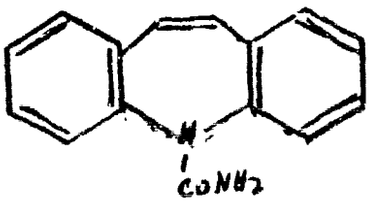
April 19, 1967

MEDICAL OFFICER REVIEW OF NDA 16-608

Product: Carbamazepine whose proposed trade name is Tegretol.

Chemical Name: 5H-dibenz-(b,f)-azepine-5-carboxamide.

Structural Formula:



Proposed Dosage Form:

Tablet (200 mg of the active drug). The dosage recommended is quite variable, anywhere from 200-1200 mg/day, depending upon the dose required to relieve the pain. Minimal effective doses are recommended. The drug is strictly prescription.

I. The drug is proposed exclusively for use in patients with trigeminal neuralgia (tic douloureux).

III. The only route of administration is oral.

IV. Related Drugs:

The most important related drugs are Ensidon (Opipramol HCl) and Imipramine (Tofranil).

Ensidon, like Tegretol a dibenz azepine, is a tranquilizer and mood elevator drug. It has an IND (405) and an NDA (13-654). The IND was discontinued because of a question of teratogenicity and other toxic reactions and no especially significant efficacy. The NDA was incomplete for similar reasons. The toxic reactions include dizziness, tremor, dermatitis, leucopenia, altered hepatic functions, alopecia, Stevens-Johnson syndrome, etc. - reactions similar to some of those seen with Imipramine and Tegretol.

The significant adverse reactions seen with Imipramine which is an iminodibenzyl anti-depressant drug are spontaneous profuse perspiration, dizziness, mental confusion, insomnia and gastro-intestinal symptoms. The occurrence of eosinophilia, urticaria, angioneurotic edema and pruritis suggest that Imipramine can cause sensitization. There have been a few reports of leucopenia and transient jaundice and blood cell counts and liver function tests have been recommended for patients receiving the drug.

Imipramine tends to prolong atrio-ventricular conduction time, manifested by a first degree A-V block. Neurologic reactions include a Parkinson-like syndrome, myoclonia, hyper-reflexia, muscular fasciculation and a tremor of the extremities present at rest and not attenuated by purposeful movements and sometimes of such intensity that it prevents standing or walking. The drug may also cause brief generalized tonic muscular contractions resulting in hyper-extension. Generalized convulsions occurred in one patient, indicating the need for cautious use in epileptic patients.

Orthostatic hypotension is not uncommon, especially in hypertensive patients. The drug enhances pressor responses to levarterenol and has no ganglionic blocking effect in therap doses. It is contra-indicated in patients with congestive h failure, angina pectoris and paroxysmal tachycardia. Becaus its atropine-like action, it has to be used with caution in patients with glaucoma, pyloric stenosis or benign prostatic hypertrophy. It cannot be used with or for at least two wee after discontinuing the use of a mono-amine oxidase inhibito The drug has to be used cautiously in non-hospitalized serio depressed patients in whom the possibility of suicide is a major problem. Imip[illegible]ne has been approved since 1959 and stated to be an effective agent in the treatment of endogeno and exogenous depressions. Many of the adverse reactions described for Imipramine are also seen following treatment w[illegible] Tegretol.

V. Pharmacology:

Please refer to the review of Dr. Farber whose conclusion was that the margin of safety for the drug was rather narrow. No clear-cut organ toxicity has been demonstrated in subacute and chronic studies.

Analysis of the one year dog study by me revealed a mild suppression of the white cells of the marrow at the higher dosage levels which reached a maximum at 13 weeks and apparently disappeared despite continued drug therapy. Reproduction studies have indicated no teratogenicity.

It is my feeling, based upon the pharmacologic study that while Tegretol is a moderately toxic drug most of the side effects will disappear either by lowering the dosage of drug or by adaptation on continuous therapy. This will be discussed further under "Clinical Adverse Reactions".

