CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 16-608/S090, NDA 18-281/S039, NDA 18-927/S031, AND NDA 20-234/S017

Trade Name: **Tegretol**

Generic Name: **Carbamezepine**

Sponsor: **Novartis Pharmaceuticals Corporation**

Approval Date: **3/7/2001**

CENTER FOR DRUG EVALUATION AND RESEARCH

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	
Tentative Approval Letter (ANDA)	
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Bioequivalence Review(s)	
Administrative and Correspondence Document(s)	X

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 16-608/S-090
NDA 18-281/S-039
NDA 18-927/S-031
NDA 20-234/S-017

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Ms. Stiles:

Please refer to your supplemental new drug applications dated April 21, 2000, received April 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tegretol (carbamezepine) Drug Products.

These "Changes Being Effected" supplemental new drug applications provide for the replacement of the sentence "Damaged tablets should not be consumed" with the following sentence in the Dosage and Administration section of labeling:

"Damaged tablets or tablets without a release portal should not be consumed."

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Melina Fanari, R.Ph., Regulatory Management Officer, at (301) 594-5526.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Russell Katz
3/7/01 11:12:10 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
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APPROVED LABELING

NOVARTIS

T2000-04
89007002

Tegretol®
carbamazepine USP

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

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

Rx only

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/5 mL (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 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, 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.

Usage in Pregnancy

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. In treating or counseling women of childbearing potential, the prescribing physician will wish to weigh the benefits of therapy against the risks. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard 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, if therapy is to be continued, monotherapy may be preferable for pregnant women.

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

Carbamazepine 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 (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m^2 basis. 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.

Antiepileptic drugs should not be discontinued abruptly 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.

Tests to detect defects using currently accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal Tegretol and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have also been reported in association with maternal Tegretol use. These symptoms may represent a neonatal withdrawal syndrome.

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 or hypersensitivity reaction to other drugs, including reactions to other anticonvulsants; or interrupted courses of therapy with Tegretol.

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure have been reported (see ADVERSE REACTIONS and PRECAUTIONS,Laboratory Tests). In some cases, hepatic effects may progress despite discontinuation of the drug.

Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases (see ADVERSE REACTIONS,Other and PRECAUTIONS,Information for Patients).

Discontinuation of carbamazepine should be considered if any evidence of hypersensitivity develops.

Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anticonvulsants including phenytoin and phenobarbital. A history of hypersensitivity reactions should be obtained for a patient and the immediate family members. If positive, caution should be used in prescribing carbamazepine.

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, as well as dermatologic, hypersensitivity or hepatic reactions, These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

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 (see PRECAUTIONS,General and ADVERSE REACTIONS). Carbamazepine should be discontinued, based on clinical judgment, if indicated by newly occurring or worsening clinical or laboratory evidence of liver dysfunction or hepatic damage, or in the case of 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

There has been a report of a patient who passed an orange rubbery precipitate in his stool the day after ingesting Tegretol suspension immediately followed by Thorazine® solution. Subsequent testing has shown that mixing Tegretol suspension and chlorpromazine solution (both generic and brand name) as well as Tegretol suspension and liquid Mellaril® resulted in the occurrence of this precipitate. Because the extent to which this occurs with other liquid medications is not known, Tegretol suspension should not be administered simultaneously with other liquid medicinal agents or diluents. (See Dosage and Administration).

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, clarithromycin, fluoxetine, loratadine, 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.

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*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, lamotrigine, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, tiagabine, topiramate, 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 and subdermal implant 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.

Usage in Pregnancy

Pregnancy Category D (See WARNINGS).

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 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, liver, 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; very rare cases of hepatic failure.

Pancreatic: Pancreatitis.

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: Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases. Signs or symptoms may include, but are not limited to fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests. These signs and symptoms may occur in various combinations and not necessarily concurrently. Signs and symptoms may initially be mild. Various organs, including but not limited to, liver, skin, immune system, lungs, kidneys, pancreas, myocardium, and colon may be affected (see PRECAUTIONS, General and PRECAUTIONS, Information for Patients).

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, 3.2 g (a 24-year-old woman died of a cardiac arrest and a 24-year-old man died of pneumonia and hypoxic encephalopathy); children, 4 g (a 14-year-old girl died of a cardiac arrest), 1.6 g (a 3-year-old girl died of aspiration pneumonia).

