There are a number of problems with this study which render it unreliable.

1. The first of these is inaccuracy in tabulating the raw data by the investigator. Raw seizure counts were reviewed and retabulated and are not in agreement with those of the sponsor. Based upon the raw data and the guidelines in the protocol for counting all seizures during the last 10 days of each period, the following table results reflect the clinical reviewer's calculation of the mean seizure frequencies.

Baseline	I	II	III	[illegible]	ID
BL	q4h	q2h	q6h	PBL	
11	9.2	10.4	12	9.4	346
1	0.4	0.4	0.6	0.8	843
BL	q6h	q4h	q2h	PBL	
0.9	0.9	0.7	0	0.1	777
3.3	3.8	2.2	2.9	1.4	881
BL	q2h	q6h	q4h	PBL	
1.4	1	0.7	0.4	0	428
1.1	1.4	1.3	1.7	0.8	882
BL	q2h	q4h	q6h	PBL	
2	0.5	0.2	0.5	0.5	516
20.9	12	9.1	12.9	16.4	776
BL	q4h	q6h	q2h	PBL	
12.6	8.3	8.9	11.6	10.1	405
12.6	8.7	5.5	7.9	5.6	579
BL	q6h	q2h	q4h	PBL	
	euthanized				835

These data also demonstrate a high degree of variability among animals and with some animals failing to exhibit even one seizure per day. Such an event rate would hardly show a response to fluctuating plasma concentrations within a given 24 hour period.

2. The 14 day duration of dosing was sufficient to achieve steady state on each dosing regimen.

3. Evaluation of anticonvulsant effect was confounded by differences in CBZ absorption from the three dosage regimens. Progressively higher average plasma levels were attained after dosing every 2, 4, and 6 hours respectively. However the drug/metabolite ratio was not different for the three regimens indicating that this effect was not related to clearance changes but was due to changes int he total amounts absorbed. This was assumed (by the firm) to be species specific, it nevertheless renders the interpretation of the seizure results questionable at best.

5. The aluminum gel injection was completed while the monkeys were in the quarantine period. This resulted in a 6 month baseline period rather than a 4 month baseline period as specified in the protocol. Because no historical data was provided and because the seizure counts were also

not submitted during this time period it cannot be determined whether the baseline period represented a stable period for seizures or whether there was attenuation of seizure rates over time resulting in the low seizure counts seen in the majority of animals.

7. The animals used for this study were of the species *fascicularis*, rather than *rhesus*. The investigators did not provide supportive documentation of validation of this model with a new species.

8. Monkeys 428, 405, 579 and 346 received antibiotics, either 50 mg/kg Ampicillin suspension BID for 7 days or 1.5 ml Bactrim suspension. The possible interaction of these interventions with either treatment or the model itself was not discussed.

9. An incomplete study report with no statistical analysis was submitted by the sponsor. Sponsor was unable to obtain further information from the investigator.

10. The study is extremely small, calculations were not submitted to justify sample size.

In summary, there are problems with the consistency of seizure frequencies in this model, consisitent and reliable delivery of drug via the various regimens, adequacy of sample size and failure to adequately analyze results.

The sponsor has concurred that this is a failed study.

8.0 SAFETY FINDINGS

The purpose of this section is to assess the safety data submitted in this NDA in order to identify if any additional analysis may be needed to establish the reasonable safety of the new formulation. The firm asserts that the safety of carbamazepine was established by NDA 16-608 and submits the prior evidence for support of this application, through reference to the above NDA. There are no new indications proposed in this submission. While carbamazepine was studied sufficiently for approval, the characteristics of this new formulation do raise new safety issues. While the peaks and valleys of carbamazepine levels are not as prominent in Tegretol XR® as seen in commercial product they are not identical and therefore the potential for new safety issues to arise with this formulation is real. In addition to the previously identified adverse effect of bone marrow suppression, the clinical data base was evaluated for additional new findings.

8.1 Methods

In evaluating the safety of Tegretol XR® the Tegretol XR®-exposed population was examined for serious adverse events and commonly collected and reported safety data were reviewed. The data that were relied upon for the assessment of serious adverse events were the tabular summaries of adverse events determined to be serious by the investigators. No case report forms were provided in this submission. The population relied upon for these was the total exposed population including subjects and patients. Additional materials that were reviewed for this analysis included the Integrated Safety Summary (NDA Vol 1.20 filed October 31, 1991),

the Amendment#1 (NDA Vol. 2.1-2.6[2] filed May 11, 1992), and the tabular summaries as provided as part of each individual study report. There has been no formal Safety Update filed to this NDA since there have been no exposures since study 36. Nevertheless the firm was asked to file a cumulative report to encompass the new information provided in the May 11, 1992 amendment. This safety review is current as of May 11, 1992 in the drug's development.

The total number of individuals exposed to drug in all studies as of May 11, 1992 was 192. Patient exposure to TEGRETOL XR® should have totalled 155 and is summarized in the following table of dose and duration of exposure. Note that the totals do not add up to 155 since patients who dropped out prior to Tegretol XR® exposure are not included. In actuality a total of 143 patients were exposed to Tegretol XR® in this NDA.

TABLE: SUMMARY OF EXPOSURE TO TEGRETOL XR® BY DOSE AND DURATION--ALL PATIENTS

Dose	<4 weeks	4-6 weeks	6-10 weeks	10-13 weeks	13-16 weeks	Total
400 mg	8	0	6	1	0	15
600 mg	2	0	0	0	0	2
800 mg	11	1	35	0	0	47
1000 mg	8	0	0	0	0	8
1200 mg	17	0	27	1	0	45
1400 mg	0	1	0	0	0	1
1600 mg	3	0	15	0	0	18
2000 mg	3	0	3	1	0	7
Total	52	2	86	3	0	143

8.2 Deaths

There were no deaths associated with exposure to Tegretol XR® in any of the clinical trials covered under this NDA.

8.3 *Assessment of Dropouts*

There were 16 discontinuations during the clinical trials involving Tegretol XR® . Two subjects and two patients withdrew from trials. Both patients were terminated because they did not meet study criteria. One subject refused to continue in the trial because of discomfort associated with blood tests. A second subject was lost to follow-up after relocating.

In addition there were 14 patient withdrawals from study 36. A clinical comparison study of Tegretol XR® and commercial Tegretol. Of these 5 withdrew during the run-off phase during which patients received their standard Tegretol monotherapy in their accustomed dose. In addition there were 4 withdrawals during the Tegretol XR® treatment phase and 5 during the commercial Tegretol treatment. Patients were blinded during treatment.

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[2] Study 36 reported in volumes 2.1-2.6 filed May 11, 1992.

Overall Pattern of Dropouts
Discontinuations were classified according whether they occurred because of adverse events or administrative reasons. The overall dropout incidence by TEGRETOL XR®-treated patients and subjects from TEGRETOL XR® studies is quite low seen in the table below.

Withdrawal Rates by Treatment Group

Reason for Withdrawing	Percent Withdrawals TEGRETOL XR®	Percent Withdrawals Commercial Tegretol
All Clinical Studies		
Subjects	N= 37	N= 37
Adverse Events	0	0
Criteria not met	0	0
Other/Administrative	3	0
Subtotal	3	0
Patients	N= 155	N=155
Adverse Events	0	
Criteria not met	0	
Other/Administrative	16[1]	
Subtotal	16	
Total	N= 192	N= 192
Adverse Events	0	
Criteria not met	0	
Other/Administrative	19	

[1] Patient 506 Center 6 withdrew from study 36 because of a cardiac arrythmia for which he was hospitalized. This was recorded as a concomitant illness and not as an adverse event.

Adverse Events Associated with Dropout The most common reason for discontinuation from treatment with TEGRETOL XR® was administrative--that is the patient was noted not to meet the study criteria. No adverse events were listed as a reason for withdrawal from clinical studies with Tegretol XR®

8.4 Other Safety Findings

There were no commonly observed adverse events associated with the use of TEGRETOL XR® (incidence of 5% or greater) that were not seen at an equivalent incidence among commercial tegretol patients.

8.5 LABORATORY FINDINGS

No new laboratory patterns emerged with Tegretol XR® which were not previously described with the commercial formulations. The most common finding in clinical laboratory evaluations was decreased white count. Depressed white counts were

reported with similar frequency in the active control group, that is, those patients treated with Commercial Tegretol.

Summary
The changes seen in clinical laboratory evaluations during TEGRETOL XR® adjunctive therapy were infrequent, small in magnitude, and generally not clinically significant. In addition, there were no reports of withdrawals due to abnormal laboratory variables.

Vital Signs: No unexpected adverse effects on vital signs were demonstrated in this NDA.

ECG's The percentage of patients in a pool of active controlled studies with ECG judged to be "more abnormal" as compared to an earlier tracing is very low. There were no reports of patients withdrawing from clinical trials due to arrhythmias or other ECG abnormalities during TEGRETOL XR® therapy.

Withdrawal Phenomena/Abuse Potential
Abuse potential was not evaluated in clinical trials with Tegretol XR®.

Human Reproduction Data
There have been no pregnancies reported during clinical trials in epilepsy with

8.7 Overdose Experience
There were no drug overdoses associated with Tegretol XR® reported in this NDA.

8.8 Summary of Serious Events
As required by 21 CFR 312.32 (a), the sponsor used the term 'serious' to describe certain kinds of AEs. No serious adverse events associated with use of Tegretol XR® were reported in this NDA.

8.9 Summary of Drug Interactions

Drug demographic Interactions
The demographics of the TEGRETOL XR® development program are insufficient to determine if there is an interaction with regard to this formulation and age, sex, or racial background. The adverse event profile for men and women was similar in all epilepsy studies with TEGRETOL XR®. Caucasians were overrepresented in TEGRETOL XR® studies. It is not possible to determine, based on the small numbers of blacks and orientals if there is an interaction with race. No effect of sex on the incidence of particular adverse events was appreciated. demographic/adr tables)

Drug-Disease Interactions

There is limited clinical experience with the use of TEGRETOL XR® in systemic disease. In the development program for commercial Tegretol, there have been several interaction studies specifically performed in an effort to explore the possibility of interaction between Tegretol and systemic disease, specifically renal and hepatic disease, using limited doses and duration of treatment.

8.10 SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

As of the most recent submission of data, specifically May 11, 1992 data from clinical studies involving 192 subjects and patients indicate that TEGRETOL XR® has a safety profile that is comparable to what is known about commercially available tegretol formulations. In its limited clinical database of 192 patients and subjects, TEGRETOL XR® has a risk profile that is generally favorable.

While the limited data presented in this NDA may indeed reflect the expected safety profile of Tegretol XR® as compared to the currently available compound, there is at least the theoretical possibility that with the altered pharmacokinetic profile of the drug, the risks associated with the commercially available compound may be increased in this formulation. That is to say that with more consistent blood levels, target organs for toxicity may not have the benefit of recovery. Without more safety data it is not possible to determine if this compound has the same risks as the commercial compound. In the 192 exposures there was not an abundance of adverse events. However, an increase in the incidence of rare events such as agranulocytosis or aplastic anemia would not expected to be apparent in such a small group.

9.0 Conclusions

There is a failure of the Tegretol XR® formulation to meet current bioequivalence standards. In the absence of bioequivalence, clinical studies should have been performed. The monkey model study is not an acceptable substitute for human efficacy studies.

10.0 Recommendations

In conclusion NDA is not approvable because of failure to meet the current standards of bioequivalence which should reflect both the parent drug and the active metabolite of tegretol. Absent bioequivalence and clinical efficacy data there are no grounds on which this NDA can be approved. It is recommended that the sponsor obtain appropriate controlled clinical trial experience in an effort to establish the drug's efficacy and to further define the safety profile of this new formulation. Alternatively, reformulation of the product such that it meets current standards for bioequivalence would be agreeable.

Cynthia McCormick MD

Cynthia G. McCormick, M.D.
Clinical Reviewer

August 2, 1995

MAY 28 1993

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-234/ Drug Class 3S

APPLICANT: Ciba-Geigy Corporation

NAME OF DRUG: Tegretol-XR (Carbamazepine, USP)

INDICATION: Treatment of Epilepsy

DOCUMENTS REVIEWED: Volume 2.1-2.5, dated May 11, 1992 **(Monkey Model).**

MEDICAL REVIEWER: Cynthia McCormick, MD (HFD-120). This review has been discussed with the medical reviewer who is in agreement with the conclusions stated.

RELEVANT ISSUE BROUGHT OUT IN THIS REVIEW: Since the results of this study are inconclusive, there is still a need for conducting a well-controlled study for the use of **Tegretol-XR** for the treatment of epilepsy. The sponsor should conduct another study incorporating the suggestions given by this reviewer.

I. INTRODUCTION

Carbamazepine (**Tegretol**) is used for the treatment of patients with epilepsy. The therapeutic plasma concentration range for carbamazepine is generally accepted to be 4-12 µg/ml. To maintain levels within this range requires multiple daily dosing with the existing commercial tablets up to a total of 2000 mg/day. Decreasing the dosing frequency could benefit patients on chronic therapy by simplifying their treatment regimens. However, in achieving this effect, tolerability and efficacy may be compromised as a result of increased fluctuations in plasma concentrations during the dosing interval. The design of **Tegretol-XR** permits precise control of drug delivery to be achieved, allowing blood levels to be maintained within narrow limits. The effects of three dosing regimens on the anticonvulsant and pharmacokinetic behavior of carbamazepine (CBZ) was investigated in a **Monkey Model** of epilepsy.

This review has been arranged in 3 sections: Section I contains an introduction and background of Tegretol-XR, section II contains sponsor's results, section III contains this reviewer's conclusions and recommendations.

KEY WORDS: Epilepsy, Latin Square Design, Crossover.

II. SPONSOR'S DESCRIPTION OF RESULTS (MONKEY MODEL)

Objective

The sponsor did not spell out the objective of the study. Apparently, the study was conducted to determine if the rate of CBZ administration had significant impact on the drug's ability to abate chronic, uncomplicated seizures in an animal model of epilepsy.

Design

The study was a randomized, crossover, balanced, Latin square design with three treatments:

Treatment A: 36 mg/kg CBZ given q4hr (Q4);
Treatment B: 18 mg/kg CBZ given q2hr (Q2);
Treatment C: 54 mg/kg CBZ given q6hr (Q6).

Thus the total daily dose for each monkey was 216 mg/kg. The study consisted of six dosing sequences within 5 sequential phases:

Phase 1 (Weeks 1-2): No drug, baseline phase;
Phase 2 (Week 3): Auto-induction phase (18 mg/kg CBZ, q2hr);
Phase 3 (Weeks 4-9): Treatment phase according to the following schedule:

Dose Sequence	***Weeks 4-5***	***Weeks 6-7***	***Weeks 8-9***
A - B - C	q4hr	q2hr	q6hr
A - C - B	q4hr	q6hr	q2hr
B - C - A	q2hr	q6hr	q4hr
B - A - C	q2hr	q4hr	q6hr
C - B - A	q6hr	q2hr	q4hr
C - A - B	q6hr	q4hr	q2hr

Phase 4 (Week 10): Drug-clearance phase;
Phase 5 (Weeks 11-12): Post-baseline phase.

Monkeys

Fourteen monkeys were acquired for this study: 12 for treatment and 2 spares. All monkeys eventually were enrolled into the study. All of these animals received intercortical injection of aluminum hydroxide during the 4-month preparation period. Three of the monkeys developed *status epilepticus* either during the preparation period or before the formal study start date, and one monkey developed *status epilepticus* during the post-baseline period and was euthanized. Thus, 10 monkeys completed all phases of the study.

Efficacy Variables

The drug effect data consisted of seizure frequency, number of seizure-free days, percent CBZ fluctuation and white cell counts. The data were reported according to study phases including initial baseline (B), the three different dosing regimens (Q2, Q4, and Q6), and the baseline following drug withdrawal (called Post-Baseline (PB)).

Sponsor's Results

Following the aluminum hydroxide preparation period, seizure frequency was recorded round the clock for a two-week period. The final ten daily polygraphs were read and recorded as baseline seizure rates. Following the drug administration period, the same procedure was followed and reported as post-baseline rates. These data were reported by the investigators as average daily seizure frequency and are shown below.

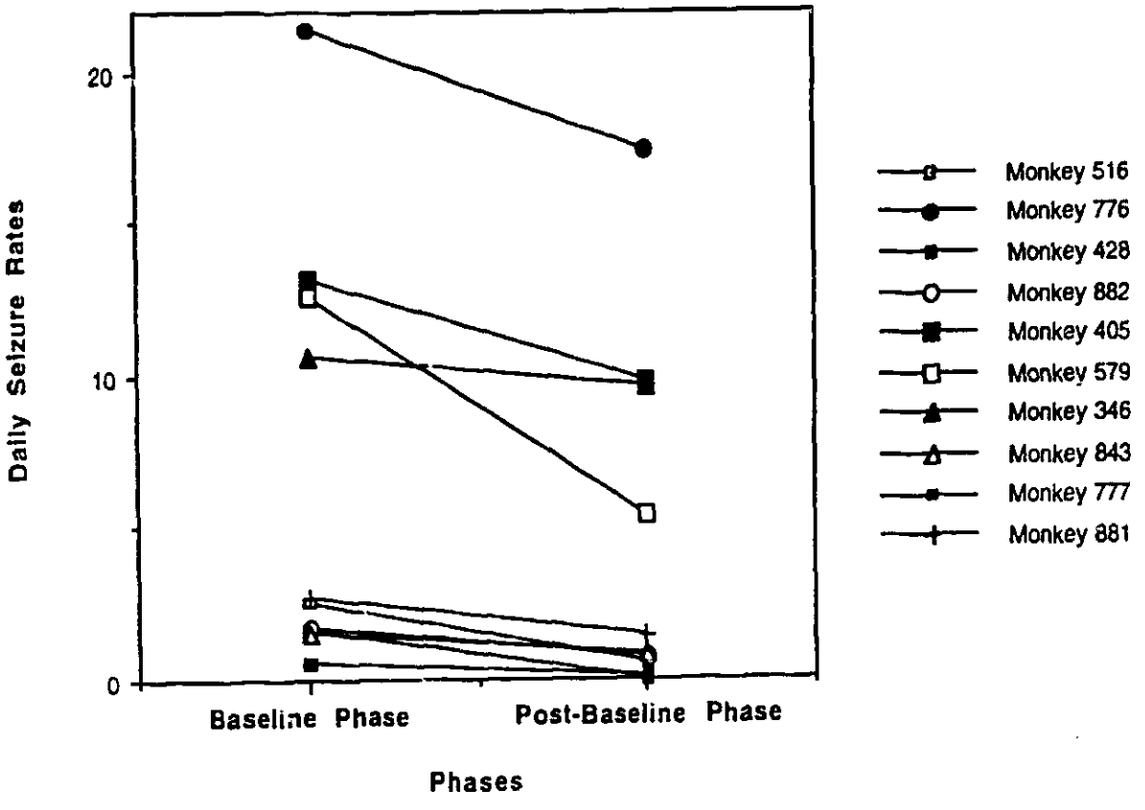
Daily Seizure Rates for Baseline and Post-Baseline Periods
(Table entries represent average daily rates over a 10-day period)

Monkey ID	Baseline	Post-Baseline
516	2.6	0.5
776	21.4	17.4
428	1.6	0.0
882	1.7	0.7
405	13.2	9.8
579	12.6	5.4
346	10.6	9.6
843	1.5	0.8
777	0.5	0.1
881	2.7	1.4
Mean	6.8	4.6
SD	6.8	5.6

It is clear from these results that not only is the daily seizure rate highly variable within this group, but the majority of animals failed to exhibit a seizure frequency much greater than one per day. Given that the apparent objective of this study was to determine if the extent of CBZ plasma concentration fluctuation has an impact on its anticonvulsant activity and the means of causing those fluctuations is variation in administration ranging from every 2 hours to every 6 hours, according to the sponsor, it seems very unlikely that a baseline seizure rate of less than 4 per day is sufficient to expect to see any differences if they exist.

Another complicating factor in the daily seizure rates is the lack of stable seizure counts between the two baseline periods. In the figure below, it can be seen that all 10 animals exhibited lower daily seizure rates in the post-baseline period.

DAILY SEIZURE RATES DURING BASELINE AND POST-BASELINE PERIODS



The 6 monkeys who exhibited few seizures during the initial baseline period (mean 1.77/day) demonstrated 67% fewer daily seizures (mean 0.58/day) during the post-baseline period. These animals are clearly not evaluable within the design of this study. The sponsor concluded that, without a placebo control group to characterize the rate of change of baseline and considering the paucity of seizures exhibited by these animals, there is no valid means to evaluate the effects of the CBZ treatment periods.

The 4 monkeys who exhibited a reasonable seizure frequency during the initial baseline period also demonstrated a reduction during the post-baseline period. On balance, however, the mean daily seizure rate during the post-baseline period was still 73% of that observed during the initial baseline period and data collected from these animals may be evaluable.

The third complicating factor in this study is the periodicity of seizure occurrence as a function of the time of the day. This apparent diurnal dependence of seizure occurrence appears to be a new finding for this model. The effect appears in each of the monkeys and, in fact, there is a hint of a secondary periodicity within the day for some of the animals (see Figure 2, p. 136, vol 2.1). A copy of this figure is attached.

III. CONCLUSIONS AND RECOMMENDATIONS

There are several problems with this NDA submission. Some of them are listed below.

1. Protocol

The protocol itself was very poorly written. There was, for example, no mention of the objective of the study.

An insufficient number of monkeys were used in this study. Appropriate calculations were not done to compute a reasonable sample size.

Also, efficacy variables were not spelled out. Only the quantification of seizure frequency was mentioned. The protocol did not spell out the plans for statistical analyses.

The sponsor's analyses should include appropriate confidence intervals comparing different regimens.

2. Sponsor's Inconclusive Results

The sponsor concluded that there were no valid means to evaluate the effects of the CBZ treatment periods. Some of the reasons for this conclusion are given below.

First, only 4 monkeys of the 10 who completed the study achieved sufficient daily seizure frequency to have a reasonable opportunity to see differences in the three dosing regimens.

Second, since a placebo control group of monkeys was not included in the study, there is no valid method to evaluate the effects of the CBZ treatment periods.

Third, this monkey model exhibits a consistent diurnal seizure frequency pattern.

Recommendation

In view of the problems and complications observed in this study, the sponsor should conduct another study incorporating the suggestions given by this reviewer.

BKTaneja

Baldeo K. Taneja
Mathematical Statistician (Biomed)

Concur: Dr. Nevius SEN 5-20-93

Dr. Dubey 5-28-93

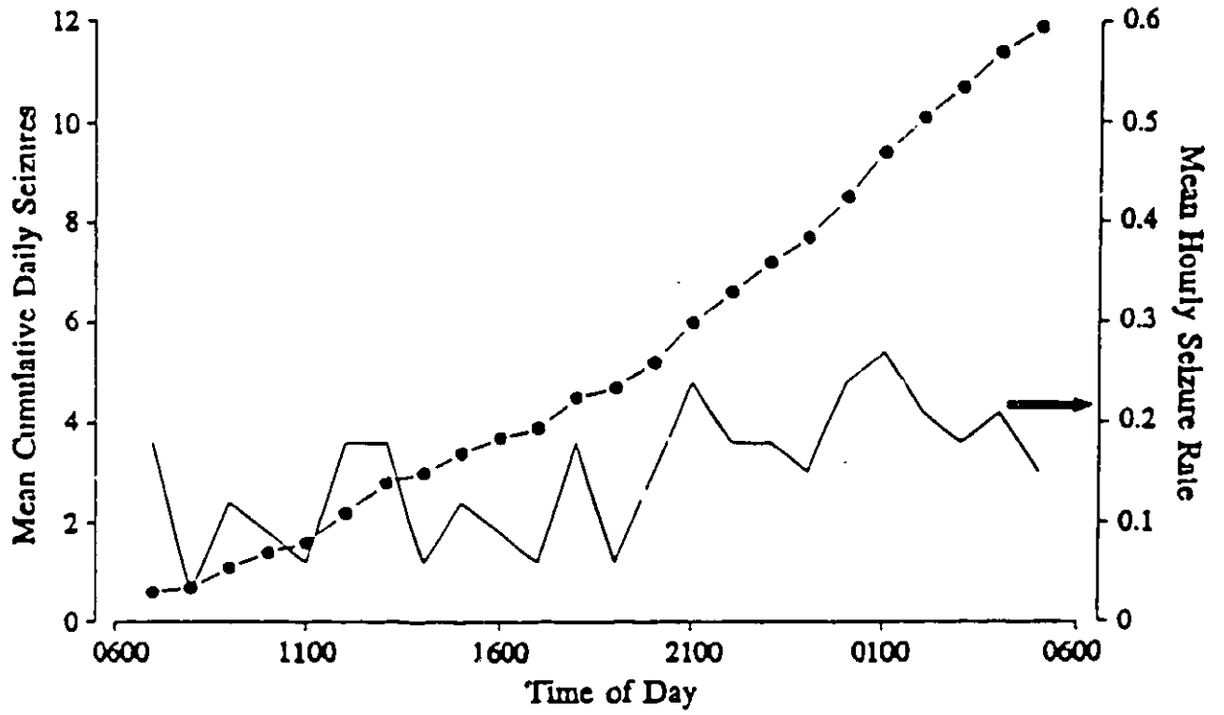
cc:
Orig. NDA 20-234
HFD-120
HFD-120/Dr. Leber
HFD-120/Dr. Katz
HFD-120/Dr. McCormick
HFD-120/Ms. Chamberlin
HFD-713/Dr. BTaneja
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Group 2 File
HFD-344/Dr. Lisook

Chron.
BKT/NDA 20-234/WordPerfect/05-05-93

This review contains 6 pages of text plus 1 page containing figure.

Figure 2

Mean daily occurrence of seizures in monkey #579 as a function of time of day. Cumulative curve represents hourly averages of the 10 day recording period during baseline assessment. The hourly rate data are averaged for the 10 day period as well.



OCT 16 1995

NDA 20-234 Submission Date: Oct. 4, 1995

COMPLETED

SPONSOR: Ciba Geigy
Summit, NJ

OCT 17 1995

DRUG: Tegretol-XR (carbamazepine; 100, 200, and 400 mg extended release tablets)
INDICATION: Anti-epileptic
TYPE OF SUBMISSION: Reanalysis of data
REVIEWER: Robert Harris, Ph.D.

SUMMARY

In order to demonstrate that Tegretol-XR is bioequivalent to the marketed immediate release dosage form, the sponsor previously submitted the results of a steady state bioequivalence study (91024). While the study demonstrated bioequivalence for parent drug, it failed to demonstrate equivalence for carbamazepine 10,11 epoxide, a major metabolite which is believed to have activity comparable to that of carbamazepine. The epoxide fell below the acceptable range for the demonstration of equivalence for Cmin and AUC in children and Cmin in adults. Per the suggestion of the Agency, the sponsor reanalyzed the data to determine whether the products were bioequivalent in terms of total activity. Total activity is defined as the summation of the carbamazepine and epoxide concentrations. The sponsor performed this analysis by using both total and unbound concentrations. In each case, the products were shown to be bioequivalent for all parameters in adults and children (Attachment 1).

COMMENTS

1. The sponsor has adequately demonstrated bioequivalence for total activity (parent + epoxide) in adults and children. The demonstration of bioequivalence is valid only if it is assumed that the epoxide has activity (and toxicity) comparable to, or less than that of the parent drug.

2. All of the parameters (AUC, Cmax and Cmin) for total activity fall within the lower portion of the acceptable confidence interval with the OROS product as the test. This result suggests that patients would be exposed to approximately 10% less activity if switched from the immediate release product to the sustained release product. This change in exposure should be described in the labelling.

RECOMMENDATION: In adults and children, bioequivalence is observed between Tegretol OROS and conventional tablets for AUC, Cmax, and Cmin, based on the analysis of total activity (using either total or unbound concentrations). Please see Comments 1-2.

Robert Harris 10/16/95

Robert Z. Harris, Ph.D.
Pharmacokinetics Evaluation Branch I

R. Baweja 10/16/95

FT initialed by Raman Baweja, Ph.D.

cc: NDA 20-234, HFD-120, HFD-426 (Harris, Baweja, Malinowski), Chron, Drug and Reviewer files.

ATTACHMENT 1

Exhibit 4.1.-1. Summary of total active drug pharmacokinetics for adult patients (unweighted data) (N = 21)

Adult Patient	Tablet			OROS			Ratios (OROS:Tablet)		
	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}
Mean	228.4	11.31	8.02	213.8	10.31	7.17	0.94	0.92	0.90
SD	46.6	2.58	1.72	43.8	2.15	1.63	0.09	0.11	0.14
CV%	20.4	22.8	21.5	20.5	20.9	22.7	9.7	11.6	15.7

Exhibit 4.1.-2. Summary of total active drug pharmacokinetics for pediatric patients (unweighted data) (N =12)

Pediatric Patient	Tablet			OROS			Ratios (OROS:Tablet)		
	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}
Mean	251.7	12.34	8.63	222.5	10.72	7.87	0.88	0.87	0.91
SD	60.3	2.89	2.10	55.7	2.48	2.17	0.08	0.06	0.14
CV%	23.9	23.4	24.3	25.0	23.2	27.6	9.5	6.9	14.9

Exhibit 4.1.-3. Summary of total active drug pharmacokinetics for all patients (unweighted data) (N = 33)

All Patient	Tablet			OROS			Ratios (OROS:Tablet)		
	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}
Mean	236.8	11.7	8.24	217.0	10.5	7.43	0.92	0.90	0.91
SD	52.3	2.70	1.86	47.8	2.25	1.84	0.09	0.09	0.14
CV%	22.1	23.1	22.5	22.0	21.5	24.8	10.0	10.5	15.1

Exhibit 4.1.-4. Summary of total active drug pharmacokinetics for adult patients (weighted data) (N = 21)

Adult Patient	Tablet			OROS			Ratios (OROS:Tablet)		
	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}
Mean	62.9	3.09	2.21	58.3	2.81	1.95	0.93	0.92	0.89
SD	14.4	0.77	0.51	12.7	0.64	0.45	0.09	0.10	0.14
CV%	22.9	25.0	23.2	21.8	22.9	23.0	10.2	11.3	15.4

Exhibit 4.1.-5. Summary of total active drug pharmacokinetics for pediatric patients (weighted data) (N =12)

Pediatric	Tablet			OROS			Ratios (OROS:Tablet)		
Patient	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}
Mean	67.6	3.29	2.35	59.4	2.84	2.11	0.88	0.87	0.89
SD	16.6	0.79	0.58	15.4	0.68	0.60	0.09	0.06	0.14
CV%	24.6	24.1	24.9	25.9	23.8	28.3	9.9	6.6	15.5

Exhibit 4.1.-6. Summary of total active drug pharmacokinetics for all patients (weighted data) (N = 33)

All	Tablet			OROS			Ratios (OROS:Tablet)		
Patient	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}	AUC	C_{max}	C_{min}
Mean	64.6	3.16	2.26	58.7	2.8	2.01	0.91	0.90	0.89
SD	15.1	0.77	0.54	13.5	0.65	0.50	0.09	0.09	0.14
CV%	23.4	24.5	23.7	23.0	22.9	25.1	10.4	10.3	15.2

4.2. Statistics

- Log transformed results of unweighted and weighted total active drug (CBZ + CBZE)

The results of statistical analyses of log transformed, unweighted and weighted, total active drug data is summarized below in Exhibits 4.2.-1 to 4.2.-3. Detailed results are displayed in Tables 4.2.-1 and 4.2-2. The results of this analysis showed that the confidence intervals are within the acceptable limit (between 0.80 and 1.25) for AUC, C_{max}, and C_{min} for establishing bioequivalence between the OROS and conventional tablets.

Exhibit 4.2.-1. Summary of the 90% confidence intervals for adult patients (N =21)

90% confidence intervals	ln (AUC)	ln (C_{max})	ln (C_{min})
Unweighted			
Lower	0.90	0.87	0.84
Upper	0.97	0.96	0.95
Weighted			
Lower	0.89	0.87	0.82
Upper	0.97	0.96	0.94

Exhibit 4.2.-2. Summary of the 90% confidence interval for pediatric patients (N =12)

90% confidence intervals	ln (AUC)	ln (C_{max})	ln (C_{min})
Unweighted			
Lower	0.83	0.84	0.82
Upper	0.92	0.90	0.98
Weighted			
Lower	0.83	0.83	0.81
Upper	0.92	0.90	0.96

Exhibit 4.2.-3. Summary of the 90% confidence interval for all patients (N = 33)

90% confidence intervals	ln (AUC)	ln (C_{max})	ln (C_{min})
Unweighted			
Lower	0.88	0.86	0.85
Upper	0.94	0.92	0.94
Weighted			
Lower	0.87	0.86	0.84
Upper	0.93	0.92	0.93

- Log transformed CBZ & CBZE data

The log transformed data of CBZ and CBZE from Protocol 37 were reanalyzed due to a programming error in the statistical program used to generate the original results (submitted to NDA 20-234 on March 27, 1992). Results of the reanalysis were very similar to those originally submitted, and are still consistent with the reported conclusions. The results of statistical reanalyses are summarized in Exhibits 4.2.-4 to 4.2.-6. Detailed results are displayed in Tables 4.2.-3 and 4.2.-4.

Exhibit 4.2.-4. Summary of the 90% confidence intervals on log-transformed data for adult patients

90% confidence intervals	ln (AUC)	ln (C_{max})	ln (C_{min})
CBZ (N = 22)			
Lower	0.91	0.86	0.85
Upper	0.98	0.95	0.97
CBZE (N = 21)			
Lower	0.85	0.87	0.77
Upper	0.94	0.97	0.87

Literature was surveyed for CBZ and CBZE unbound free fractions. The results are listed below in Exhibit 3.1.

Exhibit 3.1. Summary of literature values, mean (range), reported for the unbound free fraction of CBZ and CBZE

Literature references	CBZ	CBZE
Kodama et al., 1994 (Lit. 3)	0.24 (0.19 - 0.33)	0.47 (0.30 - 0.57)
MacKichan et al., 1984 (Lit. 4)	0.24	0.55
Kodama et al., 1993 (Lit. 5)	0.22 (0.15 - 0.30)	0.47 (0.33 - 0.67)
Kodama et al., 1993 (Lit. 6)	0.24 (0.23 - 0.25)	0.42 (0.40 - .42)
Liu et al. 1995 (Lit. 7)	0.19	0.38
Average	0.23	0.46

Weighted total active drug levels at each time point were derived by the summation of weighted CBZ and CBZE concentrations:

1. weighted CBZ concentration = 0.23 * CBZ concentration and;
2. weighted CBZE concentration = 0.46 * CBZE concentration.

Figure 4.1.-1: Mean ± S.D. (N = 21) steady-state plasma levels of total active drug (CBZ + CBZE) in adult patients (Day 21)

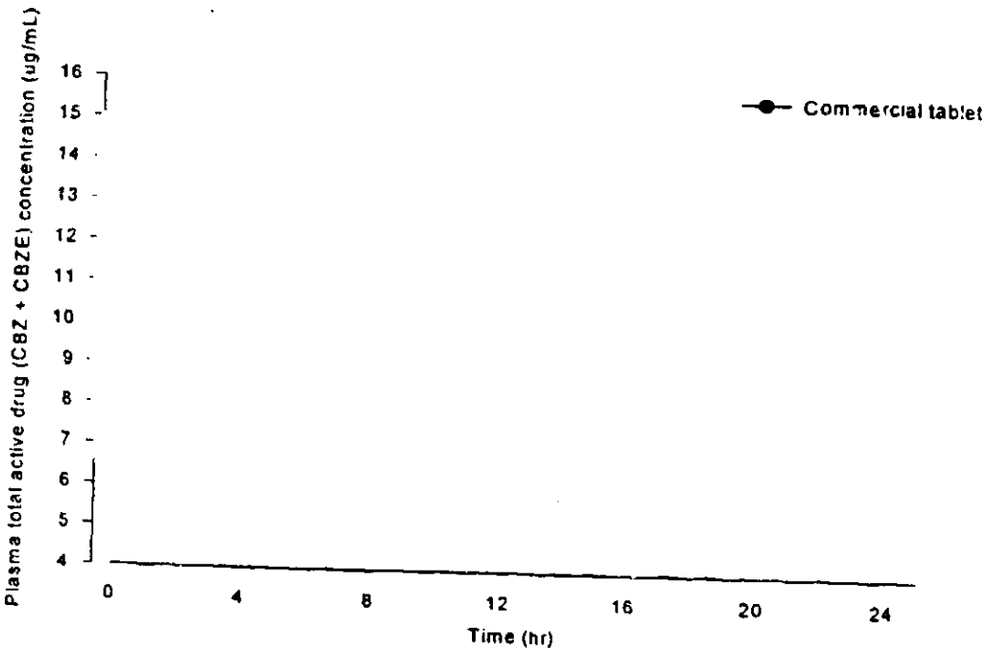
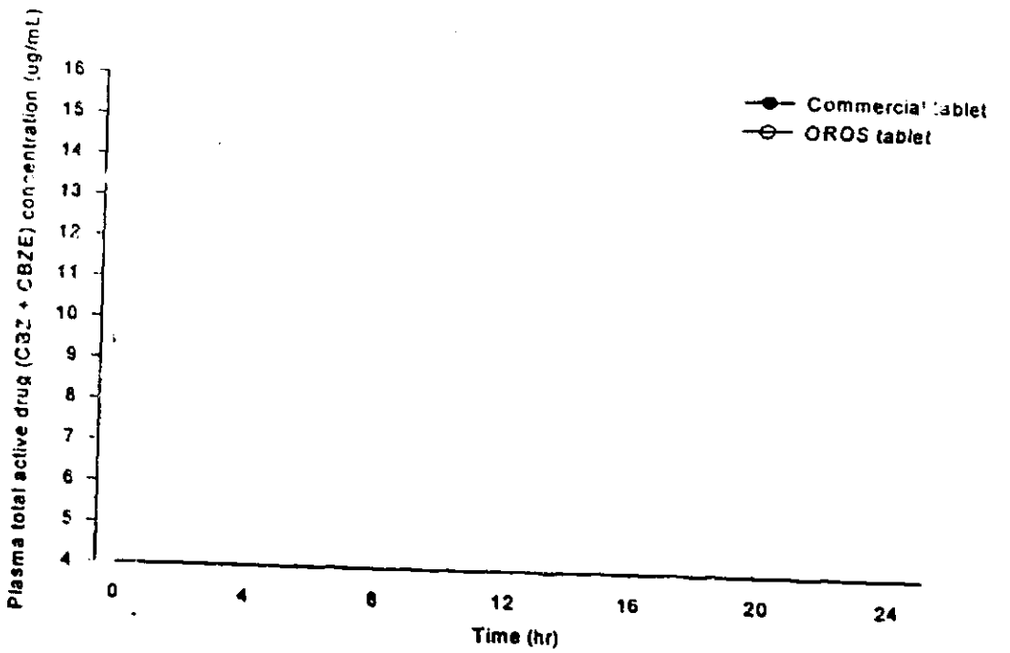


Figure 4.1.-2: Mean ± S.D. (N = 12) steady-state plasma levels of total active drug (CBZ + CBZE) in pediatric patients (Day 21)



Supervisory Comments for File

NDA 20-234
Tegretol XR (OROS)

Reviewer Atiqur Rahman, PhD

Supervisor Victoria Hale, PhD

Through Tom Ludden, PhD, Director, Div Biopharmaceutics

date December 14, 1994

Advantages of dosage form:

The Division of Biopharmaceutics believes that this formulation of carbamazepine (Tegretol XR) is an advantage over the old formulation (Tegretol). Immediate release Tegretol exhibits extreme variability in performance as related to absorption. Tmax can be as late as 24 hours with this old formulation, probably due to slow release of drug from the formulation. Tegretol XR is a controlled-release OROS formulation which approximates zero-order release for several hours. Therefore, this new formulation performs much more consistently with regard to absorption.

The Division of Biopharmaceutics believes that drug absorption (secondary to release from the formulation) is an important component of therapy and that as Tegretol XR improves absorption performance, Tegretol XR offers a significant advantage over Tegretol.

Results: see data tables (attached).

Important issues:

1. The bicequivalence argument proposed by the sponsor is based on parent drug: BID XR vs QID & BID immediate release formulation. On this basis alone the product is approvable; however, the epoxide metabolite is as active as the parent drug in animal models and therefore deserves some consideration.

2. The Office of Generic Drugs does not measure carbamazepine epoxide as a basis for approval. The metabolite falls out of the 80-125% CI range (see tables - relevant parameters circled) in several cases.

3. It is important to note that both the parent and metabolite are on the low side of the confidence interval range in most studies, often failing to include 100%.

Conclusion:

Because parent and metabolite parameters produced with the XR formulation often fail to include 100% in the CI and because the metabolite occasionally fell below 80%, it is recommended that the sponsor consider incorporating more drug into the XR dosage form. The OROS type of product is commonly overfilled; this additional amount of drug would increase the overfill slightly.
Assuming the results of a bioequivalence test are as expected, the Agency could then have more confidence in the ability of the product to produce equivalent plasma drug concentrations of the active species when it is substituted for the conventional immediate release product.

Recommendation:
1. The sponsor should increase the amount of active drug in the dosage form.
2. The sponsor should perform a multiple dose bioequivalence test with the new dosage form under multiple dosing conditions in epilepsy patients comparing BID XR with QID Tegretol in a crossover manner (repeat the study performed in this NDA).

Victoria G Hale, PhD
Pharmacokineticist

CC NDA 20234
HFD-120 - 3 copies
HFD-426 - drug, reviewer, chron, CR file, Ludden, Fleischer, Rahman, Hale, Baweja
HFD-340 - Viswanathan
FOI
FT 12/14/94

9102A- multidose
BID OROS vs. QID IR

Steady-State pharmacokinetics of carbamazepine and carbamazepine-10, 11- epoxide after treatment with Tegretol conventional and Tegretol OROS tablet (Pediatric)

Parameters (units)	Tegretol OROS	Tegretol conventional tablet
CARBAMAZEPINE		
C_{Max} (µg/ml)	9.10 ± 2.10	10.39 ± 2.41
90% CI	83.65% - 91.40	
C_{Min} (µg/ml)	6.57 ± 1.82	7.07 ± 1.70
90% CI	88.86% - 96.97	
$AUC_{(0-24)}$ (µg.hr/ml)	186.87 ± 46.00	209.38 ± 49.94
90% CI	86.59% - 91.90%	
FI	0.34 ± 0.17	0.38 ± 0.17
p value	0.48	
T_{Max} (hours)	15.00 ± 8.16	13.67 ± 6.76
p value	0.61	
CARBAMAZEPINE 10,11- EPOXIDE		
C_{Max} (µg/ml)	1.78 ± 0.61	2.05 ± 0.07
90% CI	81.77% - 91.26%	
C_{Min} (µg/ml)	1.27 ± 0.54	1.48 ± 0.56
90% CI	78.78% - 93.01%	
$AUC_{(0-24)}$ (µg.hr/ml)	35.61 ± 13.86	42.32 ± 14.92
90% CI	79.64% - 88.67%	
T_{Max} (hours)	13.67 ± 10.88	11.67 ± 8.73
p value	0.61	
FI	0.40 ± 0.28	0.33 ± 0.14
p value	0.48	

N = 12
Mean ± Standard deviation

91024- multidose
BID OROS vs. QID IR

Steady-State pharmacokinetics of carbamazepine and carbamazepine-10, 11- epoxide after treatment with Tegretol conventional and Tegretol OROS tablet (Adult)

Parameters (units)	Tegretol OROS	Tegretol conventional tablet
CARBAMAZEPINE		
C_{Max} (µg/ml)	8.21 ± 1.92	9.05 ± 2.08
90% CI	86.98% - 94.45%	
C_{Min} (µg/ml)	5.72 ± 1.53	6.25 ± 1.54
90% CI	86.44% - 96.46	
$AUC_{(0-24)}$ (µg.hr/ml)	170.15 ± 41.16	179.94 ± 40.03
90% CI	91.79% - 97.33%	
FI	0.35 ± 0.18	0.38 ± 0.15
p value	0.57	
T_{Max} (hours)	11.73 ± 8.31	14.73 ± 5.87
p value	0.23	
CARBAMAZEPINE 10,11- EPOXIDE		
C_{Max} (µg/ml)	1.98 ± 0.89	2.19 ± 1.07
90% CI	85.17% - 95.94%	
C_{Min} (µg/ml)	1.26 ± 0.54	1.56 ± 0.73
90% CI	75.15% - 86.75%	
$AUC_{(0-24)}$ (µg.hr/ml)	39.62 ± 17.29	44.96 ± 22.02
90% CI	82.81% - 93.67%	
T_{Max} (hours)	10.38 ± 8.33	15.43 ± 7.30
p value	0.01	
FI	0.41 ± 0.20	0.32 ± 0.14
p value	0.012	

N = 22
Mean ± Standard deviation

9/023 - multidose
BID: OROS & IR

Steady-State pharmacokinetics of carbamazepine and carbamazepine-10, 11- epoxide after treatment with Tegretol conventional (200 mg) and Tegretol OROS (200 mg) tablet

Parameters (units)	Tegretol OROS	Tegretol conventional tablet
	CARBAMAZEPINE	
C_{Max} (µg/ml)	8.65 ± 2.52	9.70 ± 2.67
90% CI	83.0% - 95.3%	
C_{Min} (µg/ml)	6.37 ± 2.44	6.46 ± 2.12
90% CI	89.1% - 108.3%	
C_{Avg} (µg/ml)	7.61 ± 2.41	8.19 ± 2.27
90% CI	87.1% - 98.7%	
$AUC_{(0-\tau)}$ (µg.hr/ml)	91.27 ± 28.93	98.22 ± 27.24
90% CI	87.1% - 98.7%	
FI	0.34 ± 0.25	0.40 ± 0.24
p value	0.37	
T_{Max} (hours)	4.68 ± 4.28	3.94 ± 1.53
p value	0.44	
	CARBAMAZEPINE 10,11- EPOXIDE	
C_{Max} (µg/ml)	1.45 ± 0.68	1.66 ± 0.63
90% CI	80.3% - 94.5%	
C_{Min} (µg/ml)	1.07 ± 0.54	1.09 ± 0.53
90% CI	86.1% - 109.8%	
C_{Avg} (µg/ml)	1.27 ± 0.61	1.39 ± 0.56
90% CI	83.5% - 99.4%	
$AUC_{(0-\tau)}$ (µg.hr/ml)	15.19 ± 7.26	16.62 ± 6.68
90% CI	83.4% - 99.4%	
FI	0.33 ± 0.12	0.44 ± 0.22
p value	0.14	
T_{Max} (hours)	3.41 ± 3.52	3.57 ± 2.57
p value	0.86	

N = 18, Mean ± Standard deviation

9/035- single dose

OROS vs. IR

Relative bioavailability of CBZ, and CBZE after a single 200 mg oral dose of carbamazepine as Tegretol OROS or conventional Tegretol tablets

Parameters (units)	Tegretol OROS	Tegretol conventional tablet
CARBAMAZEPINE		
C_{Max} (µg/ml)	1.52 ± 0.37	1.54 ± 0.44
90% CI	83.3% - 119.8%	
$AUC_{(0-\infty)}$ (µg.hr/ml)	118.51 ± 27.52	118.03 ± 34.00
90% CI	86.8% - 111.7%	
T_{Max} (hours)	24 (12-32)	12 (4-48)
p value	0.158	
$T_{½}$ (hours)	41.47 ± 7.87	45.93 ± 9.47
p value	0.4531	
CARBAMAZEPINE 10,11- EPOXIDE		
C_{Max} (µg/ml)	0.078 ± 0.018	0.088 ± 0.022
90% CI	71.0% - 104.4%	
$AUC_{(0-\infty)}$ (µg.hr/ml)	9.92 ± 3.43	8.04 ± 2.86
90% CI	84.5% - 131.2%	
T_{Max} (hours)	32 (12-48)	32 (12-48)
p value	0.131	
$T_{½}$ (hours)	70.40 ± 41.65	44.57 ± 12.60
p value	0.165	

N = 11

Mean ± Standard deviation T_{Max} Median (Range)

4

NDA:20-234 **Submission Dates:** October 31, 1991
February 27, 1992
March 27, 1992
May 11, 1992
November 17, 1992

Generic Name, Dose and Formulation: Carbamazepine, USP, 100, 200, and 400 mg oral tablets

Brand Name: Tegretol-SR™

Sponsor: CIBA-GEIGY Corporation, Summit, New Jersey 07901

Reviewer: N.A.M. Atiqur Rahman

Type of Submission: Original New Drug Application

SYNOPSIS: The sponsor has adequately studied pharmacokinetics (single and multiple dose) and the relative bioavailability of new sustained released formulation of Tegretol. Dosage strength proportionality study linking 100 mg, 200 mg, and 400 mg was adequate. The sponsor also conducted a study to evaluate any difference in performance of the sustained release formulation compared to the conventional tablets in pediatric and adult population. Substitution of conventional tablets administered four times daily for OROS tablets given twice daily showed similar pharmacokinetic profiles in both adult and pediatric population. In some bioequivalence studies carbamazepine -10,11- epoxide (active metabolite of carbamazepine) failed 90% confidence interval test for equivalence.

The assay validation for pivotal bioequivalence studies and the statistical analysis were appropriately performed.

RECOMMENDATION:

The NDA 20-234 appears to be acceptable for meeting the Biopharmaceutics requirements based on the parent drug data but not the active epoxide metabolite, provided Comments 1-9 (pages 6 and 7), are addressed satisfactorily by the sponsor.

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Abbreviations

CBZ	Carbamazepine
CBZE	Carbamazepine -10,11- epoxide
LOQ	Limit of quantitation
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from 0 to ∞
$AUC_{0-\tau}$	Area under the plasma concentration-time curve during dosing interval
AUC_{0-216}	Area under the plasma concentration-time curve from 0 to 216 hours
C_{216}	Plasma concentration at 216 hours
λ_z	Apparent first-order elimination rate
$T_{½}$	Terminal elimination half-life
C_{Max}	Maximum plasma concentration
C_{Min}	Minimum plasma concentration
C_{Avg}	Average plasma concentration at steady-state
T_{Max}	Time to reach maximum plasma concentration
T_{lag}	Lag times
CI	Confidence intervals
FI	Fluctuation index
CV	Coefficient of variation

BACKGROUND: Tegretol (carbamazepine, CBZ) is indicated for the treatment of psychomotor and grand mal seizures as well as trigeminal neuralgia. It is currently marketed as chewable tablets of 100 mg, tablet of 200 mg, and suspension of 100 mg/5 ml. The recommended dosing for adults is 800 - 1200 mg daily adjusted to the minimum effective plasma level, between 4 and 12 μg/ml. Oral formulations of carbamazepine are well absorbed and with high bioavailability. The drug in blood is 76 % bound to plasma proteins. Carbamazepine has initial elimination half-life from 25-65 hours, however, autoinduction of its own metabolism reduces the half-life to within 12-17 hours on repeated doses. The primary metabolite of carbamazepine is carbamazepine-10,11-epoxide, which is equally potent as an anticonvulsant as the parent drug. During treatment with carbamazepine the plasma concentrations of this metabolite are usually 10 to 50 % of those of the parent drug. After oral administration of ^{14}C-carbamazepine, 72 % of the administered radioactivity is found in the urine and 28 % in the feces.

The sponsor has submitted this NDA for a new sustained-release formulation. Tegretol OROS will be available as 100, 200, and 400 mg controlled release tablet. There are eight studies and two reports submitted in support of this NDA.

Submission	October 31, 1991	Original New Drug Application for Tegretol OROS tablets.
	February 27, 1992	Additional information regarding Expiration dates of tablet lots used in studies, Chromatograms, and Statistical Analysis submitted on request.
	March 27, 1992	Additional information on expiration dates of investigational and commercial clinical supplies and reanalysis of the pharmacokinetic parameter data based on log transformation.
	May 11, 1992	Amendment to NDA, consisting of additional technical, pharmacokinetic, preclinical, and clinical documentation.
	November 17, 1992	Dissolution information with or without drilled holes.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETICS

I. BIOAVAILABILITY/BIOEQUIVALENCE :

A. Relative Bioavailability: With reference to a 2% Tegretol suspension (200 mg dose), the relative bioavailability of Tegretol OROS given as a 200 mg tablet under fasting conditions, averaged about 88% (CV 17.7%) (Study CPD Report 91035).

B. Bioequivalence: The two one-sided test at the steady-state $AUC_{0-\tau}$, and C_{Max} for CBZ and CBZE did not show any difference between 200 mg Tegretol SR tablet and 200 mg conventional tablet. T_{Max} was also similar between the two formulations. Therefore the two products appeared to be bioequivalent based on both AUC and C_{Max}.

C. Food Effect: The effect of high fat meal on the absorption of carbamazepine administered as a single 200 mg OROS tablet was evaluated (protocol 32). Carbamazepine was more rapidly absorbed when the OROS tablet was administered postprandially compared to the fasting state. Except in one subject (subject number 1), T_{Max} values were the same or lower in nonfasting condition (T_{Max} ratio being 0.77 ± 0.26). However the extent of absorption reflected in the AUC was similar both under fed and fasting condition. As for the active metabolite CBZE, both the rate and extent of metabolite formation were affected by the presence of food.

II. PHARMACOKINETICS :

a) Single Dose Study:

Following a single morning 200 mg dose of Tegretol OROS tablet to 12 healthy subjects under fasting condition, the mean C_{Max} for carbamazepine (CBZ) was 1.52 μg/ml (CV 24%), the mean T_{Max} was 25 hours (range: 12 - 32 hours), and the $AUC_{(0-\infty)}$ was 116.5 μg.hr/ml (CV 23%). After similar treatment with a 200 mg conventional Tegretol tablet, the C_{Max} was 1.54 μg/ml (CV 29%), T_{Max} 15 hours (range: 4 - 48 hours), and $AUC_{(0-\infty)}$ 118.3 μg.hr/ml (CV 29%). The two one-sided test procedure on the $AUC_{(0-\infty)}$ (86.8 - 111.7), and C_{Max} (83.3 - 119.8) of CBZ showed bioequivalence between 200 mg OROS and 200 mg conventional tablet. On the other hand, under fasting condition for carbamazepine -10, 11 epoxide (CBZE), the mean C_{Max} was 0.078 μg/ml (CV 23%), the mean T_{Max} was 35 hours (range : 12 - 48 hours), and the mean $AUC_{0-\infty}$ was 9.9 μg.hr/ml (CV 35%) after 200 mg of Tegretol OROS tablet administration. The C_{Max}, T_{Max}, and $AUC_{0-\infty}$ for the marketed tablet was 0.088 μg/ml (CV 25%), 32 hours (range : 12 - 48) and 8.0 μg.hr/ml (CV 36%) respectively. The C_{Max} (71.0 - 104.4) and $AUC_{0-\infty}$ (84.5 - 131.2) parameters for CBZE failed the 90% Confidence interval test indicating that at the level of this active metabolite the products were not bioequivalent.

b) Multiple Dose Study

The steady-state plasma concentration- time profiles of both carbamazepine and 10, 11- epoxide

metabolite were characterized in terms of the minimum and maximum levels achieved, the times to peak, the fluctuation index values and areas under the dosing interval curve. The steady-state for both CBZ ($p = 0.33$) and CBZE ($p = 0.082$) were achieved by the 10th to 13th day of dosing. The C_{Min} (91.6 - 111.0), C_{Max} (105.2 - 119.1), C_{Ave} (101.4 - 113.8), and $AUC_{0-\tau}$ (101.4 - 113.8) of carbamazepine passed the 90% CI test procedure showing bioequivalence at the level of the parent compound. The C_{Min} (90.0 - 114.2), C_{Ave} (100.7 - 118.0), and $AUC_{0-\tau}$ (100.7 - 118.0) of 10, 11- epoxide carbamazepine passed the 90% CI test procedure, however C_{Max} for the active metabolite did not pass the 90% CI test. The difference in the fluctuation index between the two formulations was insignificant ($p = 0.37$).

III. METABOLISM :

Active metabolite CBZE was assessed and analyzed in bioavailability/bioequivalence studies.

IV. DOSAGE STRENGTH EQUIVALENCE :

The C_{Max} and $AUC_{(0-\infty)}$ for both CBZ and CBZE passed the 90% CI test procedure indicating equivalence among the three strengths (100, 200, and 400 mg) normalized for dose.

V. FORMULATION :

100 and 200 mg tablets are compositionally proportional. 400 mg tablets are not composionally proportional to 100 and 200 mg tablets.

VI. DISSOLUTION :

The Division of Biopharmaceutics recommends an interim dissolution specification using USP

VII. ASSAY :

GENERAL COMMENTS (comments to medical officer)

1. Carbamazepine has a long elimination half-life (25-65 hours). A 20-30% reduction of the half-life by induction of its own metabolizing enzymes sustains carbamazepine's half-life to about 12-17 hours. The long half-life most likely results in a similar plasma concentration-time profiles of carbamazepine after administration of both conventional and OROS tablets at the same dose and dosing regimen. As a result there is no added advantage of the OROS tablet over the conventional tablet.

2. The fluctuation index of carbamazepine after OROS tablet does not show any statistically significant ($p=0.37$) improvement over the conventional tablet. Therefore, any toxicity associated with peak levels of carbamazepine may not be adequately controlled by OROS formulation.

3. In some of the bioavailability studies the active metabolite (carbamazepine -10,11- epoxide) failed the 90% confidence interval test. The therapeutic as well as the toxic effects of carbamazepine epoxide after carbamazepine administration being not established concerns the Division of Biopharmaceutics regarding the outcome of those studies (please see the attested article in the **appendix**).

4. The relevance of marketing this type of product is questionable in terms of :
   a) long half life of the drug,
   b) formation of active metabolites,
   c) dissolution-rate limited absorption.

Carbamazepine is expected to be used on a chronic basis, once a steady-state is achieved with the conventional therapy after enzyme induction, the level may be maintained with Tegretol using b.i.d or t.i.d regimen. In addition, the active metabolites having a longer half-life than the parent drug, is expected to sustain the pharmacologic effect of the drug. The toxicity associated with the peak level of the drug will not improve with the OROS preparation, since the fluctuation of the peak and trough levels is not any different from the currently available fromulation. The OROS formulation is likely to perform at the same level as the conventional tablet..

COMMENTS

1. In the single-dose pharmacokinetic study (CPD Report 91035), at the level of the parent drug OROS formulation was bioequivalent to the conventional formulation, however, at the level of CBZE the two products were not bioequivalent.

2. The administration of conventional tablet resulted in greater number of samples (7/12) showing split peaks (at 2-4 hours and 16-24 hours) compared to the OROS tablet (CPD Report 91035). This anomaly needs to be investigated by the sponsor.

3. The rate of absorption seems to be more rapid postprandially (CPD Report 91035). The

statement " Medication should be taken with meals " in labeling is appropiate for this dosage form.

4. At steady-state, 200 mg conventional tablet administered twice daily on established doses (400 - 2000 mg/day) showed similar plasma concentration-time profile over 12 hour period as the OROS tablet administered in similar regimen (CPD Report 91023). This indicates that the OROS product does not give any added advantage over the conventional tablet formulation.

5. The substitution of four times daily dosing of conventional release tablets with twice daily dosing of OROS tablets is acceptable (CPD Report 91024).

6. The Division of Biopharmaceutics has established an interim dissolution specifications for testing dissolution properties of Tegretol OROS 100, 200, and 400 mg tablets. The dissolution specifications are as follows:

Apparatus:
Medium:
Volume:
Sampling time:

Q values: 3 hours
6 hours
12 hours
24 hours

The sponsor is requested to submit dissolution profiles of 12 tablets each from three consecutive production lots, upon approval, to set the final dissolution specifications for this product.

7. The report (Ref 24 and 25) on the correlation between *in vivo* absorption rate and *in vitro* dissolution rate is very interesting and encouraging. The use of plasma concentration-time data from protocol 32 should be analyzed further before the correlations may be used to allow minor changes in formulations, manufacturing processes and site changes issues.

<u>Comments on labeling:</u>

8. The relative bioavailability of carbamazepine from the OROS tablet after a single 200 mg oral dose is 88% (60.8% - 115.6%) compared to a 2% suspension (CPD Report 91035). The va. bility needs to be included in the package insert.

9. The statement in section 5 of the Annotated Version of Package Insert " whereas the SR tablet has slightly lower peak levels and higher trough levels than th ose of the conventional tablet for the same dosage regimen" has not been established in any of the multiple-dose studies. This statement should be omitted in the labeling.

N.A.M. Atiqur Rahman 02/03/94

N.A.M. Atiqur Rahman
Pharmacokinetics Evaluation Branch

RD initialed by Victoria Hale, Ph.D. Victoria Hale 2/8/94.

Biopharm Day August 12, 1993

cc: NDA 20-234 (orig), HFD-120, HFD-426 (Fleischer, Hale, Rahman), HFD-340(Viswanathan), HFD-420 (Drug, Chron), In vivo-in vitro file and Reviewer's file.

SINGLE DOSE PHARMACOKINETIC STUDY :

STUDY NO: CPD Report 91035 **VOLUME :** 1.11 **PAGES :** 1-211

INVESTIGATOR AND LOCATION:

OBJECTIVES: The objectives of this single-dose study in healthy subjects were: (1) to determine the relative bioavailability of carbamazepine after a single 200 mg dose of the drug in the form of (a) a commercial suspension (2%), (b) a commercial conventional-release tablet, and (c) an OROS tablet; and (2) to delineate the effect of food on the rate and extent of drug absorption after a single dose of 200 mg Tegretol OROS tablet.

FORMULATION: : 2% Tegretol Suspension Lot No: E-13616
Batch Size Expiration date: 3/90

200 mg Conventional-release Tegretol tablets
Lot No: E-13388 Batch Size:
Expiration date: 6/92

200 mg Tegretol OROS tablets Lot No: E-13396
Batch Size: Expiration date: Not available.

Study Period: May 16, 1988 - August 15, 1988

STUDY DESIGN: The study followed an open-label, randomized, 4 X 4 Latin-Square crossover, design with 12 healthy subjects. There was a washout period of 4 weeks in between treatments. In food effect study, the subjects were fasted 12 hours prior to, and 4 hours after AM dosing. Under fed condition, drug was administered within 10 minutes after completion of breakfast. Plasma samples were drawn at 0.0 (predose), 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 168, and 216 hour after dosing.

DATA ANALYSIS: The area under the plasma concentration-time curve from 0 to ∞ after dosing was estimated from the following equation:

$$AUC_{(0-\infty)} = AUC_{(0-216)} + C_{(216)} / \lambda_z$$

where $C_{(216)}$ was the plasma concentration at 216 hr (last time point) and λ_z was the apparent first-order elimination rate constant, determined by least-square regression analysis of the terminal phase of the log-linear plasma concentration-time profile. Peak concentration and time to peak was visually determined from the concentration-time profile. The terminal elimination half-life, $T_{½}$ was calculated using the equation:

$$T_{½} = 0.693 / \lambda_z$$

Relative bioavailability of CBZ, and CBZE after a single 200 mg oral dose of carbamazepine as Tegretol OROS tablet or as 2% Tegretol suspension

Parameters (units)	Tegretol OROS		Tegretol Suspension (2%)
CARBAMAZEPINE			
C_{Max}(μg/ml)	1.52 ± 0.37		2.56 ± 0.34
90% CI		52% - 74.1%	
$AUC_{(0-\infty)}$(μg.hr/ml)	118.51 ± 27.52		134.69 ± 25.97
90% CI		76% - 97.2%	
T_{Max}(hours)	24 (12-32)		4 (2-4)
p value		<0.001	
$T_{½}$(hours)	41.47 ± 7.87		37.13 ± 7.25
p value		0.0554	
CARBAMAZEPINE 10,11- EPOXIDE			
C_{Max}(μg/ml)	0.078 ± 0.018		0.111 ± 0.031
90% CI		57.7% - 84.0%	
$AUC_{(0-\infty)}$(μg.hr/ml)	9.92 ± 3.43		10.11 ± 1.82
90% CI		77.8% - 114.4%	
T_{Max}(hours)	32 (12-48)		24 (8-32)
p value		0.008	
$T_{½}$(hours)	70.40 ± 41.65		49.05 ± 14.47
p value		0.437	

N = 11
Mean ± Standard deviation
T_{Max} Median (Range)

RESULTS: C_{Max} and T_{Max} for carbamazepine after OROS tablet administration was significantly ($p<0.001$) different from the suspension. Both C_{Max} and $AUC_{(0-\infty)}$ failed 90% CI test. The relative bioavailability of carbamazepine from the OROS tablets, indicated by $AUC_{(0-\infty)}$, was 88%

compared with the suspension. C_{Max} and $AUC_{(0-)}$ of the metabolite carbamazepine -10,11- epoxide had 90% confidence interval limits outside 80% - 120% range.

CONCLUSIONS: The rate and extent of absorption of carbamazepine from OROS tablet appeared to be low compared with the suspension formulation.

Relative bioavailability of CBZ, and CBZE after a single 200 mg oral dos of carbamazepine as Tegretol OROS or conventional Tegretol tablets

Parameters (units)	Tegretol OROS [redacted]		Tegretol conventional tablet
CARBAMAZEPINE			
C_{Max}(μg/ml)	1.52 ± 0.37		1.54 ± 0.44
90% CI		83.3% - 119.8%	
$AUC_{(0-)}$(μg.hr/ml)	118.51 ± 27.52		118.03 ± 34.00
90% CI		86.8% - 111.7%	
T_{Max}(hours)	24 (12-32)		12 (4-48)
p value		0.158	
$T_{½}$(hours)	41.47 ± 7.87		45.93 ± 9.47
p value		0.4531	
CARBAMAZEPINE 10,11- EPOXIDE·			
C_{Max}(μg/ml)	0.078 ± 0.018		0.088 ± 0.022
90% CI		71.0% - 104.4%	
$AUC_{(0-)}$(μg.hr/ml)	9.92 ± 3.43		8.04 ± 2.86
90% CI		84.5% - 131.2%	
T_{Max}(hours)	32 (12-48)		32 (12-48)
p value		0.131	
$T_{½}$(hours)	70.40 ± 41.65		44.57 ± 12.60
p value		0.165	

N = 11
Mean ± Standard deviation T_{Max} Median (Range)

RESULTS: C_{Max} and $AUC_{(0-)}$ for CBZ passed the 90% CI test and T_{Max} was statistically non-significant (p = 0.158). However, C_{Max} and $AUC_{(0-)}$ of the metabolite carbamazepine -10,11-epoxide failed the two one-sided test procedure at 90% confidence interval.

CONCLUSIONS: At the level of CBZ the two formulations were bioequivalent, however, at the level of CBZE the products were inequivalent.

FOOD EFFECT STUDY:

Study Design: In food effect study, the subjects were fasted 12 hours prior to, and 4 hours after AM dosing. Under fed condition, drug was administered within 10 minutes after completion of breakfast. Plasma samples were drawn at 0.0 (predose), 1, 2, 4, 6, 8, 12, 16, 24, 48, 72, 96, 168, and 216 hour after dosing.

Relative bioavailability of CBZ, and CBZE after a single 200 mg oral dose of carbamazepine as Tegretol OROS tablet under fed and fasting conditions

Parameters (units)	Tegretol OROS Fast		Tegretol OROS Fed
CARBAMAZEPINE			
C_{Max}(μg/ml)	1.52 ± 0.37		1.66 ± 0.46
90% CI		72.0% - 107.9%	
$AUC_{(0-\infty)}$(μg.hr/ml)	118.51 ± 27.52		119.70 ± 24.33
90% CI		90.6% - 115.7%	
T_{Max}(hours)	24 (12-32)		16 (8-32)
p value		0.223	
$T_{½}$(hours)	41.47 ± 7.87		42.92 ± 8.98
p value		0.8147	
CARBAMAZEPINE 10,11- EPOXIDE			
C_{Max}(μg/ml)	0.078 ± 0.018		0.08 ± 0.016
90% CI		78.0% - 115.7%	
$AUC_{(0-\infty)}$(μg.hr/ml)	9.92 ± 3.43		8.73 ± 2.96
90% CI		93.1% - 131.1%	
T_{Max}(hours)	32 (12-48)		32 (8-96)
p value		0.457	
$T_{½}$(hours)	70.40 ± 41.65		57.24 ± 27.13
p value		0.2	

N = 11

Mean ± Standard deviation T_{Max} Median (Range)

RESULTS: C_{Max} for CBZ failed the 90% CI test, however the extent of absorption was similar under fasting and fed condition as shown by $AUC_{(0-\infty)}$ values being within the 90% confidence interval boundary. Both C_{Max} and $AUC_{(0-\infty)}$ of carbamazepine 10,11- epoxide failed the 90% CI test.

CONCLUSIONS: The ingestion of food before dosing with the OROS tablets resulted in an increase in peak concentration and a decrease in times to peak indicating more rapid absorption of the drug postprandially.

Report B150/1986: Comparison of the Carbamazepine OROS 20/200 to the Tegretol syrup formulation. Plasma concentration-time profiles of carbamazepine in six healthy volunteers after a single oral dose of 200 mg.

In this study, six healthy adults randomized in a two-way crossover design received 200 mg carbamazepine as a Prototype I OROS tablet (not the final NDA formulation) or as 2 ml Tegretol syrup (100 mg/ml of carbamazepine). The tablet had 91% relative bioavailability. The mean C_{Max} was 40% lower (7.8 versus 13.0 μg/ml) and T_{Max} 12 fold longer (2 versus 24 hours) for the OROS tablet compared with the syrup. The study indicated a controlled-release functionality of the Prototype I OROS formulation.

OVERALL CONCLUSIONS: The relative bioavailability of the OROS tablet after a single 200 mg oral dose is 88% compared to a 2% suspension. The peak plasma level and the time to reach peak concentration reflected slower absorption of CBZ after OROS tablet administration. At the level of CBZ , the OROS tablet (200 mg) was bioequivalent to the conventional Tegretol tablet, however at the level of the active metabolite, 5,10- epoxide, OROS tablet was inequivalent to the conventional tablet. The drug appeared to be absorbed more rapidly when administered with food, however, the extent of absorption was not affected by the presence of food.

MULTIPLE-DOSE BIOEQUIVALENCE STUDY :

STUDY NO : CPD Report 91023 **VOLUME :** 1.12 **PAGES :** 1-296

INVESTIGATOR AND LOCATION

OBJECTIVES: The objectives of this multiple-dose study in epileptic patients was to assess the relative bioavailability, average steady-state concentrations, and fluctuations of carbamazepine and its 10,11- epoxide metabolite during a dosage interval, using 200 mg doses of the drug in the form of a commercial conventional-release tablet or an OROS tablet.

FORMULATION: : 200 mg Conventional-release Tegretol tablets
Lot No: E-13388 Batch Size:
Expiration date: 6/92

200 mg Tegretol OROS tablets Lot No: E-13872
Batch Size: Expiration date: Not available

Study Period: January 4, 1989 - April 1, 1989

STUDY DESIGN: The study followed a double-dummy, double-blind, randomized, crossover design with 18 patients without any washout in between treatments. Eighteen patients with chronic seizure disorder were stabilized on established doses of carbamazepine (400 - 2000 mg/day), with commercial 200 mg Tegretol tablet twice daily for at least 4 weeks. The patients were then randomized into two groups : one receiving their established daily dose of carbamazepine as 200 mg conventional release tablets together with OROS placebos in equally divided doses every 12 hours for 21 days and the other receiving an identical regimen with the active OROS tablet and placebo for the conventional release tablet for the same number of days. At the end of this period, they were switched to the alternate regimen for an additional 21 days. Blood samples were drawn immediately before and at 1, 2, 3, 4, 6, 8, 10, and 12 hour after the morning dose on the last day of each treatment period. Steady-state trough levels were determined from the blood samples drawn immediately before the first daily dose on the 10-13th, 14-17th and 18-20th day of each treatment period.

DATA ANALYSIS: The steady-state plasma concentration, C_{Max}, C_{Min}, C_{Avg}, $AUC_{0-\tau}$, T_{Max}, and fluctuation index were determined from the plasma concentration-time data. The area under the plasma concentration-time curve from 0 to 12 hr, was calculated by using the linear trapezoidal rule. The observed C_{Max}, and C_{Min} were obtained directly from the plasma level time profile. The time to maximum concentration was taken as the sampling time after dosing at which C_{Max} occurred. The average plasma concentration was calculated using the equation:

$$C_{Avg} = AUC_{(0-12)} / 12$$

The fluctuation index (F.I) was calculated using the equation :

$$F.I = C_{Max} - C_{Min} / C_{Avg}$$

Steady-State pharmacokinetics of carbamazepine and carbamazepine- 10, 11- epoxide after treatment with Tegretol conventional (200 mg) and Tegretol OROS (200 mg) tablet

Parameters (units)	Tegretol OROS		Tegretol conventional tablet
CARBAMAZEPINE			
C_{Max}(μg/ml)	8.65 ± 2.52		9.70 ± 2.67
90% CI		83.0% - 95.3%	
C_{Min}(μg/ml)	6.37 ± 2.44		6.46 ± 2.12
90% CI		89.1% - 108.3%	
C_{Avg}(μg/ml)	7.61 ± 2.41		8.19 ± 2.27
90% CI		87.1% - 98.7%	
$AUC_{(0-t)}$(μg.hr/ml)	91.27 ± 28.93		98.22 ± 27.24
90% CI		87.1% - 98.7%	
FI	0.34 ± 0.25		0.40 ± 0.24
p value		0.37	
T_{Max}(hours)	4.68 ± 4.28		3.94 ± 1.53
p value		0.44	
CARBAMAZEPINE 10,11- EPOXIDE			
C_{Max}(μg/ml)	1.45 ± 0.68		1.66 ± 0.63
90% CI		80.3% - 94.5%	
C_{Min}(μg/ml)	1.07 ± 0.54		1.09 ± 0.53
90% CI		86.1% - 109.8%	
C_{Avg}(μg/ml)	1.27 ± 0.61		1.39 ± 0.56
90% CI		83.5% - 99.4%	
$AUC_{(0-t)}$(μg.hr/ml)	15.19 ± 7.26		16.62 ± 6.68
90% CI		83.4% - 99.4%	
FI	0.33 ± 0.12		0.44 ± 0.22
p value		0.14	
T_{Max}(hours)	3.41 ± 3.52		3.57 ± 2.57
p value		0.86	

N = 18
Mean ± Standard deviation

RESULTS: C_{Max}, C_{Min}, C_{Avg}, and $AUC_{(0-t)}$ for CBZ and CBZE were within 80% - 120% confidence interval. The fluctuation index appeared to be lowered (0.34 versus 0.4) after Tegretol

OROS tablet compared to the conventional tegretol tablet, however it was not statistically significant ($p = 0.37$).