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)

Tegretol suspension in combination with liquid chlorpromazine or thioridazine results in precipitate formation, and, in the case of chlorpromazine, there has been a report of a patient passing an orange rubbery precipitate in the stool following coadministration of the two drugs. (See Drug Interactions). Because the extent to which this occurs with other liquid

medications is not known, Tegretol suspension should not be administered simultaneously with other liquid medications or diluents.

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, or tablets without a release portal, should not be consumed. Tegretol-XR tablet coating is not absorbed and is excreted in the feces; these coatings may be noticeable in the stool.

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 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 D).

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 0083-0052-30

Unit Dose (blister pack)
Box of 100 (strips of 10).....NDC 0083-0052-32

Do not store above 30°C (86°F). *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 0083-0027-30

Bottles of 1000.....NDC 0083-0027-40

Unit Dose (blister pack)
Box of 100 (strips of 10).....NDC 0083-0027-32

Do not store above 30°C (86°F). *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°C-30°C (59°F-86°F). *Protect from moisture. Dispense in tight, container (USP).*

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

Bottles of 450 mL.....NDC 0083-0019-76

Shake well before using.

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

Dosage Information

	Initial Dose			Subsequent Dose			Maximum Daily Dose		
Indication	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 b.i.d. (200 mg/day)	½ 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)	½ 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 (½ tsp) q.i.d.	1200 mg/24 hr		

*Tablet = Chewable or conventional tablets
†XR = Tegretol®-XR extended-release tablets

Tegretol Suspension Manufactured by
Novartis Pharmaceuticals Canada Inc.
Dorval, (Quebec) H9S 1A9

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2000-04

REV: FEBRUARY 2000

2243-25-99A

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 16-608/S090, NDA 18-281/S039, NDA 18-927/S031, AND NDA 20-234/S017

MEDICAL REVIEW

Review and Evaluation of Labeling Supplement
(Changes being effected)

NDA (Serial Number)	**16-608, 18-281, 18-927, and 20-234**
Sponsor:	**Novartis**
Drug:	**Tegretol**
Proposed Indication:	**Epilepsy**
Material Submitted:	**Labeling supplement amendment**
Correspondence Date:	**July 18, 2000**
Date Received / Agency:	**July 19, 2000**
Date Review Completed	**December 21, 2000**
Reviewer:	**Norman Hershkowitz MD, PhD**

1. Introduction/Background

This submission is a response to a request for detailed information regarding a labeling supplement that contained a warning for Tegretol XR tablets that were missing release portals. The original labeling supplement (change being effected) for Tegretol® affects the package insert in four NDAs, each for a different formulation of this medication (tablets, chewable tablets, suspension and extended release tablets) and was submitted in four separate volumes, all containing identical information. The information, however, is only pertinent to the Tegretol –XR (NDA 20-234) but was submitted to all NDAs because of the shared package insert.

2. Labeling Changes and Justification

The changes are included in the Dosage and Administration section under a paragraph dealing with Tegretol-XR. The sentence "Damaged tablets should not be consumed" was replaced with "Damaged tablets or tablets without a release portal should not be consumed."

The additional requested information submitted was in the form of a "Field-Alert," "Field-Alert Follow-Up" and Novartis' response to a an "FDA 483" (1/18/00).

Novartis received a complaint in 1999 from one pharmacist that 8 tablets from one bottle of Tegretol XR were missing release portals. Examination of the problem revealed that the root cause of the problem was the design of the laser/feed assembly used in the drilling of the portal. An action plan was implemented to modify the tablet feed mechanism, conveyer design, and inspection in an attempt to reduce the error to — through these measures Novartis determined that it was able to reduce the defect incidence from — tabs per 10,000 produced to —tabs per 8,000,000 produced[1]. The FDA quality

[1] Data presented for 100 mg tabs but not for the 200 and 400 mg dosage forms.

inspector had noted that "although the acceptance criterion of — tablet without portal was not met, qualification was deemed acceptable."