CONCLUSIONS: The relative bioavailability of the OROS tablet compared to the conventional tablet at steady-state was 93.1% (CV 15%). The rate and extent of absorption of CBZ from Tegretol OROS were similar. The two formulations were bioequivalent at the level of both the parent drug and active metabolite.. At steady-state, the FI ratios of OROS to conventional tablets in 8 out of 18 patients had values greater than 1. Therefore, reduction of FI by OROS tablets is inconclusive.

PILOT STUDY:

Trial Plan TO/EP 1

The objective of this study was to compare the steady-state pharmacokinetics of three different CBZ formulations, administered b.i.d. and/or o.d.
The formulations were:

A: Tegretol CR 200 or 400 mg b.i.d. European formulation
B: Tegretol conventional tablet 200 mg b.i.d.
C: Tegretol OROS 200 mg b.i.d.
D: Tegretol OROS 200 mg o.d.

There was no statistically significant difference in the pharmacokinetic parameters (AUC and FI) between Tegretol CR b.i.d. and Tegretol OROS b.i.d.

BIOAVAILABILITY STUDY IN ADULT AND YOUNG PATIENTS :

STUDY NO : CPD Report 91024 **VOLUME :** 1.13 **PAGES :** 1-426

INVESTIGATOR AND LOCATION .

OBJECTIVES: The objective of this multiple-dose study was to compare plasma concentration-time profiles of CBZ and CBZE in adult and pediatric patients with epilepsy during four times daily dosing with conventional release tablets in equal or unequal amounts, and twice daily dosing with OROS tablets in equal amounts.

FORMULATION: : 200 mg Conventional-release Tegretol tablets
Lot No: E-14048 Batch Size
Expiration date: 4/94

100 mg Tegretol OROS tablets Lot No: E-14102
Batch Size: Expiration date: N/A

200 mg Tegretol OROS tablets Lot No: E-14043
Batch Size: Expiration date: N/A

400 mg Tegretol OROS tablets Lot No: E-14015

Batch Size: Expiration date: N/A

N/A Not available.

Study Period : April 18, 1990 - (pediatric)
May 4, 1990-

STUDY DESIGN: The study followed a two-center, open label, randomized, crossover design with 22 adult and 12 pediatric patients without any washout period in between treatments. The patients were maintained for a one-week run-in period on their established four times daily dosing regimen with conventional-release tablets. At the end of this time they were randomized into two groups : one receiving their established daily dose of conventional-release tablets four times daily in equal or unequal amounts for 21 days and the other receiving their established dose as OROS tablet twice daily in equal amounts for the same number of days. At the end of this period, they were switched to the alternate regimen for an additional 21 days.

Sample Collection: Blood samples for plasma trough level estimation were drawn immediately before the morning dose on the 10-13th, 14-17th and 18-20th day of each dosing period. No blood samples were drawn on the 18-20th day of dosing for the pediatric patients. Blood samples for the estimation of pharmacokinetic parameters were drawn immediately before, and at 2-hourly intervals for 24 hour after the morning dose on the last day of each treatment period.

DATA ANALYSIS: At steady-state, C_{Max}, C_{Min}, C_{Avg}, AUC_{0-24}, T_{Max}, and fluctuation index (FI) were determined from the plasma concentration-time profiles of CBZ and CBZE. The area under the plasma concentration-time curve from 0 to 24 hr, was calculated by using the linear trapezoidal rule. The observed C_{Max}, and C_{Min} were obtained directly from the plasma level time data. The time to maximum concentration was taken as the sampling time after dosing at which C_{Max} occurred.

The average plasma concentration was calculated using the equation:

$$C_{Avg} = AUC_{(0-24)} / 24$$

The fluctuation index (F.I) was calculated using the equation :

$$F.I = C_{Max} - C_{Min} / C_{Avg}$$

Steady-State pharmacokinetics of carbamazepine and carbamazepine- 10, 11- epoxide after treatment with Tegretol conventional and Tegretol OROS tablet (Adult)

Parameters (units)	Tegretol ORCS		Tegretol conventional tablet
CARBAMAZEPINE			
C_{Max}(μg/ml)	8.21 ± 1.92		9.05 ± 2.08
90% CI		87.0% - 94.5%	
C_{Min}(μg/ml)	5.72 ± 1.53		6.25 ± 1.54
90% CI		86.4% - 96.5	
$AUC_{(0-24)}$(μg.hr/ml)	170.15 ± 41.16		179.94 ± 40.03
90% CI		91.8% - 97.3%	
FI	0.35 ± 0.18		0.38 ± 0.15
p value		0.57	
T_{Max}(hours)	11.73 ± 8.31		14.73 ± 5.87
p value		0.23	
CARBAMAZEPINE 10,11- EPOXIDE			
C_{Max}(μg/ml)	1.98 ± 0.89		2.19 ± 1.07
90% CI		85.2% - 95.9%	
C_{Min}(μg/ml)	1.26 ± 0.54		1.56 ± 0.73
90% CI		75.2% - 86.8%	
$AUC_{(0-24)}$(μg.hr/ml)	39.62 ± 17.29		44.96 ± 22.02
90% CI		82.8% - 93.7%	
T_{Max}(hours)	10.38 ± 8.33		15.43 ± 7.30
p value		0.01	
FI	0.41 ± 0.20		0.32 ± 0.14
p value		0.012	

N = 22 Mean ± Standard deviation

RESULTS: C_{Max}, C_{Min}, and $AUC_{(0-t)}$ of CBZ passed the 90% CI test. There were no difference in the T_{Max} and FI values between OROS and conventional tablet. C_{Max}, and $AUC_{(0-t)}$ of CBZE passed but C_{Min} failed the 90% confidence interval test. The T_{Max} and FI values of CBZE were significantly different between the conventional and OROS tablets.

Steady-State pharmacokinetics of carbamazepine and carbamazepine- 10, 11- epoxide after treatment with Tegretol conventional and Tegretol OROS tablet (Pediatric)

Parameters (units)	Tegretol OROS		Tegretol conventional tablet
CARBAMAZEPINE			
C_{Max}(μg/ml)	9.10 ± 2.10		10.39 ± 2.41
90% CI		83.7% - 91.4%	
C_{Min}(μg/ml)	6.57 ± 1.82		7.07 ± 1.70
90% CI		88.9% - 97.0%	
$AUC_{(0-24)}$(μg.hr/ml)	186.87 ± 46.00		209.38 ± 49.94
90% CI		86.6% - 91.9%	
FI	0.34 ± 0.17		0.38 ± 0.17
p value		0.48	
T_{Max}(hours)	15.00 ± 8.16		13.67 ± 6.76
p value)		0.61	
CARBAMAZEPINE 10,11- EPOXIDE			
C_{Max}(μg/ml)	1.78 ± 0.61		2.05 ± 0.07
90% CI		81.8% - 91.3%	
C_{Min}(μg/ml)	1.27 ± 0.54		1.48 ± 0.56
90% CI		78.8% - 93.0%	
$AUC_{(0-24)}$(μg.hr/ml)	35.61 ± 13.86		42.32 ± 14.92
90% CI		79.6% - 88.7%	
T_{Max}(hours)	13.67 ± 10.88		11.67 ± 8.73
p value		0.61	
FI	0.40 ± 0.28		0.33 ± 0.14
p value		0.48	

N = 12
Mean ± Standard deviation

RESULTS: C_{Max}, C_{Min}, and $AUC_{(0-\tau)}$ of CBZ passed the 90% CI test. There were no difference in the T_{Max} and FI values between OROS and conventional tablet. C_{Max} of CBZE passed but C_{Min} and $AUC_{(0-\tau)}$ failed the 90% confidence interval test. The T_{Max} and FI values of CBZ and CBZE were similar between the OROS and conventional tablets.

CONCLUSIONS: 1. In adult patients Tegretol OROS administered two times daily is bioequivalent to conventional tablet taken four times daily at the level of the parent drug. However, the same is not applicable to the active metabolite.

2. In adult patients the FI of CBZE was significantly greater after OROS tablet administration compared to the conventional tablet.

3. In pediatric patients Tegretol OROS administered two times daily is bioequivalent to conventional tablet taken four times daily at the level of the parent drug. However, the same is not applicable to the active metabolite.

DOSAGE STRENGTH PROPORTIONALITY STUDY :

STUDY NO : CPD Report 91012 **VOLUME :** 1.10 **PAGES :** 1-234

INVESTIGATOR AND LOCATION :

OBJECTIVES: To determine the dosage form proportionality of four 10/100, two 20/200, and one 40/400 Tegretol OROS systems after single dosing.

FORMULATION: : 100 mg Tegretol OROS tablets Lot No: E-13870
Batch Size: Expiration date: N/A

200 mg Tegretol OROS tablets Lot No: E-13872
Batch Size: Expiration date: N/A

400 mg Tegretol OROS tablets Lot No: E-14015
Batch Size: Expiration date: N/A

Study Period : September 11, 1989 -

STUDY DESIGN: This is a single-center, open-label, single-dose, randomized three-way crossover study in 18 healthy volunteers comparing one Tegretol OROS 400 mg tablet, two Tegretol OROS 200 mg tablets, and four Tegretol OROS 100 mg tablets. Treatment sequences were randomly assigned, with a three-week washout period in between treatments. Blood samples (7 ml) were drawn at 0 (predose), 1, 2, 4, 6, 8, 12, 16, 24, 32, 48, 72, 96, 168, and 216 hr post dose.

DATA ANALYSIS: Plasma concentration-time profiles for CBZ and CBZE were characterized in terms of their areas under the curve (AUC_{0-}), peak concentrations (C_{Max}), lag times (T_{lag}), times to peak (T_{Max}), and terminal elimination half-life ($T_{½}$). AUC was calculated by linear trapezoidal rule. C_{Max}, T_{Max}, and T_{lag} was determined visually from the plasma concentration-time profile.

Comparison of C_{Max}, AUC_{0-}, and T_{Max} of carbamazepine and carbamazepine- 10, 11- epoxide after treatment with 1 X 400 mg or 2 X 200 mg Tegretol OROS tablets

Parameters (units)	2 X 200 mg		1 X 400 mg
CARBAMAZEPINE			
C_{Max}(μg/ml)	3.01 ± 0.53		2.99 ± 0.67
90% CI		89.1 - 108.5%	
$AUC_{(0-)}$(μg.hr/ml)	220 ± 43		227 ± 47
90% CI		84.8 - 107.3%	
T_{Max}(hours)	24 (6 - 32)		24 (12 - 32)
p value		0.252	
CARBAMAZEPINE 10,11- EPOXIDE			
C_{Max}(μg/ml)	0.179 ± 0.049		0.181 ± 0.049
90% CI		88.7 - 111.9%	
$AUC_{(0-)}$(μg.hr/ml)	14.2 ± 3.2		13.9 ± 4.0
90% CI		83.1 - 108.4%	
T_{Max}(hours)	32 (6 - 48)		32 (24 - 48)
p value		0.116	

N = 17
Mean ± Standard deviation
T_{Max} Median (range)

RESULTS: The C_{Max} and $AUC_{(0-\infty)}$ of CBZ and CBZE passed the 90% CI test. For CBZ and CBZE there was no difference (p=0.25, p=0.12) in T_{Max} between 400 mg and 200 mg tablets normalized for dose.

Comparison of C_{Max}, $AUC_{0-\infty}$, and T_{Max} of carbamazepine and carbamazepine- 10, 11- epoxide after treatment with **4 X 100** mg Tegretol OROS tablets versus **2 X 200** mg tablets

Parameters (units)	2 X 200 mg		4 X 100 mg
CARBAMAZEPINE			
C_{Max}(μg/ml)	3.01 ± 0.53		2.96 ± 0.5
90% CI		89.8 - 109.7%	
$AUC_{(0-\infty)}$(μg.hr/ml)	220 ± 43		227 ± 47
90% CI		91.7 - 114.8%	
T_{Max}(hours)	24 (6 - 32)		24 (16 - 32)
p value		0.438	
CARBAMAZEPINE 10,11- EPOXIDE			
C_{Max}(μg/ml)	0.179 ± 0.049		0.185 ± 0.036
90% CI		91.7 - 114.8%	
$AUC_{(0-\infty)}$(μg.hr/ml)	14.2 ± 3.2		14.6 ± 2.7
90% CI		89.8 - 115.6%	
T_{Max}(hours)	32 (6 - 48)		32 (24 - 48)
p value		0.14	

N = 17
Mean ± Standard deviation
T_{Max} Median (range)

RESULTS: The C_{Max} and $AUC_{(0-\infty)}$ of CBZ and CBZE passed the 90% CI test. For CBZ and CBZE there was no difference (p=0.44, p=0.14) in T_{Max} between 100 mg and 200 mg tablets normalized for dose.

CPD Report 90039: A Pilot Dosage Form Proportionality Study comparing 1 X 200 mg and 2 X 100 mg Tegretol OROS Tablets in Healthy Subjects.

For CBZ, the $AUC_{(0-\infty)}$ (135.6 vs 140.7 μg.hr/ml), C_{Max} (1.55 vs 1.56 μg/ml), and T_{Max} (20 vs 32 hours) were similar between the two treatment arms indicating similar bioavailability for the two dosage forms. Similar results were obtained with CBZE. However, absence of detailed analysis of the data precluded any assesment of the study. The correlation coefficients for % absorbed in vivo and % dissolved in vitro for one 200 mg and two 100 mg OROS tablets were 0.995 and 0.997 respectively.

CONCLUSIONS: The mean AUC_{0-} and C_{Max} of CBZ and CBZE for 100, and 400 mg Tegretol OROS tablet passed the 90 % CI test when compared against the 200 mg strength. This study comparing different tablet strength normalized for dose indicated equivalence with reference to $AUC_{(0-\infty)}$, C_{Max} and T_{Max} among the three strengths, both at the level of the parent compound and the active metabolite.

PILOT AND BACKGROUND STUDIES

Report UK RI/1990 A combination of gamma scintigraphy and pharmacokinetic evaluation was used to achieve the following objectives:

i. To follow the GI transit of a CBZ OROS system.

ii. To determine the plasma concentrations of CBZ as a function of time for both formulation.

Plasma CBZ concentration-time profiles after the single oral administration of a suspension of CBZ and a 20/200 CBZ OROS system were determined simultaneously in 8 healthy male volunteers using stable isotope technology. The oral suspension contained 100 mg CBZ labelled with the stable isotope Nitrogen-15 (^{15}N) while the OROS contained 200 mg unlabelled CBZ. In addition the OROS was externally labeled with indium-111 (^{111}In) to follow the position of the system within the GI tract to be followed by gamma scintigraphy. The suspension contained technetium-99-labeled DTPA to outline the anatomy of the GI tract.

Gastric emptying of the OROS system occurred between 1.1-11 hours (median, 5.3 hours) after dosing. Small intestine transit times were rapid and reasonably consistent (1.5-3.6 hours; median, 2.2 hours) There were wide individual variations in colonic transit, and the recorded total transit time ranged from 10-60 hours (median, 22 hours).

Input functions were generated to illustrate the in vivo absorption of the drug in to the systemic circulation from the OROS system, using Wagner-Nelson analysis. These functions demonstrated that absorption of CBZ was rapid in the stomach and small intestine; the rate being determined by the release of the drug from the system. In most subjects, the absorption of CBZ was slower from the OROS system in the colon, reason being unclear.

DISSOLUTION

Dissolution of each strength of Tegretol OROS tablets sampled from bio-lots used in the clinical studies was performed using USP Apparatus I (basket). The effect of different media was investigated using simulated intestinal fluid (SIF), simulated gastric fluid (SGF), 1% sodium laurylsulfate (SLS), and 0.42% sodium chloride (NaCl) in water. Additionally the effect of basket speed was investigated in water at 50, 100, 150 rpm. Dissolution media volume was 900 ml for the 100 and 200 mg tablets and 1800 ml for the 400 mg tablets. All dissolution experiments were carried out at 37°C.

Based on the dissolution information provided, the Division of Biopharmaceutics recommends that the following interim specifications be established for testing dissolution properties of Tegretol OROS 100, 200, and 400 mg tablets :

Apparatus	
Medium	
Volume	
Sampling Time	
Q Values	: 3 hours
	6 hours
	12 hours
	24 hours

IN VIVO/ IN VITRO CORRELATIONS:

REPORT BIO #89128 :

In vitro/in vivo correlations for Tegretol OROS
Protocol 32 (CPD report 91035)

The study involved a four-way crossover design where each treatment arms received the same single dose of either Tegretol OROS under fed condition or Tegretol OROS under fasting condition or Tegretol conventional tablet or 2% Tegretol suspension. The plasma CBZ concentration-time data were analyzed for percent absorption over time by comparison to the suspension. Absorption rates were determined by different methods and compared to dissolution rates of the Tegretol OROS 20/200 system.

The absorption rates were determined by three methods: 1) based on the average of the linear segments individually identified in the percent absorption-time profile of each subject, 2) based on deconvolution of average plasma concentration-time profiles, and 3) based on the linear segment of the averaged percent absorption-time profiles.

The final estimates of absorption rates determined by these three methods were compared to the linear segment of the dissolution rates of six tablets whose dissolution profiles were

In vitro dissolution rates indicated that the dosage form released 10.4%/hr in distilled water, which closely correlates to the absorption rate of 10.0%/hr under fasting condition.

REPORT BIO #91008 :

In vitro/in vivo correlation for Tegretol OROS (protocol 42).

Plasma CBZ concentration-time profiles from Tegretol OROS Protocol 42 were analyzed for percentage of dose absorbed following single oral administrations of four 100 mg, two 200 mg, and one 400 mg Tegretol OROS tablets in 17 healthy fasting subjects. Wagner-Nelson calculations were performed, and the resulting absorption-time profiles were compared to cumulative dissolution-time profiles in order to establish an in vivo/in vitro correlation.

Tegretol -SR™ C91-45 (Rev.)

Revision of C91-24 to add text referring to Tegretol-SR, sustained-release tablets, under the DESCRIPTION, DOSAGE AND ADMINISTRATION and HOW SUPPLIED sections.

Base Copy: C91-24

C91-45 (Rev.)

Tegretol-SR™
carbamazepine USP
sustained-release tablets of
100 mg; 200 mg; 400 mg

SR tablets of 100; 200; and 400 mg;

Tegretol-SR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200 mg tablets only).

and SR tablets

Tegretol

and the SR tablet slightly slower

conventional

whereas the SR tablet has slightly lower peak levels and higher trough levels than those of the conventional .

Furthermore, following a b.i.d. dosage regimen, Tegretol-SR tablets afford steady-state plasma levels comparable to conventional Tegretol tablets given q.i.d, when administered at the same total mg daiiy dose.

conventional Tegretol tablets, and 3-12 hours after administration of Tegretol-SR

~~C91-24 (Rev. 6/91)~~

Tegretol®

carbamazepine USP

Chewable Tablets of 100 mg
Tablets of 200 mg
Suspension of 100 mg/5 mL

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

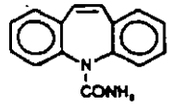
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg; tablets of 200 mg; and as a suspension of 100 mg/5 mL (teaspoon). Its chemical name is 5H-dibenz[b,f]azepine-5- carboxamide, and its structural formula is:



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Tablets: Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No.6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the intratrital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

In clinical studies oral suspension and conventional tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster than the tablet. Following a b.i.d. dosage regimen, the suspension has higher peak levels and lower trough levels than those obtained from the tablet formulation for the same dosage regimen. On the other hand, following a b.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 µg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 µg/ml. Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4 - 5 hours after administration of oral tablets. The CSF/serum ratio is 0.22, similar to the 22%

unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. *Tegretol is metabolized in the liver. After oral administration of ^{14}C-carbamazepine, 72% of the* administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 - 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. *Partial seizures with complex symptomatology (psychomotor, temporal lobe).* Patients with these seizures appear to show greatest improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10,11-epoxide metabolite to parent compound is a consistent finding.

The half-life of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels *may be reduced when these drugs are administered with Tegretol. The doses of these drugs* may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid, fluoxetine or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed fused ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, *concentration of Tegretol in milk is approximately 60% of* the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician *must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic* patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypo-

tension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, > 60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD_{50} in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

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

Respiration: Irregular breathing, respiratory depression.

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

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

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking

appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

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

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (see table below)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: ½ teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Epilepsy (see INDICATIONS AND USAGE).

Adults and children over 12 years of age — Initial: 200 mg b.i.d. for tablets or 1 teaspoon q.i.d. for suspension (400 mg per day). Increase at weekly intervals by adding up to 200 mg per day *using t.i.d. or q.i.d. regimen,* until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15

Tegretol-SR is a sustained-release formulation for convenient twice-a-day administration. When converting patients from Tegretol conventional tablets to Tegretol-SR, the same total daily mg dose of Tegretol-SR should be administered. Tegretol-SR tablets must be swallowed whole and never crushed or chewed.

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years of age. Doses up to 1600 mg daily have been used in adults in rare instances. *Maintenance:* Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age — Initial: Either 100 mg b.i.d. for tablets or 1/2 teaspoon q.i.d. for suspension (200 mg per day). Increase at weekly intervals by adding up to 100 mg per day using a b.i.d. or q.i.d. regimen until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. *Maintenance:* Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE).

Initial: On the first day, either 100 mg b.i.d. for tablets or ½ teaspoon q.i.d. for suspension for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours for tablets or 50 mg (½ teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg/daily. *Maintenance:* Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg — round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100 ..... NDC 58887-052-30
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 58887-052-32

Tablets 200 mg — capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100 ..... NDC 58887-027-30
Bottles of 1000 ..... NDC 58887-027-40
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 58887-027-32

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture. Dispense in tight container (USP).

Suspension 100 mg/5 mL (teaspoon) — yellow-orange, citrus-vanilla flavored

Bottles of 450 mL ..... NDC 58887-019-76

Shake well before using.

Do not store above 86° F.

Dispense in tight, light-resistant container (USP).

SR Tablets 100 mg — round, yellow, coated, (imprinted T on one side and 100 mg on the other), release portal on one side.
Bottles of 100 ..... NDC xxxxx-xxx-xx
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC xxxxx-xxx-xx

SR Tablets 200 mg — round, pink, coated, (imprinted T on one side and 200 mg on the other), release portal on one side.
Bottles of 100 ..... NDC xxxxx-xxx-xx
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC xxxxx-xxx-xx

SR Tablets 400 mg — round, brown, coated, (imprinted T on one side and 400 mg on the other), release portal on one side.
Bottles of 100 ..... NDC xxxxx-xxx-xx
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC xxxxx-xxx-xx

Do not store above 86°F (30°C).

Dosage Information: Tablet and Suspension

Indication	Initial Dose		Subsequent Dose		Maximum Dose
	Tablet	Suspension	Tablet	Suspension	Tablet or Suspension
Epilepsy					
6-12 years of age	100 mg b.i.d. (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 100 mg/day per day at weekly intervals, t.i.d. or q.i.d.	Add up to 1 teaspoon (100 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours
Over 12 years of age	200 mg b.i.d. (400 mg/day)	1 teaspoon q.i.d. (400 mg/day)	Add up to 600 mg/day per day at weekly intervals, t.i.d. or q.i.d.	Add up to 2 teaspoons (200 mg) per day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hours: 12-15 years 1200 mg/24 hours: over 15 years 1600 mg/24 hours: adults, in rare instances
Trigeminal Neuralgia	100 mg b.i.d. on the first day (200 mg/day)	1/2 teaspoon q.i.d. (200 mg/day)	Add up to 200 mg/day per day in increments of 100 mg every 12 hours	Add up to 2 teaspoons (200 mg) per day q.i.d.	1200 mg/24 hours

Dosage Information: Tablet, SR*, Suspension

Indication	Initial Dose			Subsequent Dose			Maximum Daily Dose		
	Tab.	SR	Susp.	Tab.	SR	Susp.	Tab.	SR	Susp.
Epilepsy									
6-12 yrs	100 mg b.i.d. (200 mg/day)	100 mg b.i.d (200 mg/day)	1/2 teasp. q.i.d. (200 mg/day)	Add up to 100 mg/day at weekly intervals, t.i.d. or q.i.d.	Add up to 100 mg/day at weekly intervals, b.i.d.	Add up to 1 teasp. (100 mg)/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hrs		
>12 yrs.	200 mg b.i.d. (400 mg/day)	200 mg b.i.d. (400 mg/day)	1 teasp. q.i.d. (400 mg/day)	Add up to 200 mg/day at weekly intervals, t.i.d. or q.i.d.	Add up to 200 mg/day at weekly intervals, b.i.d.	Add up to 2 teasp. (200 mg)/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hrs (12-15 yrs) 1200 mg/24 hrs (>15 yrs) 1600 mg/24 hrs (adults, in rare instances)		
Trigeminal neuralgia	100 mg b.i.d. the first day (200 mg/day)	100 mg b.i.d. the first day (200 mg/day)	1/2 teasp. q.i.d. (200 mg/day)	Add up to 200 mg/day in increments of 100 mg every 12 hrs	Add up to 200 mg/day in increments of 100 mg every 12 hrs	Add up to 2 teasp. (200 mg) / day in increments of 50 mg (1/2 tsp) q.i.d.	1200 mg/24 hrs		

*Tegretol-SR™ (sustained-release) Tablets

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Clinical Pharmacokinetics and Pharmacological Effects of Carbamazepine and Carbamazepine-10,11-Epoxide
An update

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Summary

Carbamazepine is a first-line drug in the treatment of most forms of epilepsy and also the drug of first choice in trigeminal neuralgia. Furthermore, it is now frequently used in bipolar depression.

Most oral formulations of carbamazepine are well absorbed with high bioavailability. The drug is 75% bound to plasma proteins. The degree of protein binding shows little variation between different subjects, and there is no need to monitor free rather than total plasma concentrations.

Carbamazepine is metabolised in the liver by oxidation before excretion in the urine. A major metabolite is carbamazepine-10,11-epoxide which is further metabolised by hydration before excretion. This epoxide-diol pathway is induced during long term treatment with carbamazepine. Co-medication with phenytoin or phenobarbitone further induces this metabolic pathway. Some but not all studies indicate an increased metabolism of carbamazepine during pregnancy. The drug crosses the placenta and the newborns who are exposed to the drug during fetal life eliminate the drug readily after birth. There seems to be no problem to nurse children during treatment with carbamazepine. Metabolism of carbamazepine is comparable in children and adults.

Several studies have tried to establish a relationship between plasma carbamazepine and clinical effect in epilepsy, but very few of these are controlled. The best anticonvulsant effect seems to be obtained at plasma concentrations of 15 to 40 μmol/L and a similar optimal plasma concentration range was found in a controlled study in trigeminal neuralgia. Side effects are more frequent at higher plasma concentrations but are also seen within that range. In some patients, with pronounced fluctuation of plasma concentrations during the dosage interval, side effects may be avoided by more frequent dosing.

Carbamazepine-10,11-epoxide is a potent anticonvulsant in animal models. During treatment with carbamazepine the plasma concentrations of this metabolite are usually 10 to 50% of those of the parent drug. It has not been possible to establish the relative contribution of the two compounds to the pharmacological effects. The epoxide has therefore been given to humans with the aim of determining the relative potency of the parent drug and its metabolite. After single oral doses of carbamazepine-10,11-epoxide to healthy subjects, the compound was rapidly absorbed. As a mean of 90% of the given dose was recovered in urine as trans-10,11-dihydroxy-10,11-dihydro-carbamazepine, a complete absorption of unchanged epoxide was shown. The mean plasma half-life of unchanged epoxide was 6.1 hours with a mean volume of distribution of 0.74 L/kg.

Six patients with trigeminal neuralgia had their optimal carbamazepine dose r with carbamazepine-10,11-epoxide for 3 to 6 days. The study was single-blind and controlled. When carbamazepine and the epoxide were given in similar doses, t control was comparable. The results show that during carbamazepine therapy, t tribution of the epoxide to the effect is considerable. No side effect was seen dur epoxide therapy. Further studies on the effect of carbamazepine-10,11-epoxide a tration in epilepsy are indicated.

Carbamazepine (CBZ) is one of the most important antiepileptic drugs and its clinical pharmacokinetics have been reviewed in the Journal (Bertilsson 1978). Since then the therapeutic indications for the drug have been broadened to include not only epilepsy and trigeminal neuralgia, but also bipolar depression (Post et al. 1984), excited psychosis (Klein et al. 1984), and alcohol withdrawal syndrome (Ritola & Malinen 1981). During the last few years considerably more knowledge has been gained about the metabolism of carbamazepine and the clinical pharmacokinetics of its active metabolite, carbamazepine-10,11-epoxide (CBZ-E). These recent studies (1978-1985) will be discussed in this updated review.

1. Analytical Methods

Simple but accurate immunotechniques (EMIT®, TDX®) have been developed for the routine monitoring of carbamazepine in plasma. These methods are specific for carbamazepine, judging from comparisons with methods based on gas chromatography and high performance liquid chromatography (HPLC) [Bertilsson & Rane 1980; Meijer et al. 1983]. As CBZ-E has much lower affinity than carbamazepine to the antibody used in EMIT, CBZ-E in plasma does not interfere in the determination of the parent drug (Monaco & Piredda 1980). The free plasma concentrations of carbamazepine measured by EMIT may, however, be overestimated by 35%, because of the higher concentrations of CBZ-E compared to carbamazepine in free than in the total plasma levels. Meijer et al. (1983) commented on the development of the many immunomethods: 'Future competition between immunotechniques will be less interesting with regard to analytical quality (which needs little improvement) or practicability than with r to economy (cost of calibration, price of reag To determine CBZ-E in plasma, HPLC see be the method of choice. Since the first m was published (Eichelbaum & Bertilsson several modifications have been reportec MacKichan (1980) and Kumps (1984).

2. Pharmacokinetics of Carbamazepin in Adults

2.1 Absorption

After a single oral dose of carbamazepine a gretol', the absorption is slow with peak p concentrations occurring as late as 24 hours drug intake (see Bertilsson 1978). In certain pa it seems important to reduce the fluctuations drug during the dosage interval (see sectior and a slow absorption seems to be of advant such patients. Hooper et al. (1985) have show the 'Tegretol' tablet and syrup were equall available, but the absorption from the syru faster and gave higher maximum plasma co trations of carbamazepine. Neuvonen (1985) pared three different brands of carbamazepin lets registered in Finland ('Tegretol', Ciba-('Neurotol', Farmos; 'Temporol', Orion). Alth they had an equal bioavailability, the 'Neu tablet was absorbed faster and gave higher plasma concentrations than the two other pr ations. 'Neurotol' also gave more pronounce effects (dizziness, ataxia) than the other two b of carbamazepine. Compared to 'Tegretol' 'Temporol' the dissolution of the 'Neurotol' *in vitro* was more rapid, probably because c microcrystalline nature of this carbamaz preparation (Neuvonen 1985).

The good absorption of the tablets with a

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tablets with a slow

dissolution (Neuvonen 1985) suggests that the drug can also be absorbed from the lower part of the intestine. This is also indicated by the study of Neuvonen and Elonen (1980), who showed that oral activated charcoal shortens the plasma elimination half-life of carbamazepine. This drug thus seems to have a significant enterohepatic or enteroenteric circulation.

2.2 Distribution and Protein Binding

The apparent volume of distribution of carbamazepine assuming complete bicavailability is about 1 L/kg as reported in most studies (see Bertilsson 1978). The drug distributes into all tissues and organs without any preferential affinity for particular organs.

The plasma protein binding of carbamazepine is 70 to 80% as determined by different techniques (Bertilsson 1978). If the protein binding varies between patients, unbound rather than total drug concentrations in plasma ought to be better related to clinical effects. In contrast to phenytoin and valproic acid, for example, the plasma protein binding of carbamazepine shows very little interindividual variation (Bertilsson 1978; Levy & Schmidt 1985; Perucca 1984). Carbamazepine may be displaced from its protein binding by valproic acid (Mattson et al. 1982), resulting in an increased free fraction of carbamazepine.

In a few patients, free rather than total concentrations of carbamazepine may be better to monitor, but today the routine monitoring of free concentrations of carbamazepine seems to be unnecessary in most cases.

2.3 Plasma Concentrations of Carbamazepine and CBZ-E in Relation to Carbamazepine Dose

Hooper et al. (1974) found indications of a curvilinear relationship between plasma concentration and dose of carbamazepine. This suggested dose-dependent kinetics similar to that reported for phenytoin (Richens & Dunlop 1975), i.e. an increase of the dose causes a disproportionately high increase in the plasma concentration. However, this finding has not been confirmed. In contrast, Perucca et al. (1980) found a positive y-axis intercept in some patients indicating that the degree of autoinduction and/or absorption was dependent on the dosage. In most of the patients, however, a doubling of the dose caused a doubling of the plasma concentration (Perucca et al. 1980). These results are similar to ours, where we studied patients with trigeminal neuralgia on monotherapy with carbamazepine (Tomson et al. 1980). Within each patient there was a positive relationship between plasma concentration and dose of carbamazepine (fig. 1). The relationship was quite different in the different patients, but there was no indication of dose-dependent kinetics.

Kumps (1981) found a curvilinear relationship between carbamazepine concentration and dose in a group of patients, where the dose was not varied within the patients. As correctly pointed out by Kumps, there may be several reasons for this, one of which is that the dose is selectively increased in the patients developing a low plasma concentration on a normal dose. It is thus difficult to draw

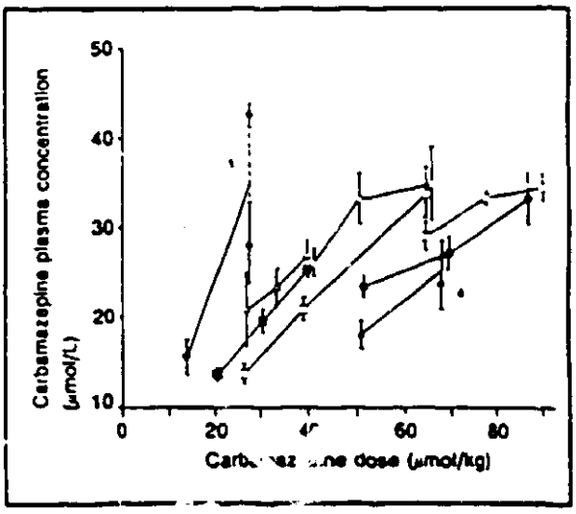

Fig. 1. Relationship between dose and steady-state plasma concentration of carbamazepine in 7 patients on carbamazepine monotherapy (mean ± SD). Most patients were given 3 different doses of carbamazepine, but patients 1 and 4 were given the same dose twice (from Tomson et al. 1980).

any conclusions from population studies concerning the relationship between concentration and dose.

The plasma concentrations of CBZ-E are (like the parent drug) poorly correlated with the given dose (see Bertilsson 1978). The plasma concentrations of the metabolite and carbamazepine are better correlated, but there is a variation in the ratio CBZ-E/carbamazepine between patients. This ratio increases when patients are treated with phenytoin and phenobarbitone (Bertilsson 1978; Brodie et al. 1983; McKauge et al. 1981). These antiepileptic drugs induce the epoxidation of carbamazepine (Eichelbaum et al. 1985; see section 2.4).

In patients with trigeminal neuralgia on monotherapy with carbamazepine, there was a linear relationship between plasma concentrations of CBZ-E and carbamazepine (fig. 2; data from Tomson et al. 1980). A change in carbamazepine dose caused a proportional change in the plasma concentrations of both carbamazepine and the epoxide. This constant ratio between the metabolite and the parent drug is one of the reasons why it has been impossible to evaluate the relative clinical effects the two compounds during treatment with carbamazepine (see section 4).

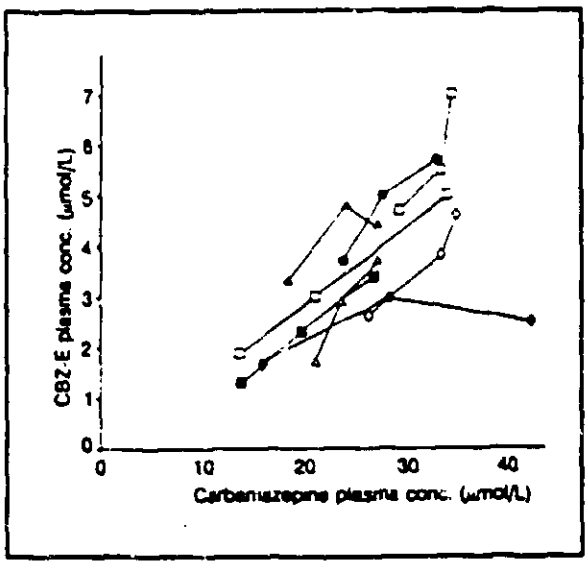

Fig. 2. Relationship between steady-state plasma concentrations of CBZ-E and carbamazepine during treatment of trigeminal neuralgia with carbamazepine as monotherapy; 7 patients were treated with different doses of carbamazepine (data from Tomson et al. 1980).

2.4 Metabolism of Carbamazepine

The metabolism of carbamazepine has been thoroughly investigated both *in vitro* and *in vivo* (Eichelbaum et al. 1984, 1985; Lertratanangkoon & Horning 1982; Tybring et al. 1981). The most important pathway is the formation of CBZ-E (Eichelbaum et al. 1985). This primary metabolite is almost completely converted to *trans*-10,11-dihydroxy-10,11-dihydrocarbamazepine (*trans*-CBZ-diol) [fig. 3], which is excreted in the urine mainly as the unconjugated form (Faigle & Feldmann 1981; Tomson et al. 1983). In a recent study (Eichelbaum et al. 1985), we found that in healthy subjects given a single oral carbamazepine dose, 21.5 ± 5.6% of the dose was excreted in urine as *trans*-CBZ-diol (table I). As seen in table I the sum of 2- and 3-hydroxy-CBZ (2- and 3-OH-CBZ) and 9-hydroxymethyl-10-carbamoylacridan (9-OH-CBZ) constitutes about 15% of the given dose.

2.4.1 Auto- and Heteroinduction of Metabolism

It is now well established that during long term therapy, carbamazepine induces its own metabolism (Bertilsson et al. 1980); Eichelbaum et al. 1979). Concomitant treatment with phenobarbitone or phenytoin further induces the metabolism (Christiansen & Dam 1973; Eichelbaum et al. 1979, 1985). In epileptic patients on monotherapy with carbamazepine (group 2 in table I) and especially in patients treated with other anticonvulsants in addition to carbamazepine (group 3), there was a marked increase in the percentage of the carbamazepine dose excreted as *trans*-CBZ-diol. The mean clearance of carbamazepine by the formation of *trans*-CBZ-diol in the 3 groups was 4.3, 14.5 and 58 ml/h/kg, respectively (table I). This clearly shows that it is the epoxide-diol pathway that is induced during both auto- and heteroinduction (Eichelbaum et al. 1985). There are indications that it is not only the epoxidation but also the formation

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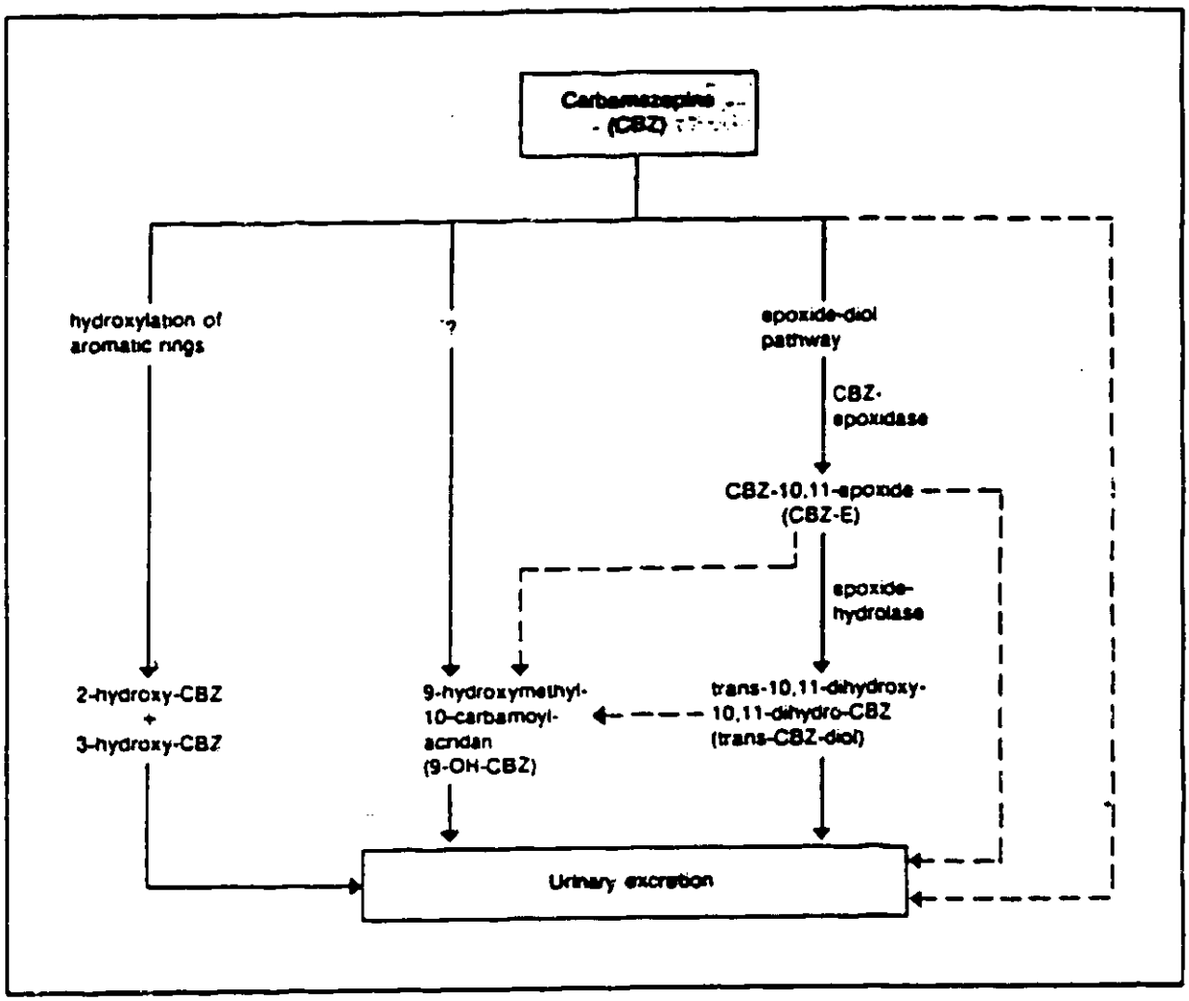

Fig. 3. Major pathways of metabolism of carbamazepine in man (from Eichelbaum et al. 1985).

trans-CBZ-diol that is induced (Bourgeois & Wad, 1984a; Eichelbaum et al. 1985; Tybring et al. 1981; Wedlund et al. 1982).

Time Course of Autoinduction

We have studied the time course of the autoinduction of carbamazepine kinetics in 3 children with a recently developed psychomotor epilepsy (Berulsson et al. 1980). Tetradeuterium-labelled carbamazepine ($CBZ\text{-}D_4$) was given as a single oral dose before the maintenance therapy with Tegretol® tablets was started. On 3 occasions part of the regular carbamazepine dose was replaced by $CBZ\text{-}D_4$. As seen in figure 4 the clearance of the $CBZ\text{-}D_4$ dose given on day 6 (second dose of carbamazepine during maintenance therapy) was increased compared to the initial $CBZ\text{-}D_4$ dose. The clearance of $CBZ\text{-}D_4$ was doubled after 21 to 36 days and was not further increased during the 5 months when the last $CBZ\text{-}D_4$ dose was given. The autoinduction of carbamazepine metabolism is already apparent during the first dose of the drug and seems to be complete during the first 3 to 5 weeks of treatment. This finding corroborates the decrease in plasma concentrations of carbamazepine seen during the first few weeks of treatment with

Table I. Disposition of carbamazepine (CBZ) in 3 groups of subjects (mean ± SD) [from Eichelbaum et al. 1985]

	Group 1[a]	Group 2[b]	Group 3[c]
Cumulative urinary excretion of metabolites (% of oral CBZ dose)			
CBZ-E	1.1 ± 0.5	1.5 ± 0.4	1.1 ± 0.2
trans-CBZ-diol	21.5 ± 5.6	26.5 ± 2.9	49.9 ± 11.2
2-OH-CBZ	6.2 ± 2.4	2.4 ± 0.8	3.1 ± 2.1
3-OH-CBZ	5.6 ± 1.7	3.0 ± 1.1	4.2 ± 2.3
9-OH-CBZ	4.5 ± 1.2	8.4 ± 2.6	6.8 ± 1.5
Total	39.2 ± 9.8	41.6 ± 4.1	65.2 ± 7.2
Half-life of CBZ (h)	26.2 ± 6.1	12.3 ± 0.8	8.2 ± 3.3
Plasma clearance of CBZ (ml/h/kg)	19.8 ± 2.7	54.6 ± 6.7	113.3 ± 33.4
Clearance of CBZ by the formation of *trans*-CBZ-diol (ml/h/kg)	4.3 ± 1.3	14.5 ± 2.7	56.6 ± 26.5

a Healthy subjects (n = 6) after a single 200mg CBZ dose.
b Epileptic patients treated with CBZ as monotherapy (n = 4).
c Epileptic patients treated with CBZ in combination with other anticonvulsants (n = 5).

the drug (Eichelbaum et al. 1975; Pynnönen et al. 1980).

The time course of the autoinduction has been studied in 2 chronic alcoholics who were treated for withdrawal symptoms with carbamazepi (Bertilsson et al. 1986). Upon admission to t clinic a single dose of 300mg each of carbama pine and CBZ-D_4 in suspension (fig. 5) was a ministered. Carbamazepine was then given in dose of 200mg × 3 for 5 days, which was follow by a single 300mg dose after the last dose of t maintenance treatment. As seen in figure 5 the sults from the 2 patients are very similar to t post-steady-state half-life of carbamazepine (hours in both patients). One week after stoppi the treatment, the half-lives of carbamazepine w much longer (46 and 45 hours). These results dicate that the patients are induced already dur the elimination of the initial CBZ-D_4 dose.

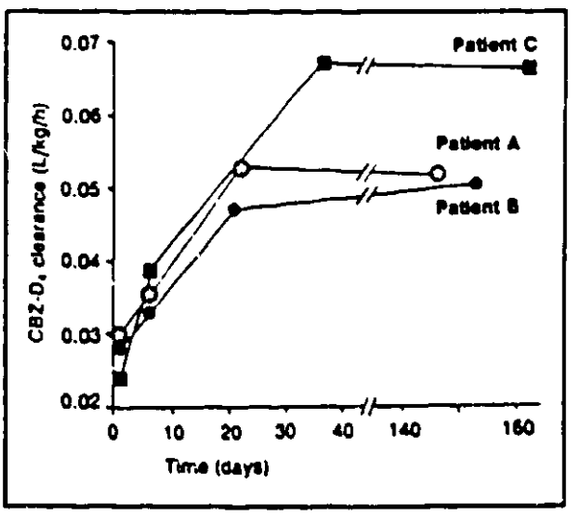

Fig. 4. Plasma clearance of tetradeuterium-labelled carbamazepine (CBZ-D_4), when given as a single oral dose before and at different times during maintenance carbamazepine treatment in 3 children with recently discovered epilepsy. Multiple dosing was started on day 5 (from Bertilsson et al. 1980).

This early induction was most probably caus by carbamazepine itself rather than by the inta of alcohol because the pharmacokinetics of ca amazepine are similar in alcoholics and healt subjects (Pynnönen et al. 1978). The disappearar of autoinduction was also rapid, as seen by t doubling of the half-life during the week of n treatment.

2.5 Pharmacokinetic Drug Interaction

Recent papers (Hansten 1985; Kutt 1984; P ucca 1982) review interactions with antiepilep

sum et al. 1985]

Group 3[a]
1.1 ± 0.2
49.9 ± 11.2
3.1 ± 2.1
4.2 ± 2.3
6.8 ± 1.5
85.2 ± 7.2
8.2 ± 3.3
113.3 ± 33.4
58.6 ± 26.5

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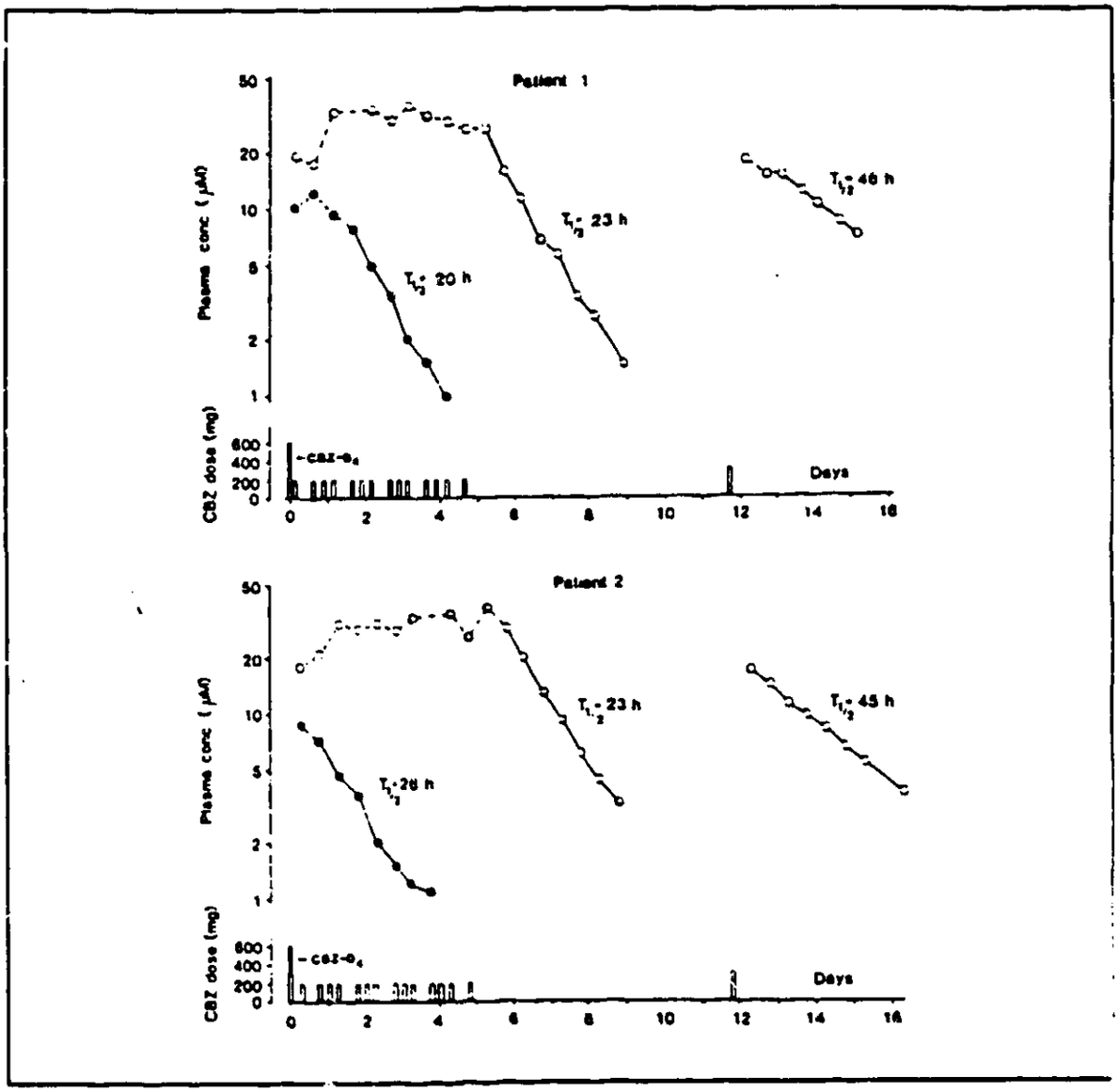

Fig. 5. Plasma concentrations of carbamazepine (O) and CBZ-D_4 (●) in 2 alcoholic patients, who were treated with carbamazepine during the withdrawal period (see also section 2.4 of text) [from Bertilsson et al. 1985].

drugs, and this will therefore be only briefly discussed here. Treatment with phenytoin and/or phenobarbitone increases the metabolism of carbamazepine (Eichelbaum et al. 1979, 1985; Perucca & Richens 1980) [see also section 2.4]. Carbamazepine is an enzyme inducer causing increased metabolism of itself (see section 2.4) and of other drugs, e.g. clonazepam (Lai et al. 1978), ethosuximide (Warren et al. 1980), doxycycline (Penttila et al. 1974), oral contraceptives (Hempel & Klinger 1976) and phenytoin and warfarin (Hansen et al 1971). The effect of carbamazepine on phenytoin plasma concentrations varies among patients Carbamazepine seems to have a dual action, i.e

enzyme inhibition and induction, and the relative importance between them may vary between different subjects. Ziellinski et al. (1985) showed that carbamazepine added to phenytoin treatment increased the plasma concentrations of phenytoin in 50% of the patients, causing acute toxicity in 20%. Carbamazepine decreases plasma concentrations of haloperidol during combination treatment (Jann et al. 1985; Kidron et al. 1985).

Several drugs have been shown to inhibit the metabolism of carbamazepine, e.g. propoxyphene (Dam & Christiansen 1977). Isoniazid (Valsalen & Cooper 1982; Wright et al. 1982) and the antibiotics triacetyloleandomycin (Mesdjian et al. 1980) and erythromycin (Hedrick et al. 1983) caused increased plasma concentrations of carbamazepine leading to intoxications. Cimetidine, a well-known inhibitor of drug metabolism, does not seem to have any effect on steady-state plasma concentrations of carbamazepine (Levine et al. 1985; Sonne et al. 1983).

Carbamazepine and valproic acid are frequently used in combination. Valproic acid seems to increase plasma concentrations of CBZ-E but not carbamazepine (McKauge et al. 1981). This is probably due to an inhibition of the elimination of CBZ-E (Levy et al. 1984). The amide derivative of valproic acid (i.e. valpromide, which is registered in some European countries) increased the plasma concentrations of carbamazepine epoxide but had no effect on the parent drug, carbamazepine (Meijer et al. 1984). Subsequently we showed that valpromide but not valproic acid is an inhibitor of epoxide hydrolase (Pacifici et al. 1985). This enzyme is responsible for the major part of the metabolism of CBZ-E (Tomson et al. 1983).

2.6 Pharmacokinetics of Carbamazepine During Pregnancy

Nau and collaborators (1982) have reviewed the literature on anticonvulsants during pregnancy and lactation. In some studies (Bardy 1981; Dam et al. 1979; Froescher et al. 1981) a decreased plasma concentration of carbamazepine has been found during pregnancy. An increased plasma ratio of CBZ-E/CBZ (Dam et al. 1979) indicates that is due to an increased metabolism rather tha other changes. Yerby et al. (1985) also foun increased plasma CBZ-E/CBZ ratio during nancy. They showed that the plasma concentra of *trans*-CBZ-diol decreased and took this as dence that the increased ratio is the result o hibition of the epoxide hydrolase rather tha increased epoxidation of carbamazepine. Ba et al. (1985) found decreased carbamazepine pla concentrations and increased CBZ-E/CBZ ratio, only during weeks 4 to 24 and not later du pregnancy. Otani (1985) found an increased parent serum clearance during pregnancy phenytoin, primidone, and valproic acid, but change for carbamazepine.

Kuhnz et al. (1984) showed that the pro binding of carbamazepine was the same in wor at term as non-pregnant women. The protein bi ing of CBZ-E was only slightly lower. In a l study (Yerby et al. 1985) the mean free fracti of carbamazepine and CBZ-E were found to be evated in pregnant women (0.25 and 0.50) c pared with postpartum women (0.22 and 0.- These small changes do not necessitate meas ment of free fractions during pregnancy.

3. Pharmacokinetics of Carbamazepine Newborns and Children

3.1 Newborns

Pynnönen et al. (1977) administered single dc of carbamazepine to pregnant women during we 12 to 16 of gestation prior to abortion. They fo that fetal plasma concentrations of carbamazep were 50 to 80% of maternal levels. Carbamazep thus crosses the placenta to the fetus. Piafsky Rane (1978) have shown *in vitro* that human f liver during weeks 15 to 21 of gestation is able metabolise carbamazepine to CBZ-E.

We studied the disposition of transplacent transferred carbamazepine in 5 newborns (Ran al. 1975). The plasma concentrations of ca mazepine in the newborns and their mothers w comparable at birth. We were surprised to find sh plasma elimination half-lives of 8.2 to 28.1 ho

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in these newborns. The metabolism of carbamazepine was probably induced in the fetal liver as they had been exposed to both carbamazepine and phenytoin during the entire gestational time. Today we know that both these drugs induce the metabolism of carbamazepine (see section 2.4), but this was not known in 1973 at the time of the investigation. Rey et al. (1979) found similar short half-lives of carbamazepine in neonates, who had been exposed to carbamazepine (and phenobarbitone) during pregnancy. Newborn children of mothers treated with carbamazepine as monotherapy during the pregnancy had a longer mean half-life: 28 ± 11 hours (n = 4) [Kuhnz et al. 1983].

3.2 Transfer of Carbamazepine and CBZ-E by Breast Milk

Pynnönen and Sillanpää showed in 1975 that both carbamazepine and the epoxide metabolites are transferred to breast milk. The ratio of the concentration in breast milk and in maternal plasma is about 0.4 for carbamazepine (Froescher et al. 1984; Kaneko et al. 1979, 1982; Kuhnz et al. 1983) and about 0.5 for CBZ-E (Froescher et al. 1984; Kuhnz et al. 1983). The doses of carbamazepine given to the newborns during breast feeding are in the range of 2 to 5mg daily (Froescher et al. 1984). These low doses were calculated to give carbamazepine plasma concentrations of about 4 μmol/L. This was the level of carbamazepine observed in all cases by Kuhnz et al. (1983), except in 1 where a maximum concentration of 20 μmol/L (= 4.7 μg/ml) was reached. Based on the available results there is no reason to discourage a mother on carbamazepine monotherapy from nursing – according to Froescher et al. (1984).

From the data presented (Froescher et al. 1984; Kuhnz et al. 1983; Pynnönen & Sillanpää 1975) on the concentrations of CBZ-E, the daily intake of CBZ-E in the nursing infant should be maximally 1 to 2mg. This is a very low dose compared to the doses of the epoxide that have been given to adult healthy subjects (Tomson et al. 1983) and patients (Tomson & Bertilsson 1984). However, CBZ-E is unstable in gastric juice and decomposes to an unknown compound (Tomson et al. 1983) and when we administered the oral doses of CBZ-E an antacid was always given concomitantly to neutralise the gastric juice. It is thus not possible to predict what will happen with CBZ-E in breast milk when it reaches the gastric juice in the stomach of the nursed child. However, with our present experience there seems to be no adverse effect of the nursing.

3.3 Pharmacokinetics in Children

As shown in adults, there is also a poor correlation between plasma concentrations and carbamazepine dose in different children (McKauge et al. 1981; Pynnönen et al. 1977; Rane et al. 1976). The plasma concentration ratio of CBZ-E/CBZ seems to be higher in children than in adults (McKauge et al. 1981; Pynnönen et al. 1977; Rane et al. 1976; Schoeman et al. 1984a,b). As in adults this ratio is increased during combined treatment with other drugs. The pharmacokinetic parameters of carbamazepine disposition in children (Bertilsson et al. 1980) are similar to those in adults.

4. Relationship Between Plasma Concentration of Carbamazepine and Clinical Effects

4.1 Total Plasma Concentration and Clinical Effects

Early reports of carbamazepine plasma concentrations in relation to antiepileptic effects were based on observations of patients on combined antiepileptic drug therapy, often with intractable seizures. The limitations of such studies are obvious. During the past decade, however, a number of studies report plasma concentrations of carbamazepine in epileptic patients receiving carbamazepine as monotherapy (table II). Good seizure control has been observed over a wide range of plasma concentrations. As an extreme example Callaghan et al. (1978) reported plasma concentrations from zero to 84 μmol/L in seizure-free patients. In general, plasma concentrations of patients with poor seizure control have not differed

significantly from concentrations observed in patients with good response.

These rather ambiguous results may be explained by methodological shortcomings. Many reports are double-blind studies comparing the antiepileptic effect of carbamazepine with that of phenytoin, clonazepam or valproate (Callaghan et al. 1985; Mikkelsen et al. 1981; Ramsay et al. 1983; Simonsen et al. 1976; Troupin et al. 1977). These studies have not been designed with the primary aim of investigating the plasma concentration-effect relationship. Therapeutic ranges have sometimes been defined in advance (Simonsen et al. 1976).

Most studies have compared plasma concentrations in groups of patients with good seizure control with those of patients with poor therapeutic outcome. When trying to establish a therapeutic range, it is essential to study each individual patient at different plasma concentrations. It is remarkable that such data are available in only one study (Shorvon et al. 1980). In this investigation 46 newly diagnosed patients with epilepsy were treated with carbamazepine as monotherapy. Five patients were uncontrolled at plasma concentrations below 17 μmol/L but became seizure-free when the dose was adjusted to reach the assumed therapeutic range of 17 to 34 μmol/L. Ten of the patients were seizure-free with plasma concentrations below 17 μmol/L. 26 patients had from the beginning of therapy concentrations within the range of 17 to 34 μmol/L; 20 of these were seizure free.

The study of Shorvon et al. (1980), like others (Callaghan et al. 1985; Mikkelsen et al. 1981; Ramsay et al. 1983; Sillanpää et al. 1979; Strandjord & Johannessen 1980), comprised newly diagnosed, previously untreated patients. Seizure control at lower plasma concentrations appears to be more common in this patient category. At the other extreme, Lesser et al. (1984) selected patients with intractable seizures. In their material, seizure control was obtained at plasma concentrations between 41 and 48 μmol/L. It may thus well be that the therapeutic range varies with the severity of the epileptic process, and that differences in patient selection may in part explain the somewhat diverging results in different studies (Lesser et al. 198 Rapeport 1985; Schmidt & Haenel 1984).

The therapeutic effect in trigeminal neuralg may be assessed after short observation periods. was therefore possible to study each of 7 patien with trigeminal neuralgia on 3 different dose leve of carbamazepine (Tomson et al. 1980). Optim pain control was achieved at 24 to 43 μmol/L. Po and co-workers (1983) studied 18 affectively patients treated with carbamazepine as monothe apy. They found no correlation between plasm concentrations of carbamazepine and clinical e fects.

The relationship between side effects and tot plasma concentrations of carbamazepine in patien on monotherapy has been studied by a number authors. Troupin et al. (1977) were unable to fir any clearcut relationship; side effects appeared ov a broad range of plasma concentrations (8 to 7 μmol/L). Also Callaghan et al. (1978) concluded th side effects were associated with a range of seru concentrations. Strandjord and Johannessen (198 reported side effects in 3 of 62 patients at plasm concentrations of 31 to 41 μmol/L. Ramsey et a (1983) noted mild sedation at concentrations e ceeding 35 μmol/L and diplopia and blurred visic with levels greater than 47 μmol/L. Callaghan al. (1985) in a prospective double-blind study cou not detect any correlation between side effects an serum blood concentrations.

Side effects at low plasma drug concentratior appear to be more frequently reported in patien on combined antiepileptic drug therapy. Thus, Ku et al. (1975) observed blurred vision, nystagm and disturbances in coordination when blood co centrations approached values greater than 1 μmol/L in patients given also phenytoin, phen barbitone or primidone in high, near toxic, dose Tomson (1984) noted dizziness in a patient o antiepileptic polytherapy as plasma concentratior exceeded 17 μmol/L.

4.2 Free Plasma Concentration and Clinical Effects

Only a few studies have attempted to correla free plasma concentrations of carbamazepine wi

udies (Lesser et al. 1984;
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Table II. Plasma concentrations and seizure control in patients on monotherapy with carbamazepine

References	No. of patients	Patient characteristics		Data presented from more than 1 plasma measurement per patient	Plasma conc. in good responders (μmol/L)	Plasma conc. in poor responders (μmol/L)
		seizure type	severity of epilepsy			
Simonsen et al. (1976)	26	Psychomotor	Majority previously treated	No	25-42	(Doses were chosen in advance to obtain a certain plasma conc. range. Separate levels for responders and non-responders not given)
Troupin et al. (1977)	47	Partial with or without generalisation	All previously treated	No	34-51	Not different from concs. in good responders
Callaghan et al. (1978)	28	Complex partial and generalised	Majority previously treated	No	0-84	33-116
Sato et al. (1979)	27	Partial with or without generalisation	Not stated	No	0-66	15-48
Sivanpää et al. (1979)	19	Partial with or without generalisation	Majority newly diagnosed, previously untreated	No	Mean 17.5	Mean 14.4
Shorvon et al. (1980)	46	Partial and generalised	Newly diagnosed previously untreated	In 5/46 patients	17-34	(Optimum conc. range defined in advance to obtain a certain plasma conc. range)
Strandjord & Johannessen (1980)	62	Partial and grand mal	24 newly diagnosed 38 previously treated	No	13-51	20-42
Mikkelsen et al. (1981)	14	Psychomotor	Newly diagnosed previously untreated	No	16-40	(Responders as well as non-responders)
Ramsay et al. (1983)	35	Partial and generalised	Newly diagnosed previously untreated	No	20-27	Mean 41
Lesser et al. (1984)	19	Partial and generalised	Intractable seizures	No	41-48	30-58
Schmidt & Haenel (1984)	11	Partial and generalised	Only patients who became seizure free	No	20-40	Non-responders excluded
Callaghan et al. (1985)	28	Partial and generalised	Newly diagnosed previously untreated	No	26 ± 10 (mean ± SD)	34 ± 11

antiepileptic effect. Lesser et al. (1984) studied 19 patients with intractable seizures. With high doses of carbamazepine in monotherapy 7 patients experienced a reduction of the seizure frequency of at least 83%. This was achieved at free plasma concentrations of 4 to 13 μmol/L. These concentrations did not differ from those obtained in patients who did not respond to therapy. Furthermore, the range of total plasma concentrations in the successfully treated patients was 41 to 53 μmol/L, i.e. more narrow than the free plasma concentration range. Troupin et al. (1977) analysed carbamazepine concentrations in saliva and concluded that no apparent difference could be discerned between patient groups having improved seizure frequency and those who did not.

In patients on high doses of carbamazepine Lesser et al. (1984) found a broad overlap between toxic and non-toxic free plasma concentrations of carbamazepine; free concentrations associated with side effects ranged from 5.9 to 12.7 μmol/L, whereas the group of patients without side effects had free plasma concentrations between 6.5 and 13.1 μmol/L. Total plasma concentrations for the respective groups were 30 to 52 μmol/L and 40 to 73 μmol/L. Riva et al. (1984), in contrast, found a good correlation between free as well as total plasma concentrations of carbamazepine and dose-related side effects in 5 epileptic patients all receiving carbamazepine in combination with phenobarbitone. Blood samples were drawn and side effects assessed every hour during a dosage interval. Side effects were associated with free concentrations above 6 μmol/L or total carbamazepine levels of 30 μmol/L. They concluded that total concentrations gave a sufficiently accurate estimate of clinical response. Wheeler et al. (1982) reported a case with intermittent nystagmus and ataxia during the peak concentration of carbamazepine. They stated that the clinical symptoms were indeed more closely related to the unbound fraction of the drug occurring with concentrations above 11 μmol/L (total concentration 63 μmol/L). The data presented in the report, however, lend little support to their conclusion.

In conclusion, good seizure control has been achieved at plasma concentrations over a v range. It has generally not been possible to sepa this range from plasma concentrations founc patients with poor therapeutic outcome. Howe very few systematic attempts have been mad investigate the effects of different plasma con trations within one individual. There is also a c siderable overlap between the range of therape plasma concentrations and the concentrations have been associated with side effects. Monito free instead of total plasma concentrations of c amazepine has, as yet, not proved advantageo

4.3 Dosage Regimen and Clinical Effects

From single-dose data it could be anticipa that a twice daily dosing regimen of carbamazep would suffice. However, induction of the met olism of carbamazepine during maintena therapy, especially when taken in combination w phenytoin, phenobarbitone or primidone, yie short plasma carbamazepine half-lives. Con quently, considerable interdosage fluctuations plasma concentrations have been observed dur a twice daily regimen (Dam & Christiansen 19 Johannessen et al. 1977; Schneider & Stenzel 197 Paxton et al. (1983) found pronounced fluctuati (32 to 100%) also in salivary carbamazepine c centrations in children receiving carbamazepine monotherapy twice daily. Höppener et al. (19 studied 43 patients on carbamazepine in comb ation with other anticonvulsants and 19 patie on carbamazepine alone, all given carbamazep 3 times daily. All patients suffered from intern tent side effects that were not correlated with trou plasma concentrations of carbamazepine. In dosage fluctuations from the average plasma c centration in the group on combination ther were 68.5 ± 21.2% and in the patients on mo therapy 32.5 ± 10.9%. The occurrence of side fects coincided in time with the peak plasma centrations. Side effects disappeared when dosing schedule was adjusted in such a way t plasma concentrations did not exceed 34 μmol The observation of the correlation between diur fluctuations in plasma concentrations of carba

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azepine and intermittent side effects has been corroborated by others (Blennow 1983; Neuvonen 1985; Riva et al. 1984; Tomson 1984; Wheeler et al. 1982) [fig. 6]. Riva and colleagues (1984) noticed side effects when plasma concentrations during the dosage interval exceeded 30 μmol/L. Tomson (1984) found a good within-patient correlation between side effects and plasma concentrations obtained hourly during the dosage interval. The threshold at which side effects appeared, however, showed marked *interindividual* variability (17 to 50 μmol/L). Lesser et al. (1984) reported a case in which adverse effects appeared to be related to incremental concentration changes rather than the concentration itself. It is (with the present documentation) surprising that Ghose et al. (1983) were unable to observe any significant differences in adverse effects and seizure frequency, when a group of patients with epilepsy, during different periods, were given carbamazepine in 3 times daily, twice and once daily regimens. Sample size and patient selection may serve as an explanation.

The importance of diurnal fluctuations for side effects is well established but their importance for therapeutic effects is very little studied. In trigeminal neuralgia, however, there seems to be a correlation between diurnal fluctuations and the pain-relieving effect (Tomson & Ekbom 1981). It does appear justified to use a 3 or 4 times daily regimen in patients with highly induced metabolism, i.e. in particular patients on combination therapy with phenytoin, phenobarbitone or primidone. Alternatively, slow release formulations of carbamazepine may prove advantageous.

5. Carbamazepine-10,11-Epoxide (CBZ-E)

5.1 Effects of CBZ-E

5.1.1 Toxicity

The fact that epoxides, other than CBZ-E, have been considered responsible for toxic effects like carcinogenesis, teratogenesis and mutagenesis has caused concern about the toxic effects of CBZ-E. This has been studied by Frigerio and Morselli (1975). The LD_{50} of CBZ-E was similar to that of

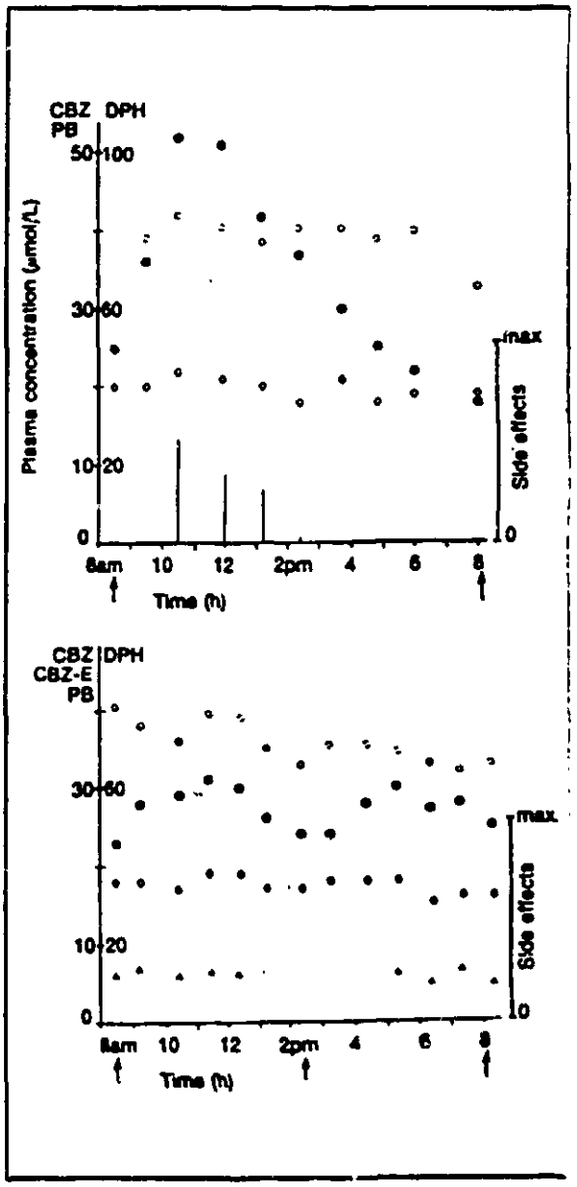

Fig. 6. Relationship between side effects (dizziness) and fluctuations in carbamazepine (CBZ) plasma concentrations. The epileptic patient received carbamazepine (●) in combination with phenytoin (○) [DPH] and phenobarbitone (○) [PB]. Carbamazepine was given twice (upper graph) and 4 times daily (lower graph) Δ = CBZ-E concentration. Arrows indicate time of active carbamazepine dosing. Placebo was given at 2 pm when dosing twice daily. Plasma concentrations were determined hourly, at the same time side effects were assessed by the patient on a visual analogue scale (bars). No side effects were recorded when administering carbamazepine 4 times daily (from Tomson 1984)

carbamazepine. The cytotoxic effects of CBZ-E *in vitro* on 3 different strains of human cells were also studied and neither CBZ-E nor carbamazepine were toxic at concentrations of 4.2 to 42 μmol/L. At higher concentrations, CBZ-E was, if anything, less toxic than carbamazepine. Both CBZ-E and carbamazepine have been shown to be negative in the Ames test (Glatt et al. 1975). CBZ-E does not react with the nucleophilic agent NBP which indicates that it has no alkylating properties (Braun et al. 1982). Königstein et al. (1984) found that neither carbamazepine nor CBZ-E had the ability to induce sister chromatid exchanges nor structural abberations in the chromosomes of human peripheral lymphocytes *in vitro*, in tests of mutagenic drug properties.