The Sponsor presents in vitro dissolution studies as well as a pharmacokinetic modeling data to support the contention that even the use of tablets missing a portal should not adversely affect patents. The tablets use an osmotic release delivery system. Presumably water taken up by the tablet forces drug into the ambient fluids. In vitro dissolution studies indicated that although tablets lacking a portal showed a 2-hour delay in dissolution the dissolution curves could be superimposed[2]. A simulation was performed that was based upon information derived from the dissolution study as well as data available for a similar osmotic delivery system (OROS) designed for the slow release of metoprolol. This simulation is presented in the following figure. Accordingly,

Tegretol with the portal present is administered BID up to hour 264 at which time steady is achieved. Tablets lacking the portal are administered following this time. A clinically minor drop in the peak and trough serum concentrations (< 0.5 ug/ml) occurs following the first damaged tablet dose. This difference narrows with subsequent damaged tab doses. According to the simulation the new steady state peak and trough are identical to that previously achieved with

[2] It is unclear if the dissolution study was performed on all doses of the tablet (100 200 and 400 mg)

normal tablets (data not shown). If the simulation can be trusted, these changes are not clinically relevant.

The Sponsor has concluded that they have achieved a maximal optimization of the manufacturing process and cannot reduce error rate to less then tabs per 8 million. With this in mind they note they have implemented a high level of surveillance policy that will examine for this manufacturing flaw. Thus spot checks are carried out on the tablets at various stages of the manufacturing process. If a flaw is noted the whole batch of tablets will be examined. It is calculated that at minimum units will be subject to 100% inspection annually.

The above noted changes in labeling were added as part of the increased vigilance program.

3. Comments

The information provided justifies the requested labeling changes. According to the information provided by the Sponsor there is presently a very low likelihood that any tablet will contain this flaw (in 8,000,000). Nonetheless, the Sponsor has taken additional effort to increase surveillance..

The Sponsor has presented pharmacokinetic modeling data to examine a scenario in which a patient receives consecutive doses of the defective tablet. Assuming manufacturing failure estimates are correct this is a rather unlikely event. Nonetheless, they demonstrate that serum concentrations are not significantly effected.

4. Recommendation

The labeling changes are justified and should be permitted.

N. Hershkowitz MD,PhD
Medical Reviewer
J. Feeney, M.D. _____

CC:
HFD-120: Fanari/Feeney/ Katz/Oliver (Chemistry)
Main and Division Files for NDA 16-608, 18,281, 18-927 and 20-234

/s/

Norman Hershkowitz
1/25/01 08:45:00 AM
MEDICAL OFFICER

John, I have made the recomended changes. Note, this labeling supple
ment is attached to 4 NDAs. Norm

John Feeney
2/1/01 01:14:52 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 16-608/S090, NDA 18-281/S039, NDA 18-927/S031, AND NDA 20-234/S017

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

Division of Neuropharmacological Drug Products

PROJECT MANAGER REVIEW

Application Number: NDA 16-608 (S-090); NDA 18-281 (S-039)
NDA 18-927 (S-031); NDA 20-234 (S-017)

Name of Drug: Tegretol (carbamazepine) Tablets, Chewable Tablets, Suspension, and Extended Release Tablets

Sponsor: Novartis Pharmaceuticals

Materials Reviewed:

Last Approved Labeling (Dated June 2000)
Supplements 090 (NDA 16-608), 039 (NDA 18-281), 031 (NDA 18-927) and 017 (NDA 20-234) and proposed labeling

Review and Evaluation:

S-090 (NDA 16-608); S-039 (NDA 18-281); S-031 (NDA 18-927); S-017 (NDA 20-234) provide for the replacement of the sentence "Damaged tablets should not be consumed" with the following sentence in the Dosage and Administration section of labeling:

"Damaged tablets or tablets without a release portal should not be consumed."

The indicated revisions have been approved by the medical reviewer. In a line by line comparison of the last approved labeling and the proposed labeling only the change indicated above was made. I recommend approval of supplements 090 (NDA 16-608), 039 (NDA 18-281), 031 (NDA 18-927) and 017 (NDA 20-234).

_____
Melina Fanari, R.Ph., Project Manager

_____
Jack Purvis, Chief Project Management Staff

/s/

Melina Fanari
2/16/01 01:55:06 PM
CSO

Jack Purvis
2/21/01 11:18:00 AM
CSO