5.1.2 Anticonvulsant Effects of CBZ-E in Animal Models

The anticonvulsant effect of CBZ-E has been tested in various animal models. CBZ-E was found to have a potency comparable to that of carbamazepine in electroshock, strychnine- and pentylenetetrazole-induced seizures in mice when the two compounds were given orally (Frigerio & Morselli 1975). Furthermore, CBZ-E and carbamazepine were equipotent in the protection against secondarily generalised convulsions and partial seizures in the 'amygdala-kindled' rat (Albright & Bruni 1984). In this experiment the drugs were given intraperitoneally.

Plasma concentrations of carbamazepine and CBZ-E were not determined in the above studies. They therefore in fact compare the effects of CBZ-E on the one hand and on the other carbamazepine plus CBZ-E formed by metabolism from carbamazepine. Thus, the effect of carbamazepine treatment in these experiments may partly be due to CBZ-E. Faigle et al. (1977) compared the time course of plasma concentrations of carbamazepine and CBZ-E and the anticonvulsant activity in the rat. They found that carbamazepine possessed an anticonvulsant effect of its own which, however, was reinforced by CBZ-E. Bourgeois and Wad (1984b) studied the protective effect of carbamazepine and CBZ-E on maximal electroshock-induced seizures and the neurotoxic activity of two compounds as determined by the Rotorod t icity tes . he experiments were performed in m who were given the drugs orally. The mice w pretreated with an inhibitor of metabolism, S 525-A, to reduce the conversion of carbamazep and CBZ-E to metabolites. Based on brain conc trations, carbamazepine and CBZ-E were ab equally neurotoxic, but carbamazepine was times more potent against maximal electrosho induced seizures, yielding a higher therapeutic dex for carbamazepine. Animal data thus indic that CBZ-E has an anticonvulsant effect comp able to that of carbamazepine.

5.1.3 Effects of CBZ-E Evaluated During Carbamazepine Therapy in Patients

Several attempts have been made to evalu the contribution of CBZ-E to the clinical effe during carbamazepine therapy in man. Dur monotherapy there is a rather close correlation tween CBZ-E and carbamazepine concentratic in plasma (see section 2.3). Hence, it has not bc possible to distinguish between the effect of parent compound and the metabolite in epilep patients treated with carbamazepine alone (Sill pää et al. 1979; Strandjord & Johannessen 198 In patients treated with carbamazepine as mor therapy for trigeminal neuralgia, steady-state c centrations of carbamazepine and CBZ-E w equally well correlated with the pain relief (To son et al. 1980). Schmidt et al. (1984) studied pain-relieving effect of single doses of carbama pine given in suspension to patients with tri minal neuralgia. This procedure results in a ti lag between the peak concentration of carbam epine and that of CBZ-E. Maximal pain relief v observed before the peak concentration of CB and achieved at carbamazepine plasma concent tions of 37 to 88 μmol/L. This is considerably hig than the optimal range of 24 to 43 μmol/L served at steady-state (Tomson et al. 1980). T discrepancy may indicate that higher carbama pine concentrations are required when the CB concentrations are low, as after single doses. D et al. (1977) made a retrospective analysis of

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patients with epilepsy, the majority on polytherapy. They found no correlation between seizure control and CBZ-E concentrations. Post et al. (1983) found no correlation between antidepressant response and plasma concentrations of carbamazepine and CBZ-E nor between antidepressant response and cerebrospinal fluid (CSF) concentrations of carbamazepine. There was, however, a significant correlation between CSF concentrations of CBZ-E and antidepressant response. The results are somewhat surprising since, in this study as in others, there was a correlation between CSF and plasma concentrations of both carbamazepine and CBZ-E. Schmidt et al. (1984) in their study of trigeminal neuralgia found side effects to be more closely correlated with plasma concentrations of carbamazepine than to those of CBZ-E. The same observation was made by Riva et al. (1984) in patients with epilepsy. Side effects were not associated with high epoxide concentrations in serum in the study of Strandjord and Johannessen (1980).

One way to distinguish between the effects of the parent compound and metabolite may be to study patients with extreme CBZ-E/CBZ plasma concentration ratios. However, these are found almost exclusively under combination therapy with drugs that interact with the metabolism of carbamazepine. Krämer et al. (1984) reported 5 epileptic patients on carbamazepine who were also given danazol, a steroid hormone which inhibits the epoxidation of carbamazepine. An improved anticonvulsant effect without disturbing side effects was recorded when danazol was added. This indicated that therapeutic effects are exerted by carbamazepine and side effects of carbamazepine therapy may be due to CBZ-E. Dextropropoxyphene also inhibits the epoxidation of carbamazepine. This results in increased plasma concentrations of carbamazepine and a concomitant fall in CBZ-E concentrations. In contrast to the results in Krämer's report, patients subject to this interaction reported symptoms of carbamazepine intoxication (Dam et al. 1980). This would infer that carbamazepine is itself the main source of side effects.

Meijer et al. (1984) reported a marked increase in CBZ-E concentrations when patients on carbamazepine changed their concomitant medication from valproate to valpromide. Five of 7 patients exhibited symptoms typical of carbamazepine intoxication despite unchanged carbamazepine concentrations. Mean CBZ-E concentrations were as high as 36 μmol/L at the time of intoxication. It is noteworthy that these levels are several-fold higher than the plasma concentrations needed for therapeutic response when CBZ-E is given as such in trigeminal neuralgia.

The inherent problems of studies that attempt to distinguish between the effect of carbamazepine and CBZ-E during polytherapy are illustrated in the study of Schoeman et al. (1984b). They postulate that CBZ-E plays an important role in the production of side effects during carbamazepine therapy and that a concentration above 9 μmol/L is more often associated with side effects. Their conclusions are based on observations of side effects in 14 of 90 epileptic children treated with carbamazepine: 25 were on monotherapy; 2 of these had side effects. There was no difference with respect to plasma CBZ-E concentrations between patients with or without side effects in this group. The remaining 12 patients with side effects had CBZ-E plasma concentrations of about 9 μmol/L or more. They were all treated with various antiepileptic drug combinations. Plasma concentrations of carbamazepine were in all but 3 patients 31 μmol/L or higher, i.e. concentrations not seldom reported in patients with symptoms of intoxication even during monotherapy. The 3 patients with side effects at low carbamazepine concentrations had polytherapy, each comprising 3 to 7 different anticonvulsants. To separate the contributions of the different drugs in such a complex combination therapy is evidently very difficult: drug therapy was changed in 5 of the 14 patients; in 1 the discontinuation of carbamazepine therapy resulted in improvement; in 2, side effects disappeared when phenytoin was discontinued; changes in concomitant valproate therapy were followed by alterations in side effects in 2. The changes in combination therapy also led to changes in CBZ-E concentrations, but whether the side effects were due to the concomitant therapy or CBZ-E as such is impossible to evaluate.

Lindhout et al. (1984) reported a high incidence of malformations in infants born to mothers treated with a combination of valproate, carbamazepine and phenobarbitone during pregnancy. High CBZ-E concentrations were found in this patient group and it was speculated that the high CBZ-E concentrations were causative for the malformations. The high CBZ-E concentrations may, however, not be teratogenic as such but rather an indication of a decreased capacity of a hydrolase which also is responsible for the detoxification of reactive substances such as aromatic hydrocarbons (Pacifici et al. 1985).

It can thus be concluded that attempts to evaluate the clinical effects of CBZ-E during carbamazepine therapy in patients have led to conflicting results. It is evident that reliable evaluations of the clinical effects of CBZ-E could be made only after the direct administration of this compound to patients.

5.1.4 Clinical Effects of CBZ-E in Man

In a pharmacokinetic study CBZ-E was given as single doses of 10 to 200mg to healthy volunteers (Tomson et al. 1983). Peak plasma concentrations up to 16.5 μmol/L were reached and no side effects were recorded. The clinical effects of CBZ-E given directly to patients have been evaluated in a pilot study (Tomson & Bertilsson 1984). Six patients with trigeminal neuralgia had their optimal carbamazepine dose replaced by CBZ-E monotherapy for 3 to 6 days. Dosing was single-blind and the period of CBZ-E therapy was preceded by a 2- to 4-day period of placebo therapy to ensure that the neuralgia was active. When carbamazepine and CBZ-E were given in similar doses, the pain control was comparable. On a plasma concentration basis, CBZ-E had considerably higher pain-relieving potency than carbamazepine, indicating that during carbamazepine therapy the contribution of the metabolite to the effects is considerable (fig. 7). No side effects were seen during CBZ-E therapy.

5.2 Pharmacokinetics of CBZ-E in Man

5.2.1 Single-Dose Kinetics in Healthy Subjects

Absorption and Bioavailability

CBZ-E decomposed in gastric juice with a life of slightly under an hour when incubate *vitro* at 37°C (Tomson et al. 1983). There have hitherto only two studies in which CBZ-E has administered directly to man (Tomson et al. Tomson & Bertilsson 1984). In both, CBZ-E given orally and the problem with the instat of the substance in acid was circumvented by u an antacid to neutralise the gastric juice at the of CBZ-E administration. Four healthy sub each received 2 different single doses ranging f 10 to 200mg. CBZ-E was given as a supension ing the sam vehicle as in 'Tegretol'. The abs tion was rap peak plasma concentration reached within 1 to 2 hours. 90 ± 11% (mea SD) of the dose was recovered as the *trans*-C diol metabolite in urine, indicating complete sorption (table III).

Distribution and Protein Binding

The distribution of CBZ-E to CSF and brain sue in man has been determined only during c amazepine therapy. Johannessen et al. (1976) ported a CSF/plasma concentration ratio for C E ranging from 0.26 to 0.70 (mean 0.49). Eic baum et al. (1976) found a ratio of 0.45 i patients. The findings of Schneider and Beren (1977) were very similar to those of Johanne et al. (1976) with a range in the ratio from 0.2 0.70 and a mean of 0.49. Pynnönen et al. (1 reported a much wider range, 0 to 2.0 (mean 0. in 9 epileptic children. The brain/plasma ratio been studied by Morselli et al. (1977) who repo a ratio of 1.2 in 3 patients. Friis and Christian (1978) and Friis et al. (1978) found a ratio of in 2 children and 0.6 to 1.5 in adult epileptics

Also the protein binding of CBZ-E has been termined exclusively in patients during ca mazepine therapy. These studies have been viewed previously: a free fraction of about 50%

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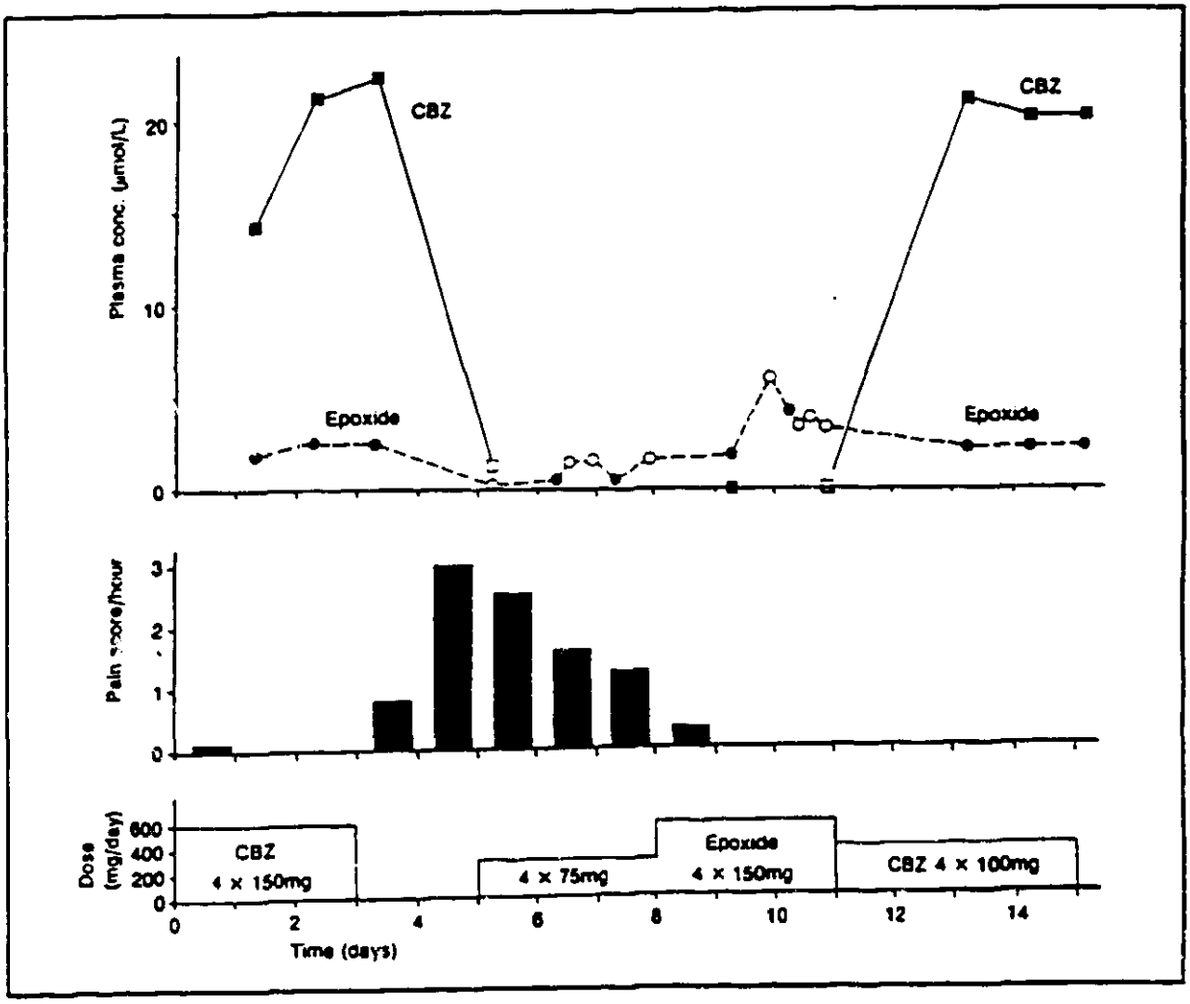


Fig. 7. Patient with trigeminal neuralgia in which carbamazepine (CBZ) therapy was replaced by placebo and carbamazepine-10,11-epoxide. Carbamazepine, carbamazepine-10,11-epoxide, and placebo were administered 4 times daily (7am, noon, 5pm and 10pm). The patient was given the same number of tablets and volume of suspension throughout the study by use of placebo preparations. Plasma concentrations of carbamazepine (squares) and carbamazepine-10,11-epoxide (circles) are indicated in top panel – solid symbols show trough morning plasma levels, open symptoms show levels immediately before dosing at noon, 5pm or 10pm. Pain scores are given as mean per hour during registration period of 7am to 10pm (data from Tomson & Bertilsson 1984).

generally been found (Bertilsson 1978). These early results have been corroborated by Riva et al. (1984) who found a range of the free fraction from 28.5 to 55.2% (mean 43%). MacKichan et al. (1981) reported a wider range in the free fraction, 16 to 50% (mean 32%). The binding of CBZ-E in serum is largely accounted for by binding to albumin. CBZ-E binds less than carabamazepine to α_1-acid-glycoprotein (Conin et al. 1985).

The apparent volume of distribution of CBZ-E has been determined after direct administration of CBZ-E to healthy subjects. It was found to be 0.59 to 0.92 L/kg (Tomson et al. 1983).

Elimination Kinetics and Metabolism

Previously reported elimination half-lives of CBZ-E in plasma have been obtained during the elimination phase after discontinuation of carba-

mazepine therapy (Eichelbaum et al. 1975; Morselli et al. 1975). These half-lives have been influenced by the continuous formation of CBZ-E by metabolism of carbamazepine. Under these circumstances the obtained CBZ-E half-lives cannot be shorter than those of carbamazepine. When CBZ-E was given orally to healthy subjects (Tomson et al. 1983) the CBZ-E plasma concentrations after reaching the peak declined monoexponentially (fig. 8). Plasma half-lives ranged from 4.6 to 6.9 hours and plasma clearance from 64 to 136 ml/kg/h (table III). There was no indication of dose-dependent elimination. CBZ-E was almost completely metabolised before excretion in urine. There was one prevailing pathway for this metabolism since practically all of the given dose could be recovered as *trans*-CBZ-diol in urine. Urinary *trans*-CBZ-diol excretion half-times were significantly longer (10.7 to 13.5 hours) than plasma half-lives of CBZ-E. *Trans*-CBZ-diol is about 50% protein bound (Schneider & Bereiquer 1977). Renal clearance of the non-protein bound *trans*-CBZ-diol was similar to the normal glomerular filtration rate (Tomson et al. 1983).

5.2.2 Multiple Dosing of CBZ-E in Patients

Carbamazepine epoxide was administered 4 times daily (7 am, noon, 5 pm and 10 pm) in the clinical study of patients with trigeminal neuralgia (Tomson & Bertilsson 1984) [see section 5.1.4 and fig. 7]. In 2 patients, blood samples were drawn

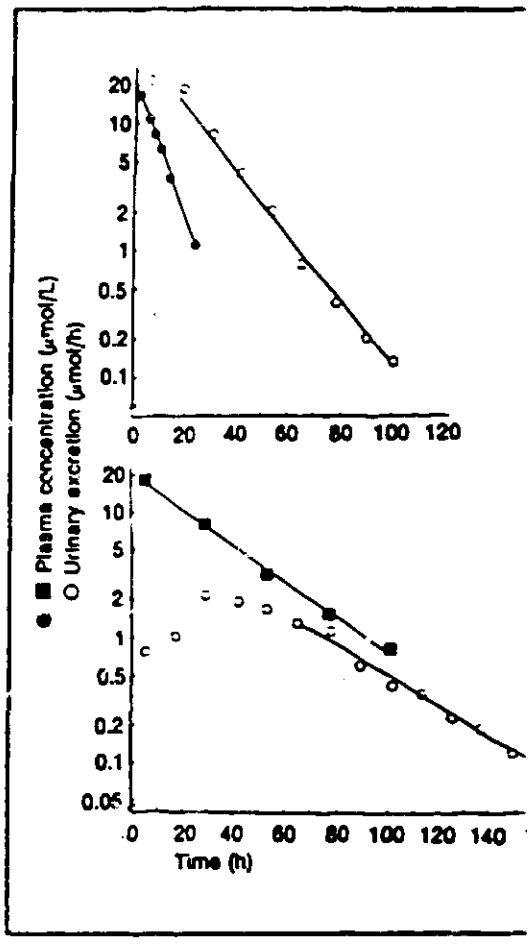
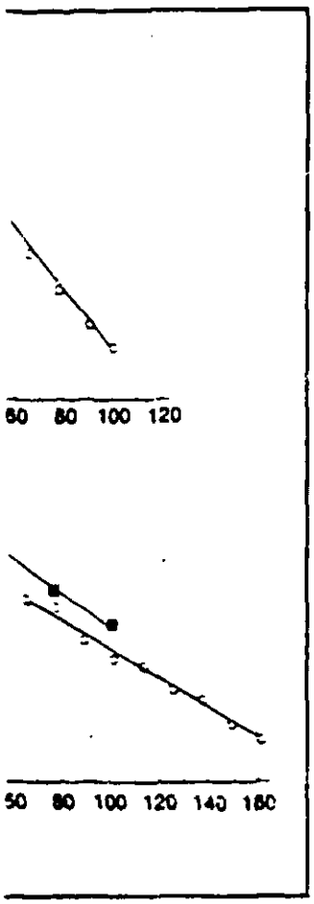


Fig. 8. Upper panel: plasma concentration of CBZ-E (
urinary excretion of *trans*-CBZ-diol (O) after administr
CBZ-E 200mg to a healthy volunteer. Lower panel: plasr
centration of carbamazepine (■) and urinary excretion c
CBZ-diol (O) after administration of carbamazepine 20
the same subject (from Tomson et al. 1983).

Table III. Pharmacokinetic data for carbamazepine-epoxide (CBZ-E) in plasma and *trans*-CBZ-diol in urine after single oral doses of CBZ-E to healthy subjects (data from Tomson et al. 1983)

Parameter	Mean ± SD
CBZ-E in plasma	
$t_{1/2}$ (h)	6.1 ± 0.88
Vd (L/kg)	0.74 ± 0.13
Clearance (ml/kg/h)	86.4 ± 24.9
Trans-CBZ-diol in urine	
$t_{1/2}$ (h)	12.4 ± 0.94
Recovery (% of CBZ-E dose)	89.6 ± 10.6

hourly during 2 dosage intervals (7 am to
in order to study interdosage fluctuations. P
concentrations of CBZ-E peaked 1 to 2 hour
dose administration and peak concentration
1.85 to 3.04 (mean 2.41) times higher than
levels. All patients had been on long term th
with carbamazepine immediately prior to
study. It may be that this induces not only th
tabolism of carbamazepine but also the me
ism of CBZ-E. The large fluctuations in p
concentrations, despite frequent dosing, c



concentration of CBZ-E (●) and
3Z-diol (○) after administration of
unteer. Lower panel: plasma con-
(■) and urinary excretion of *trans*-
stion of carbamazepine 200mg to
son et al. 1983).

: intervals (7 am to 5 pm)
:osage fluctuations. Plasma
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cate the evaluation of the clinical effects of CBZ-E. For future studies there is a need to develop an enteric-coated slow release formulation of CBZ-E.

6. Conclusions

Phenytoin has for a long time been the drug of choice in most types of epilepsy except petit mal. The problems with the curvilinear relationship between dose and plasma concentration may be improved by plasma concentration monitoring. Carbamazepine has during the last few years been shown to have anticonvulsant properties similar to those of phenytoin and the usage is steadily increasing. Monitoring of plasma concentrations of carbamazepine is frequently used today to guide therapy. In our laboratory for therapeutic drug monitoring, 1658 analyses of phenytoin and 102 of carbamazepine were requested during 1974; 10 years later during 1984 the corresponding figures were 1411 for phenytoin and 1415 for carbamazepine.

Compared with phenytoin, the therapeutic plasma concentrations of carbamazepine have not been well defined. Most studies, trying to establish such a relationship, have compared plasma concentrations in groups of patients with good and poor seizure control (table II). It is, however, essential to study each individual at different plasma concentrations and only one such study has been performed in epilepsy (Shorvon et al. 1980). The best effect seems to be obtained at plasma carbamazepine concentrations of 15 to 40 μmol/L. A similar optimal plasma concentration interval was obtained in patients with trigeminal neuralgia where three different doses of carbamazepine were given to each patient (Tomson et al. 1980). Side effects may occur within this 'therapeutic range of plasma levels', but seem to be more frequent at higher drug concentrations. In some patients, especially those treated with several antiepileptic drugs, there is a pronounced variation in plasma concentrations during the dosage interval. Side effects may be avoided by dividing the carbamazepine dose to 3 or even 4 times a day.

The active metabolite of carbamazepine CBZ-E is a potent anticonvulsant in animal models, and it has a pronounced effect on human pain in trigeminal neuralgia. In such patients this metabolite seems to contribute to the clinical effect of carbamazepine treatment. Similar studies in epilepsy have not been performed but are planned to start in the near future with the aim of determining the relative antiepileptic potency of both carbamazepine and CBZ-E. It may be essential to take both compounds into consideration in future studies on the relationship between plasma concentrations and clinical effects.

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Victoria Hale, PhD

Ciba Geigy
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Review of a Primary Efficacy (PK-PD) Study

The title of this study is "Anticonvulsants and pharmacokinetic effects of carbamazepine dosing regimens in the monkey model," performed by
neurologist) (anti-epileptic clinical pharmacologist and pharmacokineticist) at the

The objective of this experiment is to examine the effect of dosing rate on the anticonvulsant behavior of carbamazepine in the monkey model of epilepsy. The sponsor wants to claim that controlled-release carbamazepine is superior to conventional immediate release drug due to the therapeutic benefit of reduced plasma drug concentration fluctuation. Therefore, the sponsor was required to prove that reduced fluctuation results in better management of the disease. The Division of Neuropharmacology decided that it was unnecessary to document the efficacy of controlled-release carbamazepine (OROS) in humans and that this animal model could be used. Hence, this study is the pivotal efficacy trial for this NDA.

The human pharmacokinetics portion of this NDA is important also however, in that the sponsor must demonstrate reduced fluctuation with the OROS versus the conventional tablets. (See Dr Atiq Rahman's review of the human pharmacokinetics.) Bioequivalence is not being sought at this time, although the sponsor may be willing to settle for it at some point. In this case, the sponsor could advertize that OROS is as good as or equivalent to (not superior to) the conventional tablets.

This review will cursurily review the adequacy of the animal model, and primarily focus on the pharmacokinetic-pharmacodynamic component of the experiment. Fluctuation of plasma concentrations in humans is discussed in Dr Rahman's review.

Animal model:

The animal used is Macaca fascicularis. Twelve male monkeys were made experimentally epileptic by intracortical injection of aluminum hydroxide into the left pre- and post-central gyrus during sterile craniotomy. Four months post-surgery, a stomach catheter and EEG electrodes were surgically placed, followed by a two-week stabilization period.

There are significant problems with this animal model, which will be addressed in detail by the medical reviewer. Basically, there is extreme variability in the severity of disease induced by this surgical/chemial procedure: the mean seizure frequency per day at pre-study baseline varied from 0.5 to 21.4. Additionally, the model is very unstable, in that many (but not all) monkeys improve tremendously over time (weeks), such that the baseline disease before and after the experimental period are quite different: the mean seizure frequency per day at post-study baseline varied from 0.0 to 17.4. The improvement in disease between the baseline periods was 0.4 to 7.2 seizures per day, representing a 10 to 420% improvement in seizure frequency.

Experimental design:

The six-week treatment period is composed of randomized crossover two-week treatment periods with no washout time between them. The periods vary in the dosing frequency of carbamazepine: 2, 4, and 6 hours. 216 mg/kg/day of carbamazepine was delivered to each monkey during all treatment days. The initial four days at each dosing frequency were allotted as the adjustment period. The treatment period was preceeded by an auto-induction period of one week; treatment was followed by a drug clearance period. Baseline disease activities were measured before and after these induction and clearance periods.

Seizure monitoring was performed via 24-hour polygraph recording (slow speed) and cage accelerometer monitoring (for motor activity).

4 Months	Monkey Acquisition & Quarantine
4 Months	Aluminum Hydroxide Injection EEG Electrodes Stomach Catheterization
Weeks 1-2	Baseline EEG Recording Baseline Seizure Recording Laboratory Tests
Week 3	Auto-Induction Phase (18 mg/kg, q2h) Blood Sampling Toxicity Monitoring Laboratory Tests
Weeks 4-9	Blood Sampling EEG Recording Seizure Recording Toxicity Monitoring Laboratory Tests
Week 10	Drug clearance EEG Recording Seizure Recording Withdrawal Monitoring
Weeks 11-12	Post-Baseline EEG Recording Post-Baseline Seizure Recording

Pharmacokinetics:

These parameters were measured or calculated during each treatment period:

- average concentration (AUC/dosing interval)
- Cmax (measured one hour post-dosing)
- Cmin (trough)
- elimination rate constant (k)
- ratio of metabolite (carbamazepine 10,11-epoxide) to parent for AUC, Cmin and Cmax
- fluctuation ((Cmax - Cmin)/Cmean x 100)
- AUC of the metabolite, parent in plasma: AUCm, AUCp
- concentration of metabolite, parent in plasma: Cm, Cp

Mean concentrations are reported for each animal treatment, without individual values or estimates of the variability associated with these numbers throughout the treatment.

There is no information regarding analytical methodology applied to the plasma samples.

There is no formal statistical analysis of the pharmacokinetic data.

Pharmacokinetic results:

Below are the mean (of the mean) pharmacokinetic parameters calculated for individual monkeys in this study, by dosing interval (N=10, in general).

parameter (mean ± SD)	units	Q 2 hour	Q 4 hour	Q 6 hour
C mean	ug/ml	1.14 ± 0.52	1.77 ± 0.55	2.34 ± 0.85
C min	ug/ml	1.10 ± 0.43	0.79 ± 0.42	0.60 ± 0.42
C max	ug/ml	2.0 ± 0.67	4.89 ± 1.04	6.94 ± 2.45
k	1/hr	0.61 ± 0.17	0.62 ± 0.10	0.66 ± 0.08
AUCm/AUCp		0.24 ± 0.08	0.22 ± 0.08	0.22 ± 0.06
Cm / Cp min		0.22 ± 0.08	0.22 ± 0.08	0.23 ± 0.08
Cm / Cp max		0.24 ± 0.08	0.24 ± 0.06	0.24 ± 0.05
% fluctuation		51.2 ± 11.0	155 ± 35.5	236 ± 39.0

The average plasma concentration (C mean) should be the same for these three treatments, but they are not: treatments Q2 and Q6 are statistically different (p=0.0012, analysis of variance with Bonferroni correction factor applied). As average concentrations are not equivalent, conclusions regarding comparative efficacy cannot be separated from administered dose influences.

Cmin values should be different for the three treatments, as well. Only treatments Q2 and Q6 differed (p=0.001).

Cmax performed as expected, with statistically significant differences between treatments (Q2 vs Q4, p<0.001; Q2 vs Q6, p<0.001; Q4 vs Q6, p<0.003).

The cause of this observation is unknown. As the elimination rate constant and AUC (m/p) ratio are unchanged, this suggests that clearance was unchanged between treatments. Hence, the possibility of saturable clearance can be ruled out; the sponsor concluded that the reduced average concentration following Q2 hour dosing is a result of diminished absorption. There is no justification provided for this hypothesis.

Pharmacodynamic results:

The following parameters were measured and analyzed:

- mean seizure frequency per day
- number of seizure free days
- mean white cell counts
- mean seizure duration
- mean seizure amplitude
- mean interictal spikes per minute
- seizures by time of day

As the discussion of the details regarding the pharmacodynamics requires extensive effort, and since the pharmacokinetic problems in this study leave little opportunity for significant conclusions regardless of the dynamic results, dynamics will be discussed only briefly.

parameter (mean ± SD)	pre-baseline	Q2	Q4	Q6	post-baseline
seizure frequency	6.84 ± 6.76	4.43 ± 4.16	4.03 ± 4.09	4.36 ± 4.31	4.57 ± 5.61
seizure-free days	0.90 ± 1.81	2.20 ± 2.96	3.20 ± 2.75	2.20 ± 2.92	3.20 ± 3.60
white cell counts	12.47 ± 1.98	9.04 ± 2.13	9.50 ± 1.92	9.96 ± 3.10	10.22 ± 1.71
seizure duration	18.39 ± 2.76	17.03 ± 3.20	18.09 ± 2.42	17.5 ± 2.53	15.19 ± 4.5
seizure amplitude	18.83 ± 11.11	22.89 ± 13.64	24.08 ± 10.53	22.71 ± 11.56	33.73 ± 8.33
interictal spikes	2.84 ± 1.89	3.19 ± 2.64	2.12 ± 1.94	2.20 ± 1.18	7.08 ± 5.12

units are, respectively: seizures per day, days, cells/ml, minutes, mm (14 mm = 1 minute), spikes per minute

There is no difference between any of the Q2, Q4, or Q6 parameters in this study (statistics not provided in submission). Note the magnitude of the standard deviations relative to the mean values (CV% near 100 in many cases).

As mentioned above, there is a significant difference between pre- and post-baseline parameters (statistics not provided).

The sponsor concluded that what could be gathered from this study was that dynamic parameters are no worse when dosing frequency is increased from every 6 to every 2 hours. This conclusion was not the objective of the study, however.

It is significant to note that seizures were so severe in one animal that it was necessary to institute anticonvulsant therapy before the study (pre-baseline).

Comments:

1. An incomplete study report was submitted by the sponsor, probably because of the recognition of the severity of the pharmacokinetic deficiencies (inability to assure equal daily dose administration between treatments).

2. When an unexpected pharmacokinetic result occurs, as was the case with the apparent amount of carbamazepine absorbed with the two-hour dosing interval treatment period, all possible explanations should be considered and pursued. Clearance changes and reduced absorption were briefly considered by the sponsor with only a few sentences devoted to the entire subject. There was no literature search performed to attempt to support the conclusion.

3. Was the pharmacokinetics of carbamazepine ever examined in this species ? If so, this information should have been included in the report.

4. Cmax concentrations were arbitrarily taken at one hour post dosing; there is no justification for this design decision, yet Cmax is a very important parameter in this study of drug fluctuation.

5. The variability associated with the data accumulated in this study is too large to make conclusions with any statistical significance.

6. This study of 10 monkeys may serve as a pilot study, upon which the design of future studies may be based.

Deficiencies:

1. Mean pharmacokinetic parameter values are presented for each animal without individual values or estimates of the variability associated with these numbers.

2. There is no information regarding the formulation, source or lot of carbamazepine used in this study. It is not known whether the carbamazepine suspension administered to the animals was commercially available, or was compounded by the study investigators.

3. The data presented in this report is composed of results for 10 monkeys, yet 14 were prepared surgically (12 with 2 substitutes). For some parameters, only 7 are reported, meaning that almost half of the data for this parameter is missing. There is occasionally an explanation for why one monkey's data is missing, but never a justification beyond this level. When asked for the missing data, the sponsor responded with xeroxed pages from lab notebooks, which is hardly an adequate response.

4. There is no introduction in the study report which outlines studies or even addresses the pivotal question of the efficacy of varied dosing regimens of anti-epileptics (effect of different concentration fluctuations). One would expect some discussion to accompany this data, along with experimental findings and literature reports, if they exist. If none exist, there should be statements reflecting this fact and a theoretical discussion should replace it.

5. There is no discussion of additional possible explanations for the reduced concentrations in the two-hour dosing interval treatment arm; the sponsor should consider the following:

a. what was the carbamazepine suspension measuring device used in these experiments ? could there have been a "dead space" such that an incomplete delivery of the measured dose occurred ?

b. could there have been measurement method problems ? i.e., was there adequate training of the technicians who administered the drug to verify that the correct measuring technique was used ?

c. was the suspension used for all treatment periods the same product ?

d. what type of verification was there that all of the two-hour doses were administered (compliance)? i.e., can it be proven that all doses were administered throughout the night, for instance ?

6. There is no presentation of analytical methodology applied to the plasma samples obtained in this study.

7. There is no statistical component associated with this package.

Recommendations:

Regardless of the problems with the stability and inter-subject variability associated with the disease model, pharmacokinetic problems are severe enough to render this study unacceptable.

The objective of this study was to examine the effect of varied dosing intervals (of the same daily dose) on efficacy. As it is clear from plasma concentrations that insufficient carbamazepine was absorbed (or given) to the animals in the two-hour dosing interval arm, comparative analyses between treatment arms is not possible. Therefore, conclusions cannot be made regarding the effect of reduced concentration fluctuation on seizure suppression in this model.

If the sponsor chooses to further pursue this NDA and this type of efficacy study, they should consult with FDA prior to initiating another study. This study may serve as a pilot study, upon which the design of future studies may be based. If this model is to be used in the future, consideration of control animals (no drug) should be considered. It is essential that the cause of the apparently reduced absorption in the Q2 arm be further investigated. The inclusion of an intravenous infusion would be an important treatment to consider.

The comments, deficiencies and recommendations should be forwarded to the sponsor.

Victoria Hale, PhD
Pharmacokineticist

Draft reviewed by N Fleischer, PhD, 5/14/93 _____

Final reviewed by N Fleischer, PhD N. Fleischer 10/6/93

cc: NDA 20,234 (original)
HFD/426: drug, reviewer, Rahman, Fleischer, Ludden, PK-PD file
HFD/120:
HFD/340: Vish
F/T: 6/1/93

Supervisory Comments for File

NDA 20-234
Tegretol XR (OROS)

Reviewer Atiqur Rahman, PhD

Supervisor Victoria Hale, PhD

date July 18, 1984

The following studies were performed:

The following studies are pivotal:

BE argument based on parent drug: OROS vs QID & BID IR formulation = approvable.

epoxide metabolite is active.
although OGD has not used metabolite for generics, we will consider it now.

epoxide is not BE for the two products. BE test for epoxide therefore FAILS. -- in the low side details of how it fails.... Cmin, etc

however, another issue must be considered regarding the variability of the dosage form with regard to absorption. (provide refs as to variable drug release and/or absorption rate)

thw DIV of BIOPHARM supports approval of the product despite the failure of the metabolite to meet BE standards because the XR formulation will perform much better with regard to drug release (zero-order) versus erratic and unpredictable performance of the IR product.

CC NDA 20,234
HFD-120 3 copies
HFD-426 drug, reviewer, chron, Rahman, Fleischer, Hale, CR file
HFD-340 Viswanathan
HFD-019 FOI

new product considered less variable than previous

Division of Oncology and Pulmonary Drug Products

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-234 **DATE REVIEWED: 18-AUG-94**

REVIEW #: 4 **REVIEWER: Richard E. Lowenthal, M.S.**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N(BC)	03-JUN-94	03-JUN-94	22-JUN-94

NAME & ADDRESS OF APPLICANT: Ciba-Geigy Corporation
556 Morris Ave.
Summit, NJ 07901

DRUG PRODUCT NAME

Proprietary:	Tegretol XR
Established:	Carbamazepine Controlled Release
Code Name/#:	N/A
Chem.Type/Ther.Class:	

PHARMACOL. CATEGORY/INDICATION: Anti-Epileptic

DOSAGE FORM:	Controlled Release Tablet (OROS)
STRENGTHS:	100 mg, 200 mg and 400 mg
ROUTE OF ADMINISTRATION:	Oral
Rx/OTC:	Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
See Previous Reviews
5H-Dibenz[b,f]azepine-5-carboxamide
$C_{15}H_{12}N_2O$
MW 236.27

RELATED DOCUMENTS (if applicable): NDA 16-608

REMARKS: Labeling for the drug product was submitted. Comments on this labeling were originally communicated to Nancy Chamberlin and Stanely Blum of HFD-120 on June 28, 1994. Labeling should be revised as follows:

1. Storage statement should be revised to agree with present Agency and ICH requirements. "Store at controlled room temperature (15 °C-30 °C). Protect from Moisture.
2. The generic name may not state USP on the label. The drug name should state "Tegretol XR (carbamazepine extended release tablets). USP may not be used in the name for the drug substance.
3. The clinician may want to consider requesting that the warning to swallow whole be made more prominant on the labeling.

CONCLUSIONS & RECOMMENDATIONS: NDA 20-234 is **APPROVABLE** for chemistry with the labeling changes described and concurrence from compliance and EA staff. Compliance and EA approval are still outstanding.

Richard E. Lowenthal, M.S., Reviewer

11/14/94

Division of Oncology and Pulmonary Drug Products

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-234 **DATE REVIEWED: 18-FEB-94 (Revised 14-JUN-94)**

REVIEW #: 3 **REVIEWER: Richard E. Lowenthal, M.S.**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N(BC)	14-DEC-93	20-DEC-93	16-FEB-94
N(BC)	~~06~~-JUN-94 08 pps	09-JUN-94	10-JUN-94

NAME & ADDRESS OF APPLICANT: Ciba-Geigy Corporation
556 Morris Ave.
Summit, NJ 07901

DRUG PRODUCT NAME

Proprietary:	Tegretol XR
Established:	Carbamazepine Controlled Release
Code Name/#:	N/A
Chem.Type/Ther.Class:	

PHARMACOL. CATEGORY/INDICATION: Anti-Epileptic

DOSAGE FORM: Controlled Release Tablet (OROS)
STRENGTHS: 100 mg, 200 mg and 400 mg
ROUTE OF ADMINISTRATION: Oral
Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5H-Dibenz[b,f]azepine-5-carboxamide
$C_{15}H_{12}N_2O$
MW 236.27

RELATED DOCUMENTS (if applicable): NDA 16-608

REMARKS: The two submissions covered in this review include responses to deficiencies sent as a result of the April 21, 1993, review and those sent by telefax on March 21, 1994. Additional information on the manufacturing process and formulation development was provided to ustify the proposed excipient ranges and specifications. A specific weight gain target was established for each formulation and the 30% weight variation was demonstrated to be adequate (<5% change in dissolution). An adequate sampling plan was provided for the manufacturing process and testing of the drug product. The stability protocol was revised to reflect the ICH proposed conditions. The first three batches of each formulation will be placed on the full stability protocol, however, extension of the expiration date may be based on the nine batches (3 of each formulation) presently on the old stability protocol at 25 C/75% RH. The original protocol was for 12 months at the 25 C/75% RH, however, the firm has determined sufficient samples exist to complete a 5 year study at this station and the protocol will be extended. Testing will include Appearance, Assay, Release Rate (four point dissolution), Impurities and Moisture Content.

A preliminary specification of 5% for moisture content is included along with a commitment to tighten this specification after sufficient experience is obtained. The option to use a was removed from the description of the manufacturing process and the will be run for every batch without an option to

NOV 13 1993

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-234 CHEM.REVIEW #: 3 REVIEW DATE: 16-SEP-93

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	31-OCT-91	05-NOV-91	01-OCT-92
AMENDMENTS	16-AUG-93	23-AUG-93	26-AUG-93

NAME & ADDRESS OF APPLICANT:
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
556 Morris Avenue
Summit, New Jersey 07901

DRUG PRODUCT NAME

Proprietary: TEGRETOL XR® (OROS®)
Nonproprietary/USAN: CARBAMAZEPINE
Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: EPILEPSY, TRIGEMINAL NEURALGIA

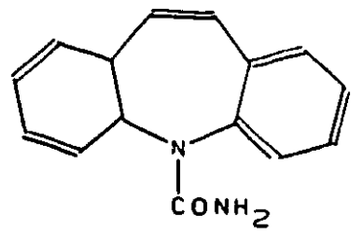
DOSAGE FORM: CONTROLLED RELEASE TABLETS
STRENGTHS: 100, 200 AND 400 MG
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: XXXX Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

$C_{15}H_{12}N_2O$

Mol. Wt. 236.27
CAS # 298-46-4

5H-dibenz[b,f]azepine-5-carboxamide



CARBAMAZEPINE

SUPPORTING DOCUMENTS: IND /NDA 16-608

CONSULTS: ENVIRONMENTAL ASSESSMENT [Dr. Vincent]--sent 17-DEC-91 & 20-OCT-92
INSPECTION REQUEST -- sent 05-OCT-92

REMARKS/COMMENTS: The submission provides for updated Drug Prod t Specifications Methods. The dissolution methodology has been changed in to following manner

The name of the drug product has also been changed officially to TEGRETOL XR, which was acceptable to the nomenclature committee.

CONCLUSIONS & RECOMMENDATIONS: The changes in this amendment are acceptable, however, no deficiencies from the primary review have been addressed. RECOMMEND THAT NDA 20-234 FOR TEGRETOL OROS (CR) TABLETS IS NOT APPROAVABLE. SATISFACTORY CORRECTION OF CHEMISTRY DEFICIENCIES IS REQUIRED [e.g., manuf. issues, in-process/specification corrections, packaging concerns and stability information].

cc:
Orig. NDA 20-234
H[redacted]sion File
HFD-120/R.Lowenthal/16-SEP-92
HFD-120/CSO-N.Chamberlin
HFD-120/S.Blum
HFD-120/C.McCormick/R.Katz [Page 1 and 2 only]
R/D Init by: S.Blum

Richard E. Lowenthal, M.S., Review Chemist

filename: N020234.BZ1

AUG 23 1993

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-234 CHEM.REVIEW #: 2 REVIEW DATE: 03-DEC-92

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	31-OCT-91	05-NOV-91	01-OCT-92
AMENDMENTS	17-NOV-92	19-NOV-92	20-NOV-92

NAME & ADDRESS OF APPLICANT: GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
556 Morris Avenue
Summit, New Jersey 07901

DRUG PRODUCT NAME

Proprietary: TEGRETOL CR® (OROS®)
Nonproprietary/USAN: CARBAMAZEPINE
Chem.Type/Ther.Class: 3 S

AUG 23 1993

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: EPILEPSY, TRIGEMINAL NEURALGIA

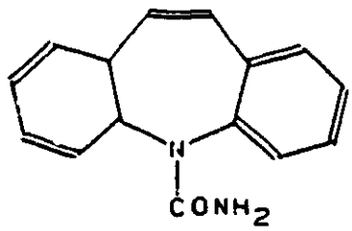
DOSAGE FORM: CONTROLLED RELEASE TABLETS
STRENGTHS: 100, 200 AND 400 MG
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: XXXX Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

$C_{15}H_{12}N_2O$

Mol. Wt. 236.27
CAS # 298-46-4

5H-dibenz[b,f]azepine-5-carboxamide



CARBAMAZEPINE

SUPPORTING DOCUMENTS: IND [illegible]/NDA 16-608

(I)

CONSULTS: ENVIRONMENTAL ASSESSMENT [Dr. Vincent]--sent 17-DEC-91 & 20-OCT-92
INSPECTION REQUEST -- sent 05-OCT-92

REMARKS/COMMENTS: Some concern was raised with the Tegretol-CR OROS drug product formulation. These concerns were related to a possibility that in the

CONCLUSIONS & RECOMMENDATIONS: We believe the Tegretol OROS tablet will preform as designed and within regulatory specifications. The anomaly seen in the in-vitro testing is insignificant when considering the in-vivo randomization of the tablet orientation. The 100% sampling techniques used by the sponsor provides assurance that every tablet will contain a portal and the dissolution testing presented in this submission demonstrates that in the event the hole is sealed the drug substance will still be delivered with only a minor delay and no chance of dose dumping. Concurrence with this view is required from biopharm.

cc:
Orig. NDA 20-234
HFD-120/Division File
HFD-120/R.Lowenthal/03-DEC-92
HFD-120/CSO-N.Chamberlin
HFD-120/S.Blum
HFD-120/C.McCormick/R.Katz [Page 1 and 2 only]
R/D Init by: S.Blum

12/3/92
Richard E. Lowenthal, M.S., Review Chemist

filename: N020234.N01

AMB 8/24/93

NOV 13 1993

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: **20-234** CHEM.REVIEW #: 1 REVIEW DATE: 21-OCT-92

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	31-OCT-91	05-NOV-91	01-OCT-92
AMENDMENTS	03-AUG-92	05-AUG-92	01-OCT-92
CORRESPONDENCE	25-AUG-92	31-AUG-92	01-OCT-92
	09-SEP-92	15-SEP-92	01-OCT-92

NAME & ADDRESS OF APPLICANT:
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
556 Morris Avenue
Summit, New Jersey 07901

DRUG PRODUCT NAME
Proprietary: **TEGRETOL CR® (OROS®)**
Nonproprietary/USAN: CARBAMAZEPINE
Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: EPILEPSY, TRIGEMINAL NEURALGIA

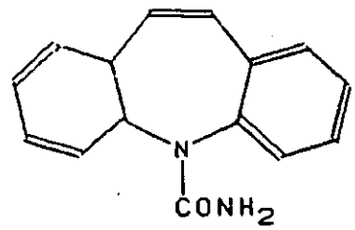
DOSAGE FORM: CONTROLLED RELEASE TABLETS
STRENGTHS: 100, 200 AND 400 MG
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: XXXX Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

$C_{15}H_{12}N_2O$

Mol. Wt. 236.27
CAS # 298-46-4

5H-dibenz[b,f]azepine-5-carboxamide



CARBAMAZEPINE

SUPPORTING DOCUMENTS: IND /NDA 16-608

CONSULTS: ENVIRONMENTAL ASSESSMENT [Dr. Vincent]--sent 17-DEC-91 & 20-OCT-92
INSPECTION REQUEST -- sent 05-OCT-92

REMARKS/COMMENTS: The drug substance, Carbamazepine, will be manufactured by CIBA-GEIGY under NDA 16-608 and will meet all specifications and obligations set forth in that document. The controlled release drug product will be formulation. The tablets will be manufactured in strengths of 100, 200 and 400 mg doses which will be different in size and color (light yellow, pink and orange respectively). The manufacturing process requires further explanation and some additional in-process controls and release specifications are needed. Sampling procedures need correction.
specifications are high and may require a restriction to the number of tablets taken daily. Dissolution studies show good control of release over a 24 hour period, however, pilot batches are less consistent and have more variation than clinical lots. No full scale production batches have been manufactured. The drug is released from the tablet as a suspension which is forced out through the portal by osmotic pressure. The drug product will be packaged in HDPE bottles of 2, 8 and 100 tablets and in unit dose blisters. Stability data submitted is only up to 3 months for pilot batches, 24 months supportive data for clinical formulation and no stability data on a full scale batch. Labeling requires additional warnings with regards to the mode of action of these tablets.

CONCLUSIONS & RECOMMENDATIONS: Agreement of Div. Biopharm. on dissolution specs. of dosage forms is required. Methods Validation has been requested. Environmental assessment has been requested. Establishment Inspections have been requested. Labeling changes need to be discussed with Medical Officer.

RECOMMEND THAT NDA 20-234 FOR TEGRETOL OROS (CR) TABLETS IS NOT APPROAVABLE. SATISFACTORY CORRECTION OF CHEMISTRY DEFICIENCIES IS REQUIRED [e.g., manuf. issues, in-process/specification corrections, packaging concerns and stability information].

cc:
Orig. NDA 20-234
HFD-120/Division File
HFD-120/R.Lowenthal/21-OCT-92
HFD-120/CSO-N.Chamberlin
HFD-120/S.Blum
HFD-102/CKumkumian [#1 only]
HFD-120/C.McCormick/R.Katz [Page 1 and 2 only]
R/D Init by: S.Blum

Richard E. Lowenthal, M.S., Review Chemist

filename: N020234.001

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE : January 25, 1995

FROM : Phillip G. Vincent, Ph. D.
ENVIRONMENTAL ASSESSMENT OFFICER
OFFICE OF THE CENTER DIRECTOR

SUBJECT: ENVIRONMENTAL ISSUES: NDA 20-234 Tegretol-XR Tablets (carbamazepine)

TO : Martha R. Heimann, Ph.D./HFD-120

Thank you for your thorough review of the EA for this submission. We concur with your conclusions and noted deficiencies.

Ciba-Geigy may not cross reference another NDA (page 010) for the EA. The annotation "to be provided", as you observed, is not adequate. All relevant information must be provided in the EA at time of filing. The firm must comply with the regulations to provide data summary tables for item 15 of the EA.

Please let me know if you have any questions.

Phillip G. Vincent, Ph.D.

CC: Original NDA 20-234/HFD-120 N. Chamberlin copy to NDA
EA File 20234

F/T January 25, 1995

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-234

TEGRETOL-XR® Tablets

(Carbamazepine)

HFD-120 REVIEW DIVISION

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-102

DATE COMPLETED 1/12/95

25.31a Environmental assessment for proposed approvals of FDA - regulated products -- Format 1.

(a) For proposed actions to approve food or color additives, drugs, biological products, animal drugs, and class III medical devices, and to affirm food substances as generally recognized as safe (GRAS), the applicant or petitioner shall prepare an environmental assessment in the following format:

Environmental Assessment

1. **Date:** October 31, 1991 - Original Submission

2. **Name of applicant/petitioner:** CIBA-GEIGY Pharmaceuticals Division

3. **Address:** 556 Morris Avenue
Summit, NJ 07901

4. **Briefly describe the requested approval;**

The firm has requested approval to manufacture, package, distribute and market TEGRETOL-XR® (Carbamazepine) Tablets. The tablets will be packaged in HDPE bottles and foil backed plastic blister packs (vinyl aclar sheeting on aluminum foil).

The drug is to be used for the treatment of epilepsy, with the extended release formulation minimizing fluctuations of the drug substance levels in plasma.

The site of manufacture for the carbamazepine drug substance is not included. NDA 16,608 is referenced for this information.

Drug product will be manufactured and packaged at:

CIBA-GEIGY Pharmaceuticals
Suffern, NY and Summit, NJ

Drug product will be packaged at:

The drug product will be marketed throughout the United States. Returned or rejected goods will be sent for incineration at the following facilities:

1C

Adequate descriptions of the environments present at and adjacent to all of the facilities listed except

DEFICIENCY: Please identify the site of drug substance manufacture.

Please provide an environmental setting description for 1

5. Identification of chemical substances that are the subject of the proposed action:

A. Drug Substance

Name: Carbamazepine

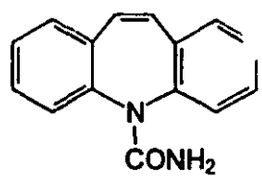
Chemical Name: 5*H*-dibenz[b,f]azepine-5-carboxamide

CAS Registration Number: 298-46-4

Molecular Weight: 236.27

Molecular Formula: $C_{15}H_{12}N_2O$

Structural Formula:



Physical Description: White to off-white powder.

Melting Point: 191 - 192 °C

NDA 16-608 is referred to for information regarding impurities and additives.

B. Drug Product

Trade Name: Tegretol ®OROS® Tablet or Tegretol®-XR® Tablet
(The designation OROS® was replaced by XR during the review process.)

Generic Name: Carbamazepine, USP OROS® (or extended release) or Tablet

EVALUATION: No information is provided regarding impurities in either the drug substance or the drug product. A physical description of, and quantitative formulations for, the drug products is provided in Appendix I. This information is adequate but should be summarized in the EA.

DEFICIENCY: Please change trade name of the drug product from Tegretol® OROS® to Tegretol®-XR®.

Please include a listing of the impurities that may be present in the carbamazepine drug substance, and in the Tegretol-XR® drug product.

Please include a summary of the excipients present in the Tegretol-XR® drug product.

6. Introduction of substances into the environment: For the site(s) of production:

A. Drug Substance:

The carbamazepine drug substance is manufactured under NDA 16-608.

B. Drug Product

The firm submitted a commitment to provide the following information for the Suffern, NY and Summit, NJ sites:

1. Aqueous effluents, and amounts, expected to be emitted during the manufacture of the drug product and control measures.

2. Air emissions, and amounts, expected during the manufacture of the drug product and control measures.

3. Solid waste, and amounts, to be generated during the manufacture of the drug product and control measures,

4. Citation of compliance with aqueous and air emissions and solid waste requirements.

The firm states that it is in compliance with the OSHA Hazard Communication Standard. Copies of MSDS's for the carbamazepine drug substance, Tegretol drug product and other regulated materials are provided in Appendix IV.

DEFICIENCY: Please provide the following information regarding the manufacture of the drug product:

1. A summary of emissions, control measures, and compliance status for the manufacture of the carbamazepine drug substance.

2. Aqueous effluents, and amounts, expected to be emitted during the manufacture of the drug product and control measures.

3. Air emissions, and amounts, expected during the manufacture of the drug product and control measures.

4. Solid waste, and amounts, to be generated during the manufacture of the drug product and control measures.

5. Citation of compliance with aqueous, air and solid waste emissions requirements at the local, state and federal levels.

7. Fate of emitted substances in the environment:

EVALUATION: The only information submitted is water solubility and Log P data for carbamazepine.

DEFICIENCY: For Item 7, "Fate of emitted substances in the environment: ...", please provide a summary of environmental fate testing studies which would support a prediction of environmental concentrations of substances entering the environment as a consequence of the use of the Tegretol-XR® drug product.

8. Environmental effects of released substances:

This information is "(To be provided)".

DEFICIENCY: Please provide the information required for Item 8, "Environmental effects of released substances: ...".

9. Use of resources and energy:

The firm indicated that the raw materials for the drug product are common compounds which are widely available. Manufacture will be done within existing buildings. Since the drug substance and product are synthetics, production should not cause a significant depletion of any natural resource. No significant increase in energy consumption due to the manufacture of the drug product is anticipated. The firm indicated that no effects are expected to occur in endangered or threatened species, or upon property listed in or eligible for listing in the National Registry of Historic Places.

10. Mitigation measures: Describe measures taken to avoid or mitigate potential adverse environmental impacts associated with the proposed action.

The firm indicates that it is their belief that mitigation is not required.

DEFICIENCY: With respect to Item 10 "Mitigation measures: ...", you have indicated that no potential adverse environmental impacts are foreseen with the manufacture of Tegretol-XR® Tablets. Due to the lack of response to Items 7 and 8, this statement is not supported.

11. Alternatives to the proposed action: If potential adverse environmental impacts have been identified for the proposed action,

The firm indicates that "There is no need to discuss alternatives to the proposed action, as no potential adverse environmental impact has been identified." The firm has not provided adequate information to support the statement that no potential adverse environmental effects have been identified.

DEFICIENCY: With respect to Item 11 "Alternatives to the proposed action: ...", you have indicated that since no potential adverse environmental impact has been identified there is no need to discuss alternatives to the proposed action. Due to the lack of response to Items 7 and 8, this statement is not supported.

12. List of preparers: Those persons preparing the assessment together with their qualifications (expertise, experience, professional disciplines) shall be listed. Persons and agencies consulted shall also be listed.

The firm submitted a list of persons involved in the preparation of the EA. While minimal, the list is acceptable.

13. Certification: The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

A statement of Certification which named Usha Wright, Executive Director, Safety, Industrial Hygiene and Ecology as the responsible official was included but not signed.

DEFICIENCY: Please include a signed statement certifying that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

14. References: List complete citations for all referenced material. Copies of referenced articles not generally available should be attached.

DEFICIENCY: For Item 14, please provide references to all materials used to prepare the environmental assessment.

15. Appendices:

Minimal information (product composition, MSDS's etc.) is included in the appendices.

Conclusions and Recommendations

The information provided was a draft EA with a commitment to provide a completed document in November, 1991. The complete EA was not submitted. Recommend tnat the deficiencies cited be communicated to sponsor.

Reviewed by:

Martha R Heimann 1/13/95

Martha R. Heimann, Ph.D., HFD-120

Review Completed: January 13, 1995

Concurrence:

Stanley W. Blum PhD 1/23/95

Stanley W. Blum, Ph.D., HFD-120

Phillip G. Vincent, Ph.D., HFD-102

cc: Orig: IND
HFD-120/Division File
HFD-120/MHeimann
HFD-120/SHardeman
HFD-120/SBlum
HFD-102/PVincent

File: N20-234.EA1

Division of Neuropharmacological Drug Products / HFD-120

REGULATORY MANAGEMENT OFFICER REVIEW

Application Number: NDA 20-234

Name of Drug: Tegretol-XR (carbamazepine extended-release tablets)

Sponsor: Ciba-Geigy Corporation

Material Reviewed

Submission Date(s): 2/6/96

Receipt Date(s): 2/8/96

Background and Summary Description: In response to the Division's approvable letter of January 22, 1996, the sponsor submitted final printed labeling, C96-9 (Rev. 2/96).

Review

A side-by-side review of the sponsor's FPL vs. the marked-up draft labeling contained in the approvable letter revealed no changes other than those specified by the sponsor.

Conclusions

Recommend approval.

Steven D. Hardeman, R.Ph.
Regulatory Management Officer

Supervisory Comment/Concurrence:

3/21/96
John S. Purvis
Supervisory Consumer Safety Officer

cc.
NDA 20-234
Div. Files
HFD-120/Hardeman/Purvis

CSO REVIEW

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-234

CHEMISTRY REVIEW: # 5 **DATE REVIEWED:** 14-FEB-96

Submission Type	Document Date	CDER Date	Assigned Date
ORIGINAL	03-AUG-92	05-AUG-92	N/A
AMENDMENT	16-AUG-94	19-AUG-94	08-NOV-94
AMENDMENT	06-OCT-95	10-OCT-95	11-OCT-95
AMENDMENT	17-OCT-95	18-OCT-95	20-OCT-95
AMENDMENT	24-OCT-95	25-NOV-95	25-NOV-95
AMENDMENT	21-NOV-95	22-NOV-95	27-NOV-95
AMENDMENT	22-NOV-95	24-NOV-95	27-NOV-95

NAME & ADDRESS OF APPLICANT: Basel Pharmaceuticals
Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901

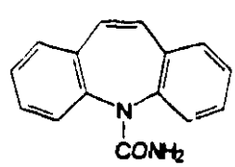
DRUG PRODUCT NAME:

Proprietary: TEGRETOL®-XR FEB 20 1996
Nonproprietary/Established/USAN: carbamazepine
Code Name/#:
Chem. Type/Ther. Class: 1 S

DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Epilepsy, trigeminal neuralgia
DOSAGE FORM: Extended release tablet
STRENGTHS: 100 mg, 200 mg, 400 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XX Rx __ OTC

CHEMICAL NAME, STRUCTURE AND MOLECULAR FORMULA:



5*H*-dibenz[b,f]azepine-5-carboxamide
CAS Registry Number: 298-46-4
Molecular Formula: $C_{15}H_{12}N_2O$ Molecular Weight: 236.27

SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS (if applicable): N/A

CONSULTS: N/A

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

NDA remains approvable for Chemistry, pending satisfactory Compliance status.

cc: Orig. NDA 20-234
HFD-120/Division File
HFD-120/MHeimann/14-FEB-96
HFD-120/SHardeman
HFD-120/SBlum/Init.: 2/17/96

Martha R Heimann 2/14/96
Martha R. Heimann, Ph.D., Review Chemist
Filename: **N20-234.999**

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Tegretol®-XR TABLETS

(carbamazepine extended-release tablets)

100-400 mg

NDA 20-234

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Neuropharmacological Drug Products

HFD-120

Finding of No Significant Impact
NDA 20-234
Carbamazepine Extended-Release Tablets

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decision maker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application (NDA 20-234) for Tegretol®-XR Tablets, Ciba-Geigy Corporation has conducted a number of environmental studies and prepared an environmental assessment (21 CFR 25.31a(a)) which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product.

Carbamazepine is a synthetic drug which is commonly prescribed for treatment of epilepsy and trigeminal neuralgia. The extended release formulation is intended for use as 100-400 mg tablets to be taken orally twice daily. This formulation offers an advantage over prompt release formulations which are typically administered four times daily. It is expected that Tegretol®-XR will be used as a replacement for prompt release formulations. For this reason, approval of NDA 20-234 is not expected to result in any change in the amount of carbamazepine released to the environment.

The drug substance will be manufactured by Ciba-Geigy, Ltd Pharmaceuticals division at two sites in Basel, Switzerland. These sites are currently used for manufacture of carbamazepine drug substance under approved NDA 16-608. The drug product will be manufactured at Ciba-Geigy facilities in Suffern, New York and Summit, New Jersey and packaged either at the Suffern site or by contract packagers. The finished drug product will be dispensed by prescription only. Patient use and disposal will be in both residences and hospitals.

Unused or expired product will be shipped for incineration at off-site facilities. Ciba-Geigy inspects, and audits, contract waste disposal facilities to verify compliance with Federal, state and local environmental regulations.

At hospital sites, empty or partially empty packages will be disposed of according to hospital regulations. Empty or partially empty containers will be disposed of as trash by consumers,

destroyed by the community's solid waste management system, and disposed in an approved sanitary landfill.

During the manufacturing of carbamazepine bulk drug substance at the Ciba-Geigy facility in Basel, Switzerland air emissions, liquid waste streams and solid waste may result. Air emissions are controlled by surface condensers, brine-cooled vent condensers, chemical scrubbers, thermal oxidation or absorption. Process wastewater is sent to a chemical wastewater treatment plant before discharge into the Rhine River. Additional treatment, e.g. oxidation, may be used for toxic or non-bio-degradable wastewater. Solid waste is incinerated in an on-site rotary kiln incinerator at approximately 1200 °C, or in a similar off-site facility.

During the Tegretol®-XR tablet manufacturing process, air emissions, wastewater discharges and solid waste may result. Air emissions from manufacture of the tablet cores at the Suffern, New York site consist primarily of particulates (carbamazepine and common drug excipients). Particulates are controlled by appropriate dust collectors. Air emissions at the Summit, New Jersey site are primarily volatile organic compounds (VOC's). Emissions of VOC's are minimal and are expected to be well below permit limits. Wastewater for the Summit, New Jersey facility is directed to an on-site sewerage system with pH neutralization capabilities from which it is discharged into the municipal sewer system. Solid process waste is shipped for incineration at off-site licensed facilities. Waste packaging materials will be recycled or incinerated. All production, packaging and waste disposal facilities operate in compliance with Federal, state and local regulations.

After oral administration, carbamazepine is extensively metabolized and excreted as hydroxylated and conjugated metabolites. Excreted drug is expected to be diluted in local sewer systems.

There are various chemical and physical tests and parameters which are predictive of environmental mobility and accumulation. This information may be obtained in a laboratory from the *n*-octanol: water partition coefficient, K_{ow} (P_{ow}) or log P which indicates the tendency of nonionized organic chemicals to accumulate in lipoid tissue and to sorb onto soil or other particles or onto the surface of organisms. Chemicals with K_{ow} of 10000 (log P greater than 4) may bioconcentrate or sorb significantly. For carbamazepine, K_{ow} was determined to be 47.9 (log P = 1.68). It is not expected that carbamazepine will significantly bioconcentrate in aquatic organisms or sorb to soils.

The effect of carbamazepine on aquatic and terrestrial microorganisms, and on aquatic species was evaluated for potential toxic effects.

In microbial growth inhibition test on representative species, e.g. *Aspergillus niger, Trichoderma viride, Clostridium perfringens, Bacillus subtilus,* and *Nostoc sp.*, carbamazepine did not inhibit growth at concentrations up to 1000 mg/L. Sublethal effects were observed in a twenty-four hour acute toxicity study in daphnids (*Daphnia magna Straus 1820*); the median effect concentration (EC_{50}) was determined to be 92 mg/L. The median lethal concentration (LC_{50}) in Zebra fish (*Brachydanio rerio*) was 43 mg/L in a ninety-six hour acute toxicity test.

Based on peak year production estimates for the Tegretol® product line, Ciba-Geigy has calculated the Maximum Expected Environmental Concentration (MEEC) for carbamazepine as a result of approval of NDA 20-234. The MEEC value can be compared to lowest concentration at which toxic effects are detectable. The minimum toxic effect concentration was determined to be 43 mg/L in Zebra fish. Comparison of this value to the calculated MEEC give a safety factor of at least 100.

Carbamazepine drug substance and Tegretol®-XR tablets will be manufactured at existing facilities, land use will not be altered. As the extended release formulation is intended to displace existing immediate release carbamazepine therapies, no significant change in drug substance production levels is expected. Tablet manufacture and packaging require minimal amounts of energy and raw materials.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

For a summary of data, see the Summary Table in the attached Freedom of Information (FOI) document. Additionally, reference is made to the attached Material Safety Data Sheet (MSDS) for carbamazepine.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Any residues of carbamazepine entering the environment as a result of administering the drug to humans are expected to be much lower than the minimum concentration at which any toxic effect is likely to occur.

03/20/96
Date

Martha R Heimann 3/20/96
Prepared by:
Martha R. Heimann, Ph.D.
Review Chemist, HFD-120

3/20/96
Date

Stanley W. Blum
Division Concurrence:
Stanley W. Blum, Ph.D.
Chemistry Supervisor/Team Leader, HFD-120

3/22/96
Date

Nancy E Sager
Approved
Nancy Sager, Acting Supervisor
Environmental Assessment Team, HFD-357
Center for Drug Evaluation and Research

cc: Original NDA 20-234/HFD-120
Division File/HFD-120
S. Blum/HFD-120
S. Hardeman/HFD-120
M. Heimann/HFD-120

FONSI File /HFD-357
N. Sager/HFD-357
Docket File/HFD-357
FOI/HFD-205°C

Revised 3/20/96
F/T / /

Environmental Assessment Information

An environmental assessment has been prepared in accordance with the requirements stated in 21 CFR Part 25.31a(a) for Tegretol®-XR.

1. Date

December 19, 1995 (revised)

2. Name of applicant

Ciba-Geigy Corporation
Pharmaceuticals Division

3. Address

556 Morris Avenue
Summit, New Jersey 07901 - 1398

4. Description of the proposed action

4.1. Requested approval

Ciba Pharmaceuticals Division has filed a New Drug Application (NDA) for Tegretol®-XR (carbamazepine extended-release tablets). Carbamazepine is the drug substance which is also the subject of approved NDA 16-608 for Tegretol®, available as 200 mg tablets, NDA 18-281 for Tegretol Chewable Tablets, 100 mg, and NDA 18-927 for Tegretol Suspension, 100 mg/5 ml. Tegretol®-XR is available as tablets for oral administration, containing 100 mg, 200 mg or 400 mg carbamazepine. This NDA requests approval of Tegretol®-XR for the same indications as currently approved for the three marketed forms of Tegretol: epilepsy and trigeminal neuralgia.

For further information regarding the subject of this assessment, please refer to the *Chemistry, Manufacturing and Controls Summary* provided for your convenience in Appendix 1 of this document. This section is identical to documentation found in the original NDA submitted October 31, 1991. Since the submission of the original NDA, the Manufacturing, Packaging and Control Sites chart has been updated. An updated copy is also provided in Appendix 1.

4.2. Need for action

Approval of this Application will result in the distribution of Tegretol®-XR throughout the United States. Tegretol is a well-established therapeutic agent for the treatment of epilepsy and trigeminal neuralgia. Approval of the Tegretol®-XR NDA will provide a formulation of Tegretol which needs to be taken only twice a day. Because of the therapeutic benefits associated with the availability and use of Tegretol®-XR to this patient population, approval is justified and preferable to non-approval.

4.3. Sites of production and environmental settings

4.3.1. Manufacture of bulk drug substance

As noted in Ciba's approved Tegretol NDA 16-608, the bulk drug substance carbamazepine is chemically manufactured by CIBA-GEIGY, Ltd. Pharmaceuticals Division at the following sites in Basel, Switzerland:

CIBA-GEIGY
Werke Schweizerhalle
CH-4133 Schweizerhalle
Switzerland

and

CIBA-GEIGY
Werke Klybeck
Klybeckstrasse 141
CH-4002 Basel
Switzerland

Environmental setting descriptions for each of these facilities are provided in Appendix 2.

4.3.2. Manufacture of finished dosage form

Finished dosage form manufacture will consist of compressing excipients into a tablet core, into the tablet. Drug product formulation will occur at the following Ciba facilities:

Ciba-Geigy Corporation
Pharmaceuticals Division
25 Old Mill Road
Suffern, New York 10901 - 7914

and

Ciba-Geigy Corporation
Pharmaceuticals Division
556 Morris Avenue
Summit, New Jersey 07901 - 1398

Environmental setting descriptions and maps for the Ciba facilities at Suffern, NY and Summit, NJ are provided in Appendices 3 and 4, respectively.

4.3.3. Packaging of finished dosage form

Drug product packaging will occur either at the following Ciba facility:

Ciba-Geigy Corporation
Pharmaceuticals Division
25 Old Mill Road
Suffern, New York 10901 - 7914

or at contract facilities. The contract packaging facilities and descriptions of their environmental settings are provided in Appendix 5.

4.4. Sites of product use and environmental settings

Tegretol®-XR will be marketed throughout the United States as a solid oral dosage form administered twice daily for the treatment of epilepsy and trigeminal neuralgia. Tegretol®-XR will be available to patients through prescription only.

4.5. Sites of product disposal and environmental settings

Waste generated by the packaging of Tegretol®-XR, as well as all returned or rejected production material, is classified as non-hazardous waste. Solid process residuals (returned or rejected production material, laboratory waste) will be shipped from Ciba for off-site incineration at permitted incineration facilities. The sites and environmental setting descriptions of the facilities currently used by Ciba are provided in Appendix 6.

Ciba publishes, on a quarterly basis, a report entitled *"Hazardous & Chemical Waste Disposal Sites"*. All hazardous waste disposal facilities listed in this report are recommended for approval by Ciba-Geigy Corporation only after Ciba personnel complete and submit an inspection and audit report. A list of non-hazardous disposal facilities is also provided, and it is the Corporation's recommendation that these facilities also be audited once every two years. The Pharmaceuticals Division makes a practice of auditing all non-hazardous waste disposal facilities. Ciba Pharmaceuticals Division notifies its contract packaging facilities as to which disposal facilities are currently approved by Ciba.

5. Identification of chemical substances that are the subject of the proposed action

5.1. Drug product

Trade name: Tegretol®-XR

Generic name: carbamazepine extended-release tablet

5.2. Drug substance

Common name: carbamazepine, USP

Chemical name: 5H-dibenz[b,f]azepine-5-carboxamide

CAS number: 298-46-4

Molecular formula: $C_{15}H_{12}N_2O$

Molecular weight: 236.3

Structural formula: Please refer to nonconfidential Appendix I.

Description:

Carbamazepine, USP is a white to off-white powder. It is soluble in alcohol and acetone, and practically insoluble in water.

5.3. Impurities

For information pertaining to the stability and control of impurities in the drug substance carbamazepine and the drug product Tegretol®-XR, please refer to Appendix 7.

5.4. Excipients

For information pertaining to the composition of the drug product Tegretol®-XR, please refer to Appendix 8.

Information on the manufacture of Tegretol®-XR is contained in Attachment II of the *Chemistry, Manufacturing and Controls Summary* (Appendix 1).

6. Introduction of substances into the environment

6.1. Sites of production

6.1.1. Manufacture of bulk drug substance

It is again noted that the drug substance carbamazepine will be chemically manufactured at the following Ciba facilities:

CIBA-GEIGY
Werke Schweizerhalle
CH-4133 Schweizerhalle
Switzerland

and

CIBA-GEIGY
Werke Klybeck
Klybeckstrasse 141
CH-4002 Basel
Switzerland

6.1.2. Manufacture of finished dosage form

The finished dosage form, Tegretol®-XR 100 mg, 200 mg and 400 mg tablets, will be manufactured at the following Ciba facilities:

Ciba-Geigy Corporation
Pharmaceuticals Division
25 Old Mill Road
Suffern, New York 10901 - 7914

and

Ciba-Geigy Corporation
Pharmaceuticals Division
556 Morris Avenue
Summit, New Jersey 07901 - 1398

The production of the tablet core will occur at the Suffern, New York facility. Subsequently, the cores will be transported to the Summit, New Jersey facility fo:

6.1.3. Packaging of finished dosage form

As previously indicated in Section 4.3.3., packaging operations will take place at Ciba's Suffern, NY facility, or at contract packaging facilities.

6.2. Substances expected to be emitted and controls exercised

6.2.1. Air emissions and controls

Ciba - Basel, Switzerland

Air emissions stemming from the micronization of carbamazepine comply with the Swiss Clean Air Act (LRV). Synthesis emissions are controlled by equipment such as surface condensers, brine-cooled vent condensers and scrubber systems, operating with either plain water or acidic, basic or oxidizing aqueous solutions. In some cases, waste air is treated by thermal oxidation or absorption for substances with high boiling points. Air emissions from the on-site incinerator are controlled by a series of scrubbers operating with aqueous absorption mediums. The equipment is operated in compliance with permits issued by federal and local authorities.

Ciba - Suffern, New York

In the manufacturing of the drug product Tegretol®-XR, the following unit operations are performed in the Suffern facility: milling,
Since these are all aqueous operations, the only emissions which must be permitted are particulates. Depending upon the unit operation, these particulates are mixtures of the materials used in the manufacturing process (carbamazepine and common drug excipients). The particulate emissions from these emissions are all controlled via dust collectors and all the source equipment are permitted by either the New York Department of Environmental Conservation (NYDEC) or the Rockland County Department of Health (RC). All sources are operating in compliance with their respective permit limits. For additonal information on air emissions for these operations, please refer to Appendix 9.

The only other operation which is to take place at the Suffern facility is packaging. Insignificant quantities of fugitive volatile organic compounds (VOCs) are associated with this operation. Since the site's total annual VOC emission is below the New York State significant source threshold, no applicable control device is required.

Ciba - Summit, New Jersey

In the manufacture of the drug product Tegretol®-XR, the following unit operations are performed in the Summit facility: coating, sorting, laser drilling, drying, and branding. Except for coating, emissions generated by the other unit operations are insignificant. For additional information on air emissions for these operations, please refer to Appendix 10.

6.2.2. Wastewater discharges and controls

Ciba - Basel, Switzerland

All process wastewater goes to the chemical wastewater treatment plant and is finally discharged into the Rhine River. Non-biodegradable or toxic waste water may undergo

treatment (i.e., wet oxidation). The wastewater treatment plant operates in compliance with permits issued by federal and local authorities.

Ciba - Suffern, New York

Process and domestic wastewater is conveyed from the facility via a gravity sewerage system to an on-site sewerage pumping station. This flow is then directed to the Village of Suffern publicly-owned treatment works (POTW). The Village system is designed to process 1.8 million gallons per day (MGD). The average flow from the facility is approximately 118,000 gallons per day (GPD). The POTW regulates the Suffern facility for its discharge through a state-authorized pretreatment permit program. This program regulates the facility for flow, pH, biochemical oxygen demand (BOD), total suspended solids (TSS), oil, grease, metals, Reporting is submitted on a semi-annual basis. For additonal information on wastewater discharges for these operations, please refer to Appendix 9.

Ciba - Summit, New Jersey

All process waters from the immediate production areas are conveyed to an on-site equalization/neutralization system through a dedicated sewerage system. The equalization/ neutralization system is in turn discharged to the Essex/Union Joint Meeting POTW. Domestic sanitary flows from the facility are also discharged via a network of domestic sewerage conveyances to this POTW. The facility possesses a permit to discharge from the pretreatment facility administered by the POTW Pretreatment Program. For additonal information on wastewater discharges for these operations, please refer to Appendix 10.

6.2.3. Solid waste and controls

Ciba - Basel, Switzerland

All process residuals (waste solvents, dusts, filter residues, rejected production material) are either burned on-site in a rotary kiln incinerator, working at approximately 1200°C, or in a similar third party facility. Residues from the incineration process are sent off-site for disposal. The incinerator plant operates in conformance with permits issued by federal and local authorities.

Ciba - Suffern, New York

All rejected production material from the packaging of Tegretol®-XR is sent off-site for incineration at facilities which must operate in conformance with permits issued under the authority of the applicable Federal, state and local regulations. All facilities utilized for the disposal of solid process residuals are inspected by Ciba personnel on an annual basis to ensure conformance with Federal and state regulations. All packaging components which can be recycled will be sold. For additonal information on solid waste for these operations, please refer to Appendix 9.

Ciba - Summit, New Jersey

All rejected production material from the packaging of Tegretol®-XR is sent off-site for incineration at facilities which must operate in conformance with permits issued under the authority of the applicable Federal, state and local regulations. All facilities utilized for the disposal of solid process residuals are inspected by Ciba personnel on an annual basis to ensure conformance with Federal and state regulations. Packaging components which can be recycled will be sold to Paper Recyclers Inc. for that purpose. For additonal information on solid waste for these operations, please refer to Appendix 10.

Returned goods

Products returned to Ciba Pharmaceuticals Division by the customer are evaluated by the Quality Control Department. Those materials which must be discarded are tested and evaluated so as to properly classify them. Those that must be managed in accordance with applicable Federal, state and local regulations are appropriately managed and shipped off-site to disposal facilities as described in section 4.5. [Sites of product disposal and environmental settings]. Incineration is the method of choice for destruction of wastes.

Contract packaging facilities

Contract packaging facilities are required to dispose of any non hazardous solid waste (i.e., product packaging materials) generated at facilities approved by Ciba, and that the method of destruction be incineration.

Incineration facilities

Only incineration facilities approved by Ciba are used for the disposal of returned or rejected products as well as wastes generated during product packaging. The incineration of returned and rejected materials generates residual solids which are disposed of by the individual disposal sites in accordance with their operating permits in permitted landfills. Expected air emission from pollution control equipment associated with the incineration of packaging wastes are water vapor, carbon monoxide, carbon dioxide and small quantities of nitrous oxides. The incineration of discarded packaging materials will also generate wastewater. This water is treated by the incineration facility before discharge in accordance with the operating permits issued by the state in which the facility is located. Whenever possible, discarded packaging components are sold to a reclaimer/recycler.

6.3. Citation of compliance with applicable emission requirements

6.3.1. Citations for air emissions compliance

Ciba - Suffern, New York

Particulate emissions for the unit operations milling, granulation, drying, blending, and compression are regulated by NYDEC under Title 6 of the New York State Codes, Rules and Regulation, Chapter 3, specifically, Part 200 (General Provisions), Part 201 (Permits and Certificates), 212 (General Process Emission Sources), and Part 257 (Air Quality Standards for Particulates).

The above regulations are promulgated by the NYDEC under the State Implementation Plan Program. As such, the Air Program in New York meets federal requirements. Thus, compliance with the state regulation also meets the applicable federal requirements. Ciba is in full compliance with the New York Air Permit Program.

For additional details on air citations for these operations, please refer to Appendix 9.

Ciba - Summit, New Jersey

VOC and particulate emissions for the unit operations coating, sorting, laser drilling, drying, and branding are regulated by NJDEP under New Jersey Administrative Code Title 7 Chapter 27, specifically, Subchapters 1 (General Provisions), 6 (Control and Prohibition of Particles from Manufacturing Process), 8 (Permits and Certificates), and 16 (Control and Prohibition of Air Pollution by Volatile Organic Compounds).

These regulations are promulgated by the NJDEP under the State Implementation Plan Program. As such, the Air Program in New Jersey meets the Federal requirements. Thus, compliance with the State regulation also meets the applicable federal requirements. Ciba is in full compliance with all applicable New Jersey air permit regulations.

For additional details on air citations for these operations, please refer to Appendix 10.

6.3.2. Citations for wastewater discharge compliance

Ciba - Suffern, New York

Aqueous emissions must be in compliance with the Clean Water Act. New York is authorized by the Federal government to regulate these emissions under *6 NYCRR*. The Suffern facility discharges wastewater to the Village of Suffern POTW under a permit issued by the Village of Suffern. The POTW, in turn, operates under a State Pollutant Discharge Elimination System (SPDES) permit issued by the State of New York under Title NYCRR.

Ciba - Summit, New Jersey

Aqueous emissions must be in compliance with the Clean Water Act. New Jersey is authorized by the Federal government to regulate these emissions under *Title 7 NJAC*. It is

under this authority that the NJDEP regulates the Joint Meeting Sewage Treatment Plant of Elizabeth, which operates in accordance with NJDES permit #NJ0024741. The Summit facility is regulated, in turn, by the Joint Meeting Sewage Treatment Plant of Elizabeth as a Significant Industrial User, under authority granted it by the NJDEP. The facility must maintain compliance with permit #JM-5510 issued it by the Joint Meeting.

6.3.3. Citations for solid waste compliance

Ciba - Suffern, New York

All solid wastes must be disposed of in accordance with the applicable regulations included in NYCRR and EPA 40 CFR 260 - 262. Since all solid wastes are sent off-site for disposal, this requires the use of licensed transporters and permitted disposal facilities.

Ciba - Summit, New Jersey

All solid wastes must be disposed of in accordance with the applicable NJDEP regulations found in NJAC Title 7, Chapter 26, Subchapters 1 through 15. Since all solid wastes are sent off-site for disposal, this requires the use of licensed transporters and permitted disposal facilities.

Contract packaging facilities

Contract packaging facilities must conform to all applicable Federal, state and local regulations, and must manage waste materials according to Ciba standards. All solid wastes generated by the contract packaging facilities listed in Section 4.3.3. are sent only to those incineration facilities approved by Ciba. Non-hazardous solid waste may be returned by the contract packager to the Ciba Summit facility for disposal, or directly routed to one of the disposal facilities as described in Section 4.5. All disposal facilities on Ciba's approved list utilize incineration as the method of treatment.

6.4. Certification of compliance

An environmental protection certificate was obtained from the Cantons of Basel-Stadt for the manufacture of carbamazepine (the active substance of Tegretol). A copy of this certificate is provided in Appendix 11.

A statement of compliance by Ciba regarding environmental permits required for the manufacture and packaging of Tegretol®-XR at Ciba's facilities in Suffern, New York and Summit, New Jersey is provided in Appendix 12.

6.5. Compliance with OSHA Hazard Communication Standard

In accordance with the requirements of the Occupational Health and Safety Administration (OSHA) Hazard Communication Standard, 29 CFR 1910.1200, Ciba Pharmaceuticals Division has established a Hazard Communication/Right-to-Know program at both the

Suffern, New York and Summit, New Jersey sites which covers all employees. Under this program, all chemicals are first evaluated to determine whether they meet the OSHA criteria for hazardous chemicals. All containers are then labeled with the chemical name, CAS number, and information regarding the nature of hazards associated with that substance. Material Safety Data Sheets (MSDSs) are available for all chemicals handled at the plant, with MSDSs prepared internally for those materials used in the production of finished dosage forms. These are available in each area where the substance is used, as well as in a central location. The program also provides the required employee training, which includes hazard recognition, interpretation of information on MSDSs and labels, the safe handling of selected classes of hazardous materials, and proper use of personal protective equipment.

To demonstrate compliance with the Federal and state occupational health requirements, an MSDS for the drug substance carbamazepine is included in nonconfidential Appendix II.

6.6. Quantities and concentrations expected to enter the environment

The concentration of carbamazepine expected to be released into the environment as a result of prescription of the drug product Tegretol®-XR for the treatment of epilepsy and trigeminal neuralgia was determined based upon market research. This research was based upon the premise that for most patients, Tegretol®-XR would replace their current commercial Tegretol tablet therapy. Consequently, the concentration of carbamazepine released to the environment would not change significantly. The marketing forecast for Tegretol®-XR during the peak year is provided in Appendix 13.

Based upon a forecasted peak year maximum sales (and therefore, production), the Maximum Expected Environmental Concentration (MEEC) for the drug substance carbamazepine has been calculated. The MEEC value, the supporting calculations and the assumptions made for this calculation are provided in Appendix 14.

7. Fate of emitted substances in the environment

7.1. Physical and chemical properties of carbamazepine

Physical and chemical properties and constants were reported for carbamazepine in Ciba's approved NDA 20-234 for Tegretol®-XR, or were determined under FDA Good Laboratory Practice (GLP) protocols utilizing Technical Assistance Documents (TAD) from the US FDA *Environmental Assessment Technical Assistance Handbook*[1] as a guide.

7.1.1. Water solubility (TAD 3.01)

The solubility of carbamazepine in water was conducted at 25°C using the shake flask method. The mean solubility was determined to be 120 µg/mL or 120 ppm. The molar concentration of carbamazepine was calculated to be:

Carbamazepine (mole/L) = (1.2 x 10^{-4} gm/L)/(236.27 gm/mole) = 5.1 x 10^{-7} M

Please refer to Appendix 15 for the complete study report.

7.1.2. n-Octanol/water partition coefficient (TAD 3.02)

The n-octanol/water partition coefficient (K_{ow}) for carbamazepine was conducted at 25°C by the shake flask method. Partitioning testing was conducted in triplicate using octanol/water ratios of 20:8 and 2:8. The mean K_{ow} was determined to be 47.9, and the log (K_{ow}) or log P was 1.68.

Please refer to Appendix 16 for the complete study report.

7.1.3. Vapor pressure (TAD 3.03)

The vapor pressure of carbamazepine was determined in triplicate by the gas saturation method at 25°C using nitrogen average flow rates of 4.75, 6.58 and 9.44 ml/min over a period of 18 days. No carbamazepine was detected in the sorbent martial at any of the flow rates. The detection limit of the instrumentation was therefore used to determine the vapor pressure of carbamazepine. The equilibrium vapor pressure of carbamazepine at 25°C was determined to be less than 1.33 x 10^{-5} Pa or less than 1.0 x 10^{-5} torr. This corresponds to a Henry's Law constant (H) less than 1.30 x 10^{-8}.

Please refer to Appendix 17 for the complete study report.

7.1.4. Ultraviolet-visible absorption spectrum

Ultraviolet/visible spectra were obtained for carbamazepine in ethanol. Absorption maxima in ethanol consisted of one major peak at 209 nm and two shoulders at 250 nm and 229 nm. Absorption spectra of carbamazepine in buffer at pH 8.96 consisted of one major peak at 207 nm and two shoulders at 229 nm and 251 nm. Please refer to Appendix 18.

7.1.5. Melting range

Carbamazepine exhibited a melting point of 189 to 193°C. Please refer to Appendix 18.

7.1.6. Density

The mean density of carbamazepine was determined to be 1.34 ± 0.01 g/cm³ at 25°C. Please refer to Appendix 18.

7.2. Carbamazepine: metabolism and elimination

The principal metabolite of carbamazepine is the 10,11-epoxide. Following a twice a day (b.i.d.) dosage regimen, Tegretol®-XR affords steady-state plasma levels comparable to conventional Tegretol tablets given four times a day (q.i.d.), when administered at the same total daily dose. The plasma clearance of carbamazepine, after a 2-hour, 10-mg intravenous infusion to two healthy subjects, was 20-30 mL/min. Approximately 76% of carbamazepine in blood is bound to plasma proteins. Plasma levels are variable and may range from 0.5-25 ug/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 ug/ml. Carbamazepine is metabolized in the liver. Because carbamazepine induces its own metabolism, the half-life is also variable. The time course of autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

8. Environmental effects of released substances

8.1. Preclinical safety evaluation of carbamazepine

For further information on the pharmacokinetics of the drug product Tegretol®-XR in laboratory animals, a copy of a report from the Clinical Pharmacokinetics and Disposition (CPD) may be found in Appendix 19 of this document. This section is identical to documentation found in the Overall summary of nonclinical pharmacology and toxicology studies of the NDA.

8.2. Effect of product use on organisms in the environment

The chemical and physical properties and constants determined for the drug substance carbamazepine (Section 7.1) were evaluated using the Environmental Assessment Technical Test Matrix (Tier 0) guidelines presented in the PhRMA's *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA*[2]. This document suggests utilizing water solubility, log P and vapor pressure as the primary indicators of environmental fate. Based upon the results of these studies (water solubility < 10^{-5} M; log P < 2; vapor pressure not detected at 10^{-5} torr - limit of detection of equipment), carbamazepine did not precisely fit any of the tiers. Therefore, the environmental effects of carbamazepine upon representative species of aqueous and terrestrial microorganisms, as well as aquatic species were examined. Protocols utilizing appropriate TADs selected from the US FDA *Environmental Assessment Technical Assistance Handbook*[1] and the Organization for Economic Cooperation and Development (OECD) guidelines were selected to ascertain the environmental concentrations of carbamazepine needed to produce effects upon species which may be expected to be encountered in the environment.

8.2.1. Microbial growth inhibition (TAD 4.02)

The agar plate dilution method was used to evaluate the toxicity of carbamazepine drug substance to pure cultures of molds, ascomycetes, free-living nitrogen-fixing and soil bacteria, and blue-green algae. The minimum inhibitory concentrations (MIC) established for carbamazepine for these five representative cultures are:

Species	MIC (mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	> 1000
Bacillus subtilis	> 1000
Nostoc sp.	> 1000

Carbamazepine did not inhibit growth of any of the five cultures during the preliminary test. Definitive testing was not required since there was no inhibitory effect for any organism at concentrations ≤ 1000 mg/L. Please refer to Appendix 20 for the complete study report.

8.2.2. Acute toxicity - *Daphnia*

Carbamazepine was tested by Ciba-Geigy's Ecotoxicology Laboratory located in Basel, Switzerland. The Laboratory tested carbamazepine in aquatic invertebrates according to protocols which followed the Organization for Economic Cooperation and Development (OECD) guidelines.

A twenty-four hour acute toxicity study was conducted on daphnids (*Daphnia magna Straus 1820*) under static test conditions following OECD Guideline No. 202, Part I (1984). The median effect concentration (EC_{50}) was determined to be 92 mg/L. Please refer to Appendix 21 for the complete study report.

8.2.3. Acute toxicity - Zebra fish

Carbamazepine was tested by Ciba-Geigy's Ecotoxicology Laboratory located in Basel, Switzerland. The Laboratory tested carbamazepine in fish according to protocols which followed the Organization for Economic Cooperation and Development (OECD) guidelines.

A ninety-six hour acute toxicity test was conducted in Zebra fish (*Brachydanio rerio*) under static test conditions following OECD Guideline No. 203, Paris, 1984. The median lethal concentration (LC50) was reported to be 43 mg/L. Please refer to Appendix 22 for the complete study report.

8.2.4. Discussion

Results of the water solubility study indicate that carbamazepine would be practically insoluble in water (120 ug/mL). However, considering the MEEC calculated for carbamazepine is in parts-per-billion (ppb) (Appendix 13), it is unlikely that carbamazepine would precipitate out within the pH range typically encountered in the environment (pH 5 - 9).

The n-octanol/water partition coefficient (K_{ow}) for carbamazepine was determined to be 47.9 (log P = 1.68). The K_{ow}, which indicates the tendency of a non ionized organic chemical to accumulate in fatty tissue and to sorb onto soil particles or other organic matter, suggests that carbamazepine would not be expected to sorb significantly to the organic material in soil or sediment, and would not be expected to bioconcentrate substantially in aquatic organisms. (Chemicals with a log P less than 1 are not expected to significantly bioconcentrate or sorb, whereas chemicals with a log P greater than or equal to 4 may be expected to bioconcentrate or sorb significantly.[1])

The melting temperature of carbamazepine (189-193°C) indicates that this substance is a solid at ambient temperatures. If this compound sorbed to the solid sediments in a wastewater treatment plant (WWTP), and, as is usually the case, these sediments were sent for incineration (at expected temperatures ranging from 1500 - 2200°F), the expected emissions would be water vapor, carbon monoxide, carbon dioxide and nitrous oxides.

Results of the ultraviolet/visible spectra scan indicated absorbance below 290 nm in pH 8.96 buffer (one major peak at 207 nm and two shoulders at 229 nm and 251 nm). Direct photodegradation would not be considered a potential mechanism of depletion.

Results of the Microbial Growth Inhibition study indicate carbamazepine did not have an inhibiting growth effect on five of the five test microorganism species tested. Carbamazepine had a sublethal effect on 50% of the population of daphnids at 92 mg/L, while the median lethal concentration in the Zebra fish was 43 mg/L. These concentrations of carbamazepine are well above the estimated maximum concentration anticipated in the aquatic environment, using "worst-case" assumptions.

8.2.4. Conclusion

Carbamazepine is a well-established therapeutic agent used in the treatment of epilepsy and trigeminal neuralgia. Results of the environmental fate studies indicated that carbamazepine

would probably not sorb significantly to the organic material in soil or sediment, or bioconcentrate substantially in aquatic organisms. Environmental fate studies in representative species of microorganisms, invertebrates and fish indicated that carbamazepine would not be expected to be toxic at the maximum expected concentration.

Comparison of the lowest concentration lethal to an aquatic organism (Zebra fish - 43 mg/L) to the MEEC for carbamazepine would result in a safety factor of 10^4.

In addition, the concentration of carbamazepine released to the environment as a result of use of Tegretol®-XR will not change significantly, since for most patients, Tegretol®-XR will replace the current commercial Tegretol tablet therapy.

9. Use of resources and energy

The drug substance carbamazepine will be chemically manufactured at the Ciba facilities in Basel, Switzerland and the drug product Tegretol®-XR will be manufactured at the Ciba US facilities in Suffern, New York and Summit, New Jersey, using raw materials which are common compounds commercially available in ample supply (Appendix 1).

Electric power consumption for the manufacturing and packaging operations in these facilities will be nominal and not excessive. Only very small increases in the utilization of energy over current levels are anticipated, since packaging occurs at existing facilities. The expected product volume will not significantly increase the consumption of either the raw materials or energy resources beyond levels presently experienced.

It should be noted that in an effort to reduce energy consumption, Ciba is a voluntary member of the Environmental Protection Agency's Green Lights Program.

The List of Endangered and Threatened Species of North America[3], published by the Department of the Interior, and the National Registry of Historic Places[4] were consulted in reference to US. packaging operations associated with the finished dosage form, Tegretol®-XR . Based upon the information presented in this assessment, no impact upon aquatic species is foreseen. Accordingly, no impact upon either endangered or threatened wildlife and plants, or the property listed in, or eligible for listing in the Registry of Historic Places is anticipated.

10. Mitigation measures

Ciba-Geigy Corporation recognizes and accepts its environmental responsibilities seriously. In fact, the Vision of the Corporation and the Pharmaceuticals Division expressly harmonize its environmental responsibilities with its economic and social responsibilities. To that end, the Pharmaceuticals Division has committed to and issued *Environmental Principles* (Attachment 1).

Ciba Pharmaceuticals Division is committed to developing and manufacturing high quality healthcare products. The *Environmental Principles* are the foundation for all measures taken by Ciba to protect and conserve the environment, and to mitigate against potential environmental impacts associated with the manufacture, use and disposal of its products.

Based upon the information and data presented in this environmental assessment, Ciba Pharmaceuticals Division has concluded that no potential adverse environmental impacts are foreseen with either the chemical manufacture of carbamazepine at the Ciba facilities in Switzerland, or the manufacture, packaging, transport, use or final disposal of Tegretol®-XR within the United States.

10.1. Manufacture and packaging of finished dosage form

The manufacture and packaging of Tegretol®-XR takes place at Ciba's US facilities under regulated and controlled conditions which mitigate against negative environmental consequences. Processors named in this application are in compliance with Federal and local regulations.

Employee protection -- As previously mentioned in Section 6.5. - Ciba Pharmaceuticals Division has established a Hazard Communication/Right-to-Know program at both the Suffern, New York and Summit, New Jersey sites which covers all employees. This program has been established in accordance with the requirements of the Occupational Health and Safety Administration (OSHA) Hazard Communication Standard, 29 CFR 1910.1200. A copy of the Division's "Hazard Communication/Right-to-Know" procedure has been included in Attachment 2.

Spill response -- Both Ciba's Suffern, NY and Summit, NJ locations have in-house spill response teams and formalized Emergency Response Plans. These programs include provisions for containment and cleanup of any spilled materials, and for mitigating any potential releases to the environment.

Packaging operations may also be conducted by contract packaging facilities. Environmental and occupational health and safety aspects of the contract packaging operations are governed by Ciba's Corporate Policy on Contractor Operations (Attachment 3) and its internal Procedure A-4, "Contract Manufacturing/Packaging of Commercial Products and Research & Development Compounds" (Attachment 4). These facilities must conform to Federal, state and local regulations, and manage their waste materials in accordance with Ciba standards.

10.2. Product distribution

Approval of this Application will result in the distribution of Tegretol®-XR throughout the United States. Any transportation incidents involving Tegretol®-XR would be addressed by Ciba's internal "Ciba Chemical Emergency Response Center" procedure (Attachment 5). This procedure establishes a system of prompt communications between personnel at the incident site and the designated Divisional Response Coordinators so that directives to achieve a rapid and proper response for containment and subsequent cleanup of an incident will be achieved.

10.3. Product use

Information on prescribed use of Tegretol®-XR by patients as therapy for epilepsy and trigeminal neuralgia is contained in the Proposed Package Insert. A copy of the proposed package insert for Tegretol®-XR is provided in Appendix 23.

The anticipated levels of carbamazepine in the environment are not expected to change significantly, since for most patients, Tegretol®-XR is expected to replace the current commercial Tegretol tablet therapy.

10.4. Disposal

It is the policy of Ciba, of which the Pharmaceuticals Division is a part, to inspect all facilities used for the disposal of wastes. This is done to ensure that these facilities are now, and continue to be, in compliance with all permit conditions. An extensive inspection format is utilized which not only verifies the facility's compliance history, but also its overall appearance, maintenance, housekeeping, financial position and employee safety records. Only those facilities which pass this inspection are approved for use by Ciba.

11. Alternatives to the proposed action

No alternatives to the proposed action are suggested, as no potential adverse environmental impacts have been identified for the manufacture, packaging, distribution, use or disposal of Tegretol®-XR. The use of Tegretol®-XR will directly benefit patients suffering from epilepsy and trigeminal neuralgia. It is our conclusion that approval of this Application is therefore preferable to non-approval.

12. List of preparers

A curriculum vitae, documenting the qualifications and credentials for each of the contributors to this environmental assessment, is provided in Appendix 24.

13. Certification

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm responsible for preparation of the environmental assessment.

12/19/95

Joseph A. LoMenzo, Ph.D. Date
Executive Director, Health, Safety & Environment

14. References

1. FDA, 1987. *Environmental Assessment Technical Assistance Handbook.* Food and Drug Administration. March 1987.

2. PMA, 1991. *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA.* August, 1991

3. "Endangered and Threatened Wildlife and Plants", 50 CFR 17.11 - 17.12, 1991.

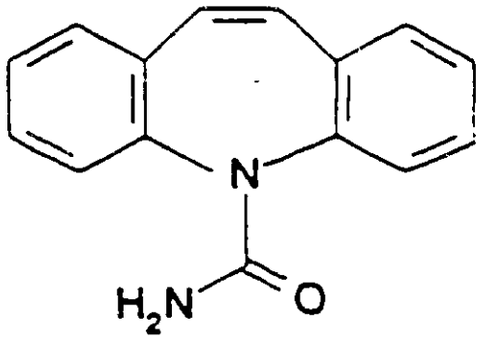
4. "National Registry of Historic Places", American Association for State and Local History, Staff and National Services, Illustration 893, PAP 89.95, p. 1991.

Appendices

Attachments

SUMMARY TABLE 1

Chemical structure of carbamazepine

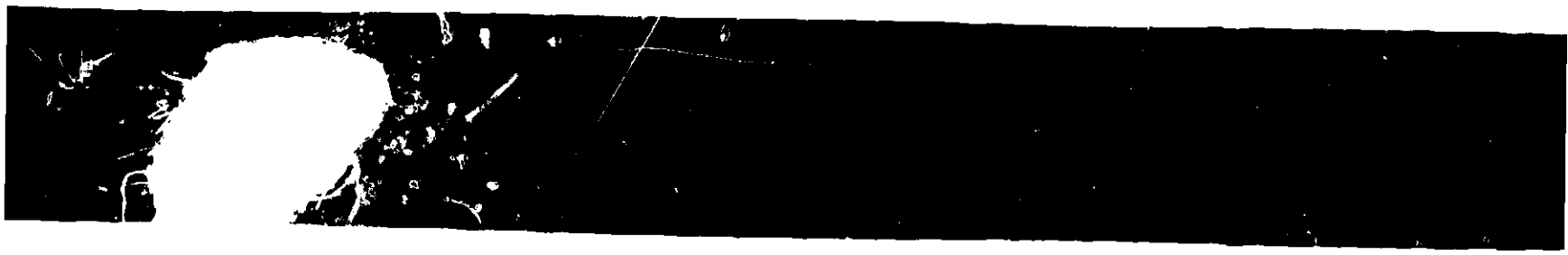


SUMMARY TABLE 2

CARBAMAZEPINE - PHYSICAL PROPERTIES AND CONSTANTS

Parameter	Reference	Value	Units
Water Solubility @ 25°C	TAD 3.01	120 5.1×10^{7}	ppm M
Partition Coefficient (K_{ow}) @ 25°C Log K_{ow}	TAD 3.02	47.9 1.68	N/A N/A
UV/VIS*: $_{max}1$	---	207	nm
Vapor Pressure @ 25°C	TAD 3.03	ND $<1.0 \times 10^{-5}$	N/A TORR
Dissociation Constant (pKa)	---	none	N/A
Melting Range	---	189 - 193	°C
Density @ 25°C	---	1.34 +/- 0.01	g/cm^3

Notes:
- * No UV/VIS absorption observed above 290 nm.
- N/A Not applicable (dimensionless constant)
- ND Not detected



SUMMARY TABLE 3

ENVIRONMENTAL EFFECTS OF

CARBAMAZEPINE IN AQUATIC COMPARTMENT

Parameter	Reference	Value	Units
MICROBIAL GROWTH INHIBITION			
Aspergillis niger	TAD 4.02	>1000	mg/L
Trichoderma viride	TAD 4.02	>1000	mg/L
Clostridium perfringens	TAD 4.02	>1000	mg/L
Bacillus subtilis	TAD 4.02	>1000	mg/L
Nostoc sp.	TAD 4.02	>1000	mg/L
ACUTE TOXICITY - *Daphnia Magna*			
Median Effects Concentration (EC_{50})	OECD 202 (Part I)	92	mg/L
ACUTE TOXICITY - *Brachydanio rerio (Zebra Fish)*			
Median Lethal Concentration (LC_{50})	OECD 203	43	mg/L

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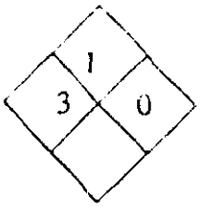


MATERIAL SAFETY DATA SHEET

CIBA-GEIGY CORPORATION
PHARMACEUTICALS DIVISION
556 Morris Avenue
Summit, NJ 07901-1398

24 Hour Emergency Telephone Numbers:
Chemical Emergency Response Center: 1-800-888-8372
Medical Emergency: 1-908-277-5000
For Non-Emergency Situation/Technical Information: 1-908-277-5397 (9:00 AM - 5:00 PM E.S.T.)

SECTION 1. PRODUCT IDENTIFICATION

PRODUCT NAME:	**Tegretol® Active Ingredient (A.I.)**
PRODUCT CODE(S):	300016
SYNONYMS:	Carbamazepine, 5-carbamyl-5H-dibenzo-(b,f)azepine, Neurotol, Karbamazepin
THERAPEUTIC CATEGORY:	Anticonvulsant/analgesic
GENERIC NAME:	Carbamazepine
CHEMICAL NAME:	5H-dibenz[b,f]azepine-5-carboxamide
CHEMICAL FORMULA:	$C_{15}H_{12}N_2O$
MOLECULAR WEIGHT:	236.29

SECTION 2. COMPOSITION/INFORMATION ON INGREDIENTS

COMPOSITION	CAS#	CONCENTRATION (% BY WT.)
Carbamazepine	298-46-4	98 - 100

*** POTENCY CLASSIFICATION = III (High)**

SECTION 3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

****

DANGER: HIGHLY TOXIC/CHRONIC
MAY CAUSE EYE AND SKIN IRRITATION
MAY CAUSE ALLERGIC RESPIRATORY AND SKIN REACTIONS
MAY DAMAGE BLOOD-FORMING ORGANS
MAY CAUSE NERVOUS SYSTEM DISTURBANCES
MAY DAMAGE LIVER AND KIDNEYS
EXPERIMENTAL TERATOGEN AND TUMORIGEN
COMBUSTIBLE: POTENTIAL DUST EXPLOSION HAZARD

****

PRIMARY ROUTE(S) OF ENTRY: Inhalation

EFFECTS OF OVEREXPOSURE:

Skin: *Direct contact may cause skin irritation. Repeated or prolonged exposure may* cause skin sensitization.

Eye: Direct contact may cause eye irritation.

Innalation: Overexposure may cause headache, dizziness, drowsiness, unsteadiness, nausea, allergic reactions, blurred vision, irregular breathing, and rapid heart rate.

Ingestion: Not a likely route of exposure during normal industrial use.

TARGET ORGAN EFFECTS:
Peripheral nerve and sensation (fasciculation)
Behavioral (ataxia, convulsions, altered sleep time, hallucinations, muscle contraction, coma)
Lungs/Respiration (other changes)
Gastrointestinal (nausea, vomiting)
Liver (impaired liver function tests)
Kidney (increased urine volume)
Blood (agranulocytosis, thrombocytopenia, aplastic anemia)
Skin (allergic dermatitis)
Specific developmental abnormalities (central nervous system, skin and skin appendages, musculoskeletal system)

REPRODUCTIVE HAZARDS: There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformation including spina bifida.

CARCINOGENICITY: There are no adequate and well-controlled studies in humans.
ACGIH: Not listed
EPA: Not listed
IARC: Not listed
MAK: Not listed
NIOSH: Not listed
NTP: Not listed
OSHA: Not listed

MUTAGENICITY: Not mutagenic in two test systems (see Section 11).

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Pregnancy: hypersensitivity to carbamazepine or any of the other tricyclic compounds; history of previous bone marrow depression; cardiac, renal or hepatic disease.

SECTION 4. EMERGENCY AND FIRST AID MEASURES

Skin Contact: Wash contaminated area with soap and water.

Eye Contact: Flush with running water for 15 minutes holding eyelids open.

Inhalation: Remove to fresh air. Restore/support breathing as needed.

Ingestion: Get medical attention immediately.

SECTION 5. FIRE FIGHTING MEASURES

Flash Point: not applicable **Method Used:** not applicable

Flammable Limits (% in air)
Lower: not applicable Upper: not applicable

Autoignition Temperature: Not available

Extinguishing Media: CO_2, dry chemical or water spray.

Special Fire Fighting Procedures and Precautions: Combustible. Potential dust explosion hazard. Evacuate area and fight fire from safe distance.

Fire and Explosion Hazards: Not available

Fire-Fighting Equipment: Wear full protective clothing and pressure-demand, self-contained breathing apparatus.

Decomposition Products: May emit toxic nitrogen oxide vapors when heated to decomposition.

NFPA Ratings: Health = 3 Flammability = 1 Reactivity = 0 Special Hazard = None
Hazard Rating Scales: 0 = Minimal 1 = Slight 2 = Moderate 3 = Serious 4 = Severe U = Unknown

SECTION 6. ACCIDENTAL RELEASE MEASURES

Steps to be taken if Material is Released or Spilled: Using appropriate protective equipment, sweep up and containerize spilled material. Residues may be flushed to the sanitary sewer with water.

SECTION 7. HANDLING AND STORAGE

Storage Temperature (Min./Max.): Do not store above 86°F (30°C).

Shelf Life: Not known.

Special Sensitivity: Protect from light and temperatures exceeding 86°F (30°C).

Handling and Storage Precautions: Store in a clean, cool, well-ventilated area away from heat. Keep containers tightly closed. Protect containers from physical damage.

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Eye Protection: Safety glasses with side shields. Wear safety goggles if airborne dust is present.

Skin Protection: Rubber gloves. Use disposable sleeves or apron as needed. Wear disposable coveralls if dusty conditions exist.

Respiratory Protection: A NIOSH-approved full-face respirator equipped with HEPA cartridges must be worn. A supplied air respirator offers a greater level of protection.

Ventilation Requirements: Use local exhaust as needed to control airborne dust.

Exposure Limits (Definition of terms):

ACGIH:	American Conference of Governmental Industrial Hygienists
Ceiling:	Ceiling Value
DTEL:	Derived Target Exposure Limit
MAK:	Federal Republic of Germany Maximum Concentration Values in the Workplace
NIOSH:	National Institute for Occupational Safety and Health
OSHA:	Occupational Safety and Health Administration [USA]
PEL:	Permissible Exposure Limit
PIEL:	Permissible Internal Exposure Limit [Ciba internal]
REL:	Recommended Exposure Limit
Skin (notation):	absorbed through skin
STEL:	Short Term Exposure Limit
TLV:	Threshold Limit Values
TWA:	Time-Weighted Average

Component	Exposure Limit
Carbamazepine	PIEL = 0.2 mg/m^3

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance :	powder		
Color:	white to off-white	**Odor Threshold:**	not available
pH:	not available	**Odor Characteristics:**	not available
Boiling Point:	not applicable	**Vapor Pressure (mm Hg):**	$< 1.0 \times 10^{-5}$ torr
Melting /Freezing Pt:	189-193 °C	**Vapor Density:**	not applicable
Solubility:	Alcohol, acetone, prop. glycol	**Specific Gravity:**	1.34 g/cm³
	120 ppm (water)	**Partition Coeff. (log Po):**	1.68
		Combustibility:	2 @ 100°C

Dust Explosion Class: 2-3 (Hartmann tube); **Hazard Class for Milling:** 1; **Hazard Class for Drying:** 0

SECTION 10. STABILITY AND REACTIVITY

Stable (yes/no):	Yes
Hazardous Polymerization:	Will not occur.
Conditions and Materials to Avoid:	Protect from light and temperatures above 86°F (30°C). Avoid raising dust.
Incompatibility	Avoid contact with strong oxidizing agents.
Hazardous Decomposition Products:	May emit toxic nitrogen oxide vapors when heated to decomposition.

SECTION 11. TOXICOLOGICAL INFORMATION

Eye Irritation:	Minimally irritating to the eyes of albino rabbits.
Skin Irritation/Sensitization:	Non-irritating to the skin of albino rabbits.
Oral Toxicity:	LD_{50} (Rats) = 1957 mg/kg; LD_{50} (Mice) = 529 mg/kg LD_{50} (Rabbits) = 2680 mg/kg; LD_{50} (Dogs) = 5620 mg/kg LD_{50} (Guinea Pig) = 920 mg/kg
Dermal Toxicity:	LD_{50} (Rabbits) >3,000 mg/kg. Barely perceptible skin irritation was observed.
Inhalation Toxicity:	LC_{50} (Rats) >1,540 mg/m^3 air following a 4 hour exposure.
Subchronic:	Albino male rats were injected with carbamazepine for 3 months immediately after weaning. A decrease in prostate weight was found in the treated rats. A lowered epididymal sperm content was observed which did not affect fertility.

Chronic/Carcinogenicity: Experimental carcinogen. In a 2 year feeding study in rats, a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males were observed at doses of 25, 75, and 250 mg/kg/day.

Mutagenicity: Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results.

Reproductive Effects: **FDA Use-in-Pregnancy Category C: Risk cannot be ruled out.** Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily human dosage of 1,200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies. In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg. Rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and decreased sperm production.

SECTION 12. ECOLOGICAL INFORMATION

Minimum Inhibitory Concentration (MIC):

Aspergillus niger > 1000 mg/L
Trichoderma viride > 1000 mg/L
Clostridium perfringens > 1000 mg/L
Bacillus subtilis > 1000 mg/L
Nostoc sp. > 1000 mg/L

Median effect concentration: EC_{50} (*Daphnia magna Straus* 1820) = 92 mg/L. (24 hour; static test conditions)

Median lethal concentration: LC_{50} (Zebra fish - *Brachydanio rerio*) = 43 mg/L. (96 hour; static test conditions)

SECTION 13. DISPOSAL CONSIDERATIONS

Waste Disposal Method: All waste must be disposed of in accordance with local, state and federal laws and regulations. (Contact local or state environmental agency for specific rules).

EPA Hazardous Waste Number: None

SECTION 14. TRANSPORTATION INFORMATION

DOT Shipping Name:	Drugs, N.O.I. NMFC Item 60000
Symbols:	None
DOT Hazard Class:	None
DOT Identification:	None
Packing Group:	None
Hazard Label:	None
Exceptions:	None
Non-Bulk Requirements:	None
Bulk Requirements:	None
Max. Passgr. Air/Rail:	None
Max. Cargo Only Air/Rail:	None
Stowage:	None
Other Requirements:	None

SECTION 15. REGULATORY INFORMATION

OSHA (Occupational Safety & Health Administration): This Material Safety Data Sheet contains the information required by the Federal Hazard Communication Standard (29 CFR 1910.1200).

OSHA PSM (Product Safety Management): Not regulated

NJ TCPA (Toxic Catastrophe Prevention Act): This material is not subject to the reporting requirements of Section N.J.A.C. 7:31 of this act.

TSCA (Toxic Substance Control Act): Not regulated

CERCLA (Comprehensive Response Compensation & Liability Act): Not listed

SARA Title III (Superfund Amendments & Reauthorization Act):

Section 302 Extremely Hazardous Substances: Not listed

Section 311/312 Hazard Categories: Immediate health, delayed health

Section 313 Toxic Chemicals: Not listed

RCRA (Resource Conservation & Recovery Act): Not regulated

Other State Regulatory Information:

New Jersey: NJ RTK Threshold Planning Quantity (TPQ) = 10,000 lbs.

Other USA Regulations: None

California Proposition 65: The following statement is made in order to comply with the California Safe Drinking Water and Toxic Enforcement Act of 1986. *This chemical is not known to the State of California to cause cancer or reproductive toxicity.*

Canada:	WHMIS Ingredient Disclosure List Not listed
EEC Classification (European Economic Community):	Warning Symbol: not available Risk Phrases: not available Safety Phrases: not available

SECTION 16. OTHER INFORMATION

Reason for Issue: Update to new format

Supersedes Date:	29 Nov 93		
Written By:	C. Perino	**Date:**	15 Dec 95
Approved By:	L Sinno	**Date:**	15 Dec 95

To the best of our knowledge, the information contained herein is accurate. However, Ciba-Geigy Corporation does not assume any liability whatsoever for the accuracy or completeness of the information contained herein except for the product's administration/use as intended. Final determination of the suitability of any material is the sole responsibility of the user. All materials may present unknown hazards and should be used with caution. Although certain hazards are described herein, we cannot guarantee that these are the only hazards which exist.

In separate communications to CDER, the applicant agreed to reclassify appendices 2-4, 11, 12 and 24 as non-confidential. The information in these appendices follows this page.

Appendix 2

Description of environmental settings: Ciba Overseas Facility - Schweizerhalle, Switzerland (Section 4.3.1.)

CIBA-GEIGY Limited
Werke Schweizerhalle
CH-4133, Schweizerhalle
Switzerland

This CIBA-GEIGY Pharmaceutical Chemical production facility is located within the "CIBA-GEIGY Werke Schweizerhalle AG" site. This site is situated in the industrialized zone of Schweizerhalle, approximately five miles east of the City of Basle, adjacent to the Rhine River which is also the boundary to the Federal Republic of Germany. CIBA-GEIGY works Schweizerhalle occupy an area of approximately 52 acres. Approximately 2,250 people are employed at the site. The surrounding neighborhood consists mainly of chemical industry.

Air Resources

Air quality in this area is in compliance with cantonal and federal standards set for sulfur oxides, nitrous oxides and ozone.

Water Resources

Potable water is supplied by the public Hardwasser AG. Non-potable water is drawn from wells within the works (Rhine water). The waste water streams stemming from chemical production are separated into "polluted" and "non-polluted" (cooling water) waste water. The "non-polluted" water is discharged directly into the Rhine River. The "polluted" water, after an on-site pretreatment (if necessary), as well as sanitary waste water and storm water drainage goes to the "ARA Rhein"- a sewage treatment plant jointly used by the public and the industry. This is finally discharged into the Rhine River.

Land Resources

The Schweizerhalle site, a level terrain, lies over essentially sedimentary type formations. It is fully developed, being covered by buildings, roadways and railroads.

6.2. Controls in Effect

Air Controls

Air emissions stemming from the synthesis of bulk drug substances are controlled by equipment such as surface condensers, brine-cooled vent condensers (- 15°C) and scrubber systems operating with either plain water or acidic, basic or oxidizing aqueous solutions. Air emissions from the on-site incinerator are controlled by a series of scrubbers operating with aqueous absorption mediums. The equipment is in compliance with permits of the Department of Commerse, Industry and Employment of the Canton of Basel-Landschaft (= Amt fuer Gewerbe, Handel und Industrie des Kantons Basel-Landschaft) and the Department of Air Pollution Control (= Lufthygieneamt).

Liquid Controls

All waste solvents are burned in an on-site incinerator. All process waste water goes, if necessary after on-site pretreatment, to the "ARA Rhein", a public-owned Joint Waste Water Treatment Plant. The effluent of this plant is discharged into the Rhine River. This procedure is in compliance with the permit issued by the Department of Commerce, Industry and Employment of the Canton of Basel-Landschaft (= Amt fuer Gewerbe, Handel und Industrie des Kantons Basel-Landschaft) and the Water Protection Agency (= Kantonales Gewaesserschutzamt).

Solids Controls

All solid process residuals (like dusts, filter residues or rejected production material) are sent to the rotary kiln, working at approximately 1200°C owned by CIBA-GEIGY at its Basle site.

6.3. Citations

All the Ciba-Geigy facilities in Switzerland must be in compliance with the following regulations issued by the Swiss Federal Government:

Air Citations

Federal Air Pollution Control Regulation = "Luftreinhalteverordnung" (LRV) 814.318.142.1 (12/16/85, latest edition 1/1/87).

Water Citations

Federal Regulation to Introduce Waste Waters into Rivers and Lakes = "Verordnung ueber Abwassereinleitungen" 814.225.21 (12/8/75, latest edition 4/1/87).

Solid Waste Citations

Federal Regulation for the Transport and Disposal of Special Waste = "Verordnung ueber den Verkehr mit Sonderabfaellen," 814.014 (11/12/86 latest edition, 1/10/89).

Appendix 2

Description of environmental settings: Ciba Overseas Facility - Klybeck, Switzerland (Section 4.3.1.)

CIBA-GEIGY Limited
Werke Klybeck
Klybeckstrasse 141
CH-4002 Basel
Switzerland

This CIBA-GEIGY Pharmaceutical Chemical production facility is located within the Klybeck site (100 acres) of CIBA-GEIGY Ltd. works in the City of Basle (population 180,000), at the northern end of the urban industrialized areas of the town, close to the borders of the Federal Republic of Germany and France. The agglomeration Basle, situated in Switzerland, France and Germany, has a population of approximately 500,000 people. The site is partly adjacent to the Rhine River; the small Wiese River divides the area. The surrounding neighborhood includes, among others, a food processing plant, transportation, printing and retail businesses as well as a large number of dwellings. In Basle, CIBA-GEIGY occupies an area of approximately 130 acres. Totally, over 11,000 people are employed.

Air Resources

Air quality in this area is in compliance with cantonal and federal standards set for sulfur oxides, nitrous oxides and ozone.

Water Resources

Potable water is supplied by the City of Basle. Non-potable water is drawn from the Rhine River by filtration. Storm water drainage and sanitary waste water are discharged to the City of Basle Sewage Treatment plant and then to the Rhine River. The waste water streams stemming from chemical production are separated into "polluted" and "non-polluted" (cooling water) waste water. The "non-polluted" water is discharged into the Rhine River. The "polluted" water goes to a Chemical Waste Water Treatment plant where it is finally discharged into the Rhine River.

Land Resources

The site is on level terrain and lies over essentially sedimentary type formations. It is fully developed, being covered by buildings, roadways and railroads, and is sparingly landscaped.

6.2. Controls in Effect

Air Controls

Air emissions stemming from the synthesis of bulk drug substances are controlled by equipment such as surface condensers, brine-cooled vent condensers (- 15°C) and scrubber systems operating with either plain water or acidic, basic or oxidizing aqueous solutions. Air emissions from the on-site incinerator are controlled by a series of scrubbers operating with aqueous absorption mediums. The equipment is in compliance with permits of the Construction Supervision Department of the Canton of Basel-Stadt (= Bauinspektorat des Kantons Basel-Stadt) and the Department of Air Pollution Control (= Kantonales Lufthygieneamt).

Liquid Controls

All waste solvents are burned in an on-site incinerator. All process waste water goes to the on-site Chemical Waste Water Treatment system which consists of stripping the volatile solvents, neutralization, flocculation, separation of solids and biological treatment. The resulting waste water is discharged to the City of Basle Sewage Treatment plant and finally into the Rhine River. This procedure is in compliance with the permit issued by the Construction Supervision Department of the Canton of Basel-Stadt (= Bauinspektorat des Kantons Basel-Stadt) and the Water Protection Agency (= Kantonales Gewasserschutzamt).

Solids Controls

All solid process residuals (like dusts, filter residues or rejected production material) are burned on-site in a rotary kiln at approximately 1200°C. The residues of the incineration process are washed with water (which is fed to the industrial waste water pipe system) and then sent off site for disposal. The incinerator plant must operate in conformance with permits issued by the Swiss Association of Owners of Pressure Vessels (= Schweizerischer Verband der Druckbehaelterbesitzer) and the Construction Supervision Department of the Canton of Basel-Stadt (Bauinspektorat des Kantons Basel-Stadt).

6.3. Citations

All the Ciba-Geigy facilities in Switzerland must be in compliance with the following regulations issued by the Swiss Federal Government:

Air Citations

Federal Air Pollution Control Regulation = "Luftreinhalteverordnung" (LRV) 814.318.142.1 (12/16/85, latest edition 1/1/87).

Water Citations

Federal Regulation to Introduce Waste Waters into Rivers and Lakes = "Verordnung ueber Abwassereinleitungen" 814.225.21 (12/8/75, latest edition 4/1/87).

Solids Citations

Federal Regulation for the Transport and Disposal of Special Waste = "Verordnung ueber den Verkehr mit Sonderabfaellen," 814.014 (11/12/86 latest edition, 1/10/89).

Appendix 3

Description and map of environmental settings of Ciba facility: Suffern, NY
(*Section* 4.3.3.)

Ciba-Geigy Corporation
Pharmaceuticals Division
25 Old Mill Road
Suffern, New York 10901-7914

This Ciba pharmaceutical manufacturing facility is located in the Villages of Suffern and Montebello, Rockland County, New York (combined population 14,950) on 162 acres, approximately 30 miles northwest of New York City. The manufacturing facility, which resides within the boundaries of the Village of Suffern, consists of two main buildings, a new docking facility, an automated warehouse structure and several auxiliary buildings with a combined total floor space of approximately 454,000 square feet. The site is bounded by the New York State Thruway on the north, Hemion Road on the east, the Conrail Piermont Line on the south and the Plaza Material Corp. quarry on the west. Wooded ridges on its east and west sides border a flat valley where the facility, parking area and landscaped area lie. The site employs an average workforce of approximately 550 people. The surrounding neighborhood includes retail businesses, light industry and private residences. The topography of the region is varied. The climate is temperate, with an average annual rainfall of 43.5 inches. A map of the facility follows.

Terrain - The developed portion of the site, approximately 33 acres, is generally flat, with an average elevation of approximately 320 feet above sea level. The nature of the soil is characterized as glacial deposits, consisting of sand, gravel and a till mixture of sand, gravel, boulders and clay, with sandstone and shale bedrock.

Water Resources - The Suffern facility is located in a drainage basin with a total of 295 acres. During storm events, stormwater runoff from this basin is channeled naturally through the Ciba's property, eventually discharging through a culvert under Route 287, to Lake Antrim, which eventually feeds into the Mahwah River. Stormwater runoff from the facility is directed to this system through a standard gravity-flow conduit system designed specifically for stormwater runoff conveyance. Four (4) distinct wetland areas have been delineated at the site, totaling 18.6 acres. None of these areas fall under the New York Department of Environmental Conservation (NYDEC) regulations governing wetlands protection (12.4 acres or greater).

However, three of these four wetlands areas do fall under both Federal Clean Water Act (CWA) regulations and the US Army Corps of Engineer Environmental Protection Regulations.

Process and domestic wastewater are conveyed from the facility via a gravity sewerage system to an on-site sewerage pumping station. This flow is then directed to the Village of Suffern publicly owned treatment works (POTW) at an average flowrate of 118,000 gallons per day (GPD). This POTW is designed to process 1.8 million gallons per day (MGD). The POTW regulates the Suffern facility for its discharge through a Federally-authorized pretreatment permit program. This program regulates the facility for flow, pH, biochemical oxygen demand (BOD), total suspended solids (TSS), toluene and methylene chloride. Reporting is submitted on a semi-annual basis.

All domestic and fire protection water is purchased from the Village of Suffern, which operates a well field, and is interconnected with the Spring Valley Water Company for supplemental purposes.

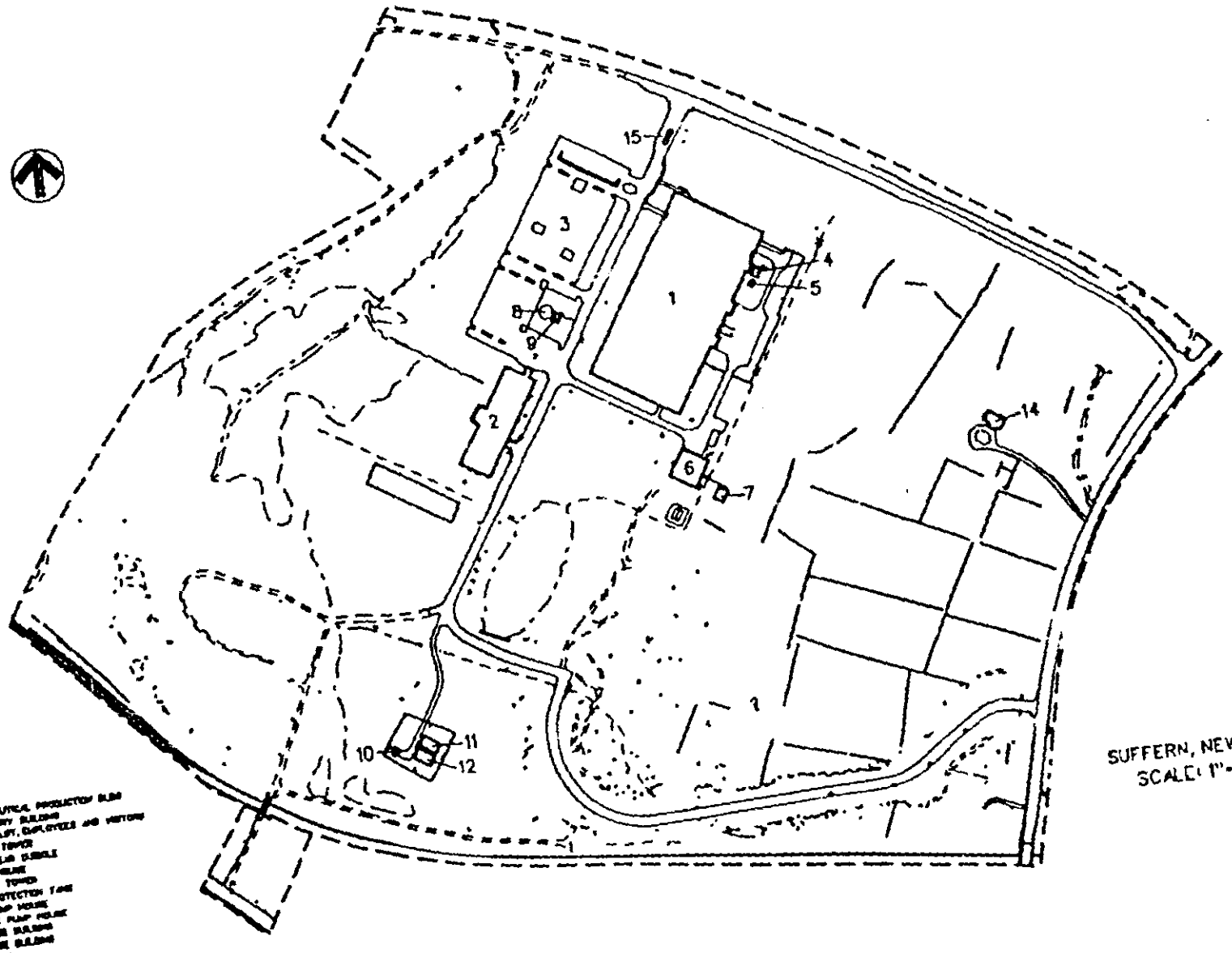
Air Quality - Suffern is part of the air quality geographical area regulated under the New York -New Jersey - Connecticut Interstate Air Quality Control Region of the Environmental Protection Agency (EPA). Locally, Suffern air quality is regulated by both the NYDEC and the Rockland County Department of Health. Enforcement issues are handled jointly.

Regional air quality designations are given in Part 81 of the 40 Code of Federal Regulations (CFR). Suffern is currently in compliance with the National Ambient Air Quality Standards (NAAQS) for particulate matter, nitrogen dioxide, sulfur oxides and carbon monoxide. However, Suffern, along with the entire State of New York, is in non-compliance with the NAAQS for ozone.

Emissions of regulated substances into the air are reported to Federal, state and local authorities under Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA). SARA Title III requires affected facilities to track and submit emission inventories annually. Ciba-Geigy Corporation has been meeting the requirements of SARA Title III since the inception of the program in 1987 and will continue to comply. New York is required to submit to the EPA a State Implementation Plan (SIP) detailing how New York meets all Federal air quality requirements. Ciba fully complies with the SIP outlined by New York. The Clean Air Act Amendments of 1990 promulgated many new air regulations. New York is currently revising their SIP to reflect these new regulations. Ciba intends to fully comply with the new SIP.

In the State of New York, air emissions are regulated under Title 6 of the New York State Codes, Rules and Regulation (NYCRR). As required by these regulations, Ciba maintains an active air permit program. All permits have been, and will continue to be, renewed and updated as process/facility changes occur. New permits will be obtained as required. Where appropriate, Ciba has installed state-of-the-art pollution controls to minimize air emissions. In addition, stack tests have been, and will continue to be, performed for all relevant emission points to ensure compliance.

In the County of Rockland, air emissions are regulated under Article XII of the Sanitary Code of the County of Rockland. As required by County regulations, Ciba maintains an active air permit program. All permits have been, and will continue to be, renewed and updated as changes occur.



SUFFERN, NEW YORK
SCALE: 1"-500'

7-31-90

590

Appendix 4

Description and map of environmental settings of Ciba facility: Summit, NJ
(Section 4.3.3.)

Ciba-Geigy Corporation
Pharmaceuticals Division
556 Morris Avenue
Summit, New Jersey 07901-1398

This Ciba Pharmaceutical Division facility is located on approximately 88 acres of land in the City of Summit (population 25,000), Union County, New Jersey, approximately 30 miles southwest of New York City. The site consists of forty-five buildings covering over 2.2 million square feet and employs an average work force of approximately 2,200 people. It is adjacent to the Passaic River, a source of potable water. The surrounding neighborhood includes retail businesses, light industry and private residences. The topography of the region is varied. The climate is temperate, with an average annual rainfall of 43.5 inches. A map of the facility from the site's Emergency Response Plan follows.

Terrain - The 92 acre site lies over essentially sedimentary type formations and glacial till. The majority of the site, which is level terrain, is developed, covered by buildings, roadways and parking lots, with landscaped areas.

Water Resources - The Summit facility is located within the Passaic River watershed basin. The facility's stormwater drainage system consists of a complex network of conduit, which ultimately discharges to the Passaic River via four (4) outfalls. The system also accepts stormwater runoff from the city of Summit. The four (4) outfalls possess a New Jersey Pollutant Discharge Elimination System (NJPDES) permit regulating this discharge to the Passaic River. Non-contact cooling water originating from the overflow of a 65,000 gallon recycled cooling water tank is permitted to be discharged to the Passaic River. Both discharges are analyzed for conventional pollutants and reported on a monthly basis.

Process water, as well as domestic water, is derived from two (2) sources: one drawn from four (4) private, on-site production wells and the other purchased from the local water purveyor, American Water Company. The production wells are regulated by the state of New

Jersey through a Water Allocation Permit. The Summit facility is allowed to draw a maximum volume of 24.5 million gallons of water from these wells per month. The total volume passes through an on-site chlorination system. Domestic purchased water usage volumes range from 18 to 22 million gallons per month. The depth of the production wells are approximately 800 feet deep. The primary aquifer affected by the pumpage of these wells is the Towaco formation, consisting of fractured shale, siltstone, and sandstone.

The Towaco formation is overlain by a glacial till deposit/weathered bedrock zone. The facility possesses a state-administered discharge-to-groundwater permit (DGW), which has been incorporated into the NJPDES DGW Permit. This permit has required the installation of thirteen (13) groundwater monitoring wells within the glacial till/weathered bedrock zone. Trace amounts of contaminants have been detected in the groundwater from this zone. However, this groundwater is not hydraulically connected to the water-bearing formation currently utilized for production/domestic usage on site. Ciba is in the process of installing additional monitoring wells to further delineate shallow contamination.

All pharmaceutical related wastewater from the site are conveyed to an on-site pretreatment system through a dedicated sewerage system. The pretreatment system consists of equalization and pH neutralization using carbon dioxide and sodium hydroxide. Process wastewater from this pretreatment system is discharged to the Essex/Union Joint Meeting POTW at an average flowrate of 550,000 GPD. Domestic sanitary flows from the facility are also discharged via a network of domestic sewerage conveyances to this POTW. The facility possesses a permit to discharge from the pretreatment facility administered by the POTW Pretreatment Program.

Air Quality - Summit is part of the air quality geographical area regulated under the New York -New Jersey - Connecticut Interstate Air Quality Control Region of the EPA. Locally, Summit air quality is regulated by both the New Jersey Department of Environmental Protection (NJDEP) and the Union County Regional Environmental Health Commission (UCREHC). Enforcement issues are handled jointly.

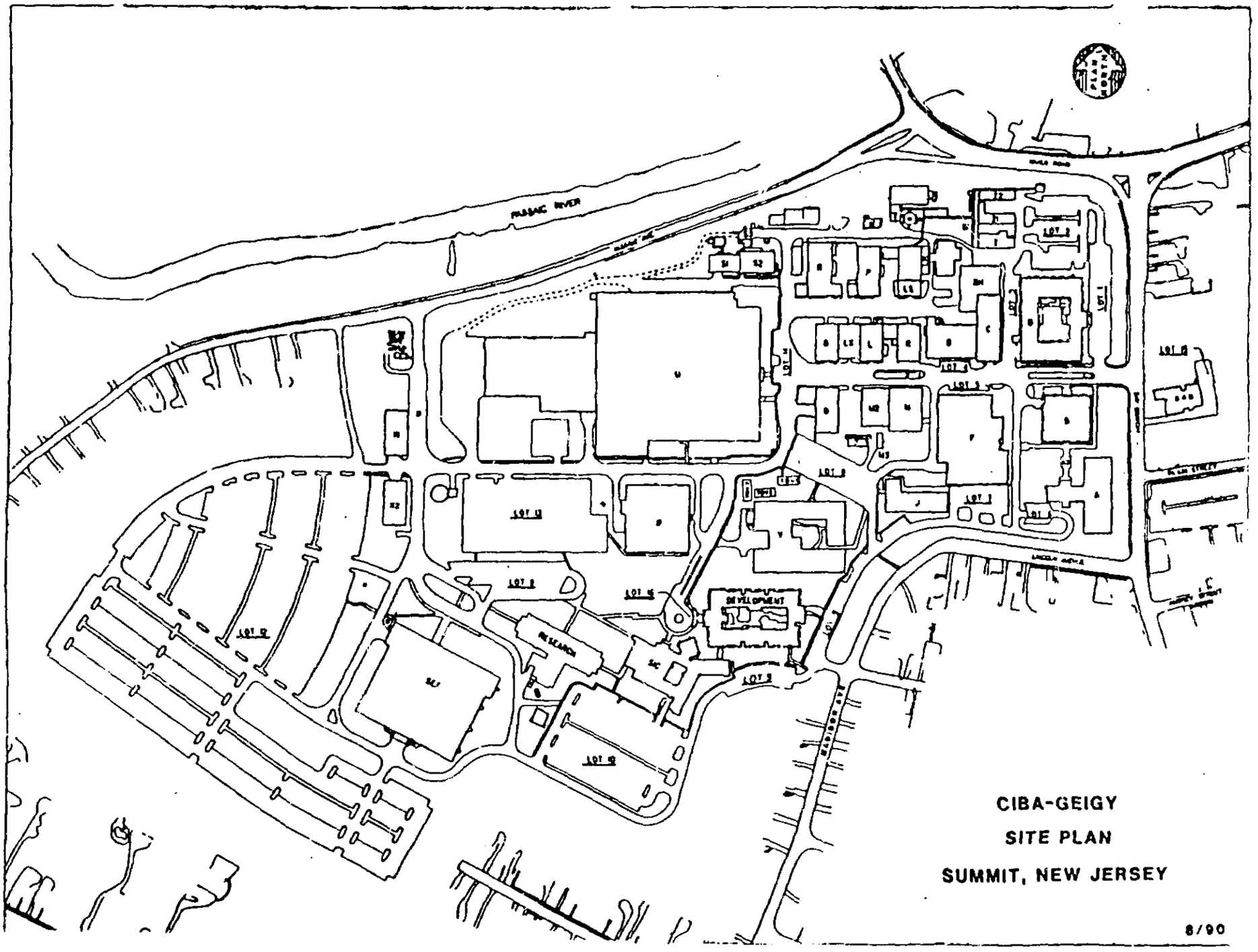
Regional air quality designations are given in 40 CFR, Part 81. Summit is currently in compliance with the NAAQS for particulate matter, nitrogen dioxide, sulfur oxides and carbon monoxide. However, the city of Summit, along with the entire State of New Jersey, is in non-attainment with the NAAQS for ozone.

Emissions of regulated substances into the air are reported to the Federal, state and local authorities under SARA Title III. SARA Title III requires affected facilities to track and submit emission inventories annually. The Summit site has been meeting the requirements of

SARA Title III since the inception of the program in 1987 and will continue to comply. New Jersey is required to submit to the EPA a SIP detailing how New Jersey meets all Federal air quality requirements. Ciba-Geigy fully complies with the SIP outlined by New Jersey. The Clean Air Act Amendments of 1990 promulgated many new air regulations. New Jersey is currently revising their SIP to reflect these new regulations. Ciba-Geigy intends to fully comply with the new SIP.

In the State of New Jersey applicable air emissions are regulated under Chapter 27 of the New Jersey Administrative Code (NJAC). As required by New Jersey regulations, Ciba-Geigy maintains an active air permit program. All permits have been and will continue to be renewed and updated as process/facility changes occur. New permits will be obtained as required. Where appropriate, Ciba-Geigy has installed Continuous Emission Monitoring (CEM) devices to quantify, and state-of-the-art pollution controls to minimize, air emissions. In addition, stack tests have been, and will continue to be, performed for all relevant emission points to ensure compliance. NJDEP requires facility-wide annual emission inventory as well as annual and quarterly emission reporting for some emission points. Ciba-Geigy has complied with this requirement and will continue to do so.

In Union County, air emissions are regulated under the Air Pollution Code of UCREHC. Under Ordinance Number 02-1989 adopted by this code, all commercial and industrial air pollution sources require registration. Ciba-Geigy has registered all applicable sources. This ordinance is currently being revised by the UCREHC. Upon completion of the revision, UCREHC will inform all affected facilities of the appropriate registration renewal methodology. Ciba-Geigy expects to be in compliance with the revised ordinance.



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BAUDEPARTEMENT

DES KANTONS BASEL-STADT

ENVIRONMENTAL PROTECTION CERTIFICATE

1. The company CIBA-GEIGY LTD operates facilities for chemical and pharmaceutical manufacturing at the following address:

   CIBA-GEIGY Ltd.
   Klybeckstrasse 141
   CH-4002 Basel
   Switzerland

2. These production facilities may only operate in accordance with permits issued by the responsible Authorities. In the permits are laid down the purpose for witch buildings and plants may be used and the legal conditions with which the Company must comply.

3. The above-described permits also cover the preparation of the Active Substance

   TEGRETOL

4. All buildings and plants of the company CIBA-GEIGY LTD must comply with the federal and cantonal laws and regulations concerning safety, protection of the environment and working conditions.

5. The relevant departments of the Cantonal Authorities perform periodic inspections.

6. It can here be stated that the undersigned Governmental Office has proved the correct building and producing permits are given.

BAUDEPARTEMENT BASEL-STADT
Der Departementssekretär

Basel, 30. Juni 1992

Dr. G. Vischer

Pharmaceuticals Division

ciba

Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901-1398
Telephone 908 277 5000

Appendix 12

Statement of Compliance

Ciba states that it is compliance with, or on a schedule to be in compliance with, all requirements set forth in all applicable Federal, state and local statutes and regulations, as well as permits, consent decrees and administrative orders applicable to the manufacture and packaging of Tegretol®-XR at our Pharmaceutical production facilities in Suffern, New York and Summit, New Jersey.

Steve J. Lesko, CSP
Environmental Compliance Officer/Waste, HS&E

EMPLOYMENT

Mr. Lesko has been employed by Ciba Corporation, Pharmaceuticals Division in Summit, New Jersey since May 1994. As Environmental Compliance Officer/Air, Mr. Lesko has the responsibility of regulatory compliance for all medical, hazardous and non-hazardous pharmaceutical wastes for the Summit site. In addition to the Environmental Compliance Officer/Waste responsibilities, Mr. Lesko is also currently responsible for managerial and daily operations of the Environmental section for the Division.

Prior to assuming the above-noted responsibilities, Mr. Lesko was employed by Ciba Corporation, Pharmaceuticals Division and held the position's of Compliance Auditor and Industrial Hygienist since November, 1988. Before joining Ciba, Mr. Lesko worked for Beecham Laboratories as an Industrial Hygienist, for Clayton Environmental Laboratories as an Associate Industrial Hygienist and for Princeton Testing Laboratories as an Industrial Hygiene Technologist.

PROFESSIONAL ACTIVITIES

Mr. Lesko is a member of the national and local sections of the American Industrial Hygiene Association and the American Society of Safety Engineers, and the Environmental Auditing Roundtable.

EDUCATION

Mr. Lesko holds a Bachelors degree in Biology from the Ramapo College of New Jersey and is currently pursuing a Masters degree in Environmental Science from the New Jersey Institute of Technology (expected graduation May, 1996).

CERTIFICATIONS AND LICENSES

Mr. Lesko also holds the designation of a Certified Safety Professional (CSP) from the American Society of Safety Engineers.

Peter Leung
Environmental Compliance Officer/Air, HS&E

EMPLOYMENT

Mr. Leung has been employed by Ciba Corporation, Pharmaceuticals Division in Summit, New Jersey since June 1991. As Compliance Officer/Air, Mr. Leung has the responsibility of regulatory compliance for all air emissions for the Summit site. Prior to joining Ciba, Mr. Leung worked for Stone and Webster Engineering Corporation as an environmental engineer.

PROFESSIONAL ACTIVITIES

Mr. Leung is a member of the American Institute of Chemical Engineers and the Air and Waste Management Association.

EDUCATION

Mr. Leung holds a Bachelor degree in Chemical Engineering from The Cooper Union, School of Engineering.

Lisa A. Lumia
Technical Coordinator, Drug Regulatory Affairs

EMPLOYMENT

Since June 1984, Ms. Lumia has been employed by Ciba Corporation, Pharmaceuticals Division in Suffern, New York. As a Technical Coordinator, Ms. Lumia is responsible for the preparation and maintenance of control documents for marketed and investigational compounds; organization and compilation of the chemistry, manufacturing and controls section of Original INDs and NDAs and subsequent submissions to support the IND or NDA; and the preparation of responses to FDA concerns regarding technical issues.

PROFESSIONAL ACTIVITIES

Ms. Lumia is a member of the American Association of Pharmaceutical Scientists.

EDUCATION

Ms. Lumia holds a Bachelors degree in biology from Lafayette College, Easton, Pennsylvania.

Christopher R. Perino
Occupational Toxicologist, HS&E

EMPLOYMENT

Mr. Perino has been employed by Ciba Corporation, Pharmaceuticals Division in Summit, New Jersey since November 1992. As an Occupational Toxicologist, Mr. Perino has the responsibility of OSHA Hazard Communication compliance for the Pharmaceuticals Division. Prior to joining Ciba, Mr. Perino worked for Gibraltar Biological Laboratories as Manager of Toxicology and Administration.

PROFESSIONAL ACTIVITIES

Mr. Perino is a member of the Occupational Toxicology Roundtable, Society of Toxicology (Mid-Atlantic chapter) and the Society for Chemical Hazard Communication.

EDUCATION

Mr. Perino holds a Masters degree in Biology from Montclair State College and a Bachelors degree in Biology from Villanova University.

PUBLICATIONS

Chemical TIMES & TRENDS: 21-28, Oct. 1991.
Chemical TIMES & TRENDS: 28-31, Jan. 1992.

Joyce Ann Sinno, Ph.D.
Environmental/Occupational Toxicologist, HS&E

EMPLOYMENT

Dr. Sinno has been employed by Ciba Corporation since November 1990 as Environmental/ Occupational Toxicologist for the Pharmaceuticals Division. In addition to responsibilities associated with her position as Occupational Toxicologist, Dr. Sinno's environmental responsibilities include the preparation of Environmental Assessments for NDA and IND submissions. Dr. Sinno was previously employed by Pfizer Pharmaceuticals.

PROFESSIONAL ACTIVITIES

Dr. Sinno is a member of the Mid-Atlantic Chapter of the Society of Toxicology, and a full member of the American Industrial Hygiene Association.

EDUCATION

Dr. Sinno holds a Bachelors degree and a Masters degree in Pharmaceutical Toxicology and a doctoral degree in Biochemical Toxicology from St. John's University College of Pharmacy and Allied Health Professions.

PUBLICATIONS

Biol. Trace Element Res. 20: 153-160, 1989.

END

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