VII. Evaluation of Efficacy:

Tegretol has been approved in fifteen foreign countries. These include England (1963), Switzerland (1963), Holland (1964), Australia (1964), France (1964), Germany (1965), Denmark, Austria, Norway, Belgium, Greece, South Africa (1965), Finland, Sweden (1966).

The drug was developed by Schindler and because of its pharmacologically demonstrated inhibition of the linguo-mandibular reflex, it was first tried clinically in the treatment of trigeminal neuralgia by Blom of Sweden. He concluded that it was more effective with less side effects than Diphenylhydantoin, the most effective previous drug. The applicant states that the drug has been used in over 1600 patients in foreign countries and close to 1200 patients in the United States. The foreign literature is fairly extensive on the use of Tegretol in trigeminal neuralgia. The drug has also been used extensively in foreign countries for the treatment of epilepsy. Applicant has included in the NDA a bibliography of all usages of Tegretol published and the number of papers is well over 150 references.

The clinical studies can be broken down into two types: those that have been published and those that are unpublished and tested, mostly in the United States. The numbers of patients treated for trigeminal neuralgia in published studies are 1616, while the number of patients treated in unpublished studies (mainly in the U.S.) are 548, giving a total of 2164 patients treated. The foreign and domestic studies are further subdivided into those that are controlled and those that are uncontrolled. The total number of controlled studies was 10 and uncontrolled, 74 comprising a total of 84 major studies.

Efficacy has been generally evaluated in terms of four results: excellent, where there is complete relief of pain; good, where there is complete relief of pain but with occasional numbness in the previously painful area; fair, where there is moderate relief of pain with occasional exacerbation but usually permitting pursuit of normal activities and poor, where there is only slight or no relief of pain, requiring further medical or surgical treatment.

The results of the major studies indicate that in all 10 controlled studies and in 73 of the 74 uncontrolled studies significant clinical efficacy was demonstrated. Of the 47 published studies of which 7 were controlled and 40 uncontrolled, all 47 demonstrated

There were five fatalities from irrever
This was clearly drug-related and appea
toxic reaction that has been encounter
Carbamazepine. Two of the reactions oc
treatment and one occurred after 10 day
reaction appears to be related to indiv
the drug in view of the small incidence
marrow injury. In the majority of thes
there was insufficient monitoring of th
counts and platelet counts during treat
the patients may have been receiving ot
drugs at the same time. The percentage
anemia observed represents .07% of all
percentage of leucopenia .87%. It is o
the material to note that many cases of
improved while the patients continued t
suggests that the pathogenesis of the l
occurred not infrequently may be quite
fatal reactions (aplastic anemia) obser
the labeling will have to contain caref
to minimize the dangers of the drug.

Toxic reactions were not a simple function of dosage. In fact, in many instances there was no correlation between the dosage and the reaction. However, the number of reactions did appear to rise when the dosage was 800 mg/day or higher.

The applicant has reported a total of 28 deaths that occurred during the course of Tegretol therapy. Of these, 5 were realted to severe bone marrow injury and/or severe thrombocytopenia and are clearly drug-related. There are 11 cases of patients with a history of previous coronary artery disease or other organic cardiac disease who succumbed during therapy. In this group it is not clear whether the reaction is, in fact, drug-related, whether the drug aggravated a pre-existing disease or whether the drug induced de-noveau a disease state. Of the three possibilities, the latter appears to be the least likely. Nevertheless, the drug should not be recommended for use in patients with a history of either coronary artery disease, myocardial infarction or other serious organic heart disease. Twelve deaths occurred that were quite clearly unrelated to the drug and, as this is a very elderly population that is receiving Tegretol for tic douloureux, it is not unexpected. For a detailed breakdown of all the adverse reactions, the reader is referred to Volume 44 of the New Drug Application.

What is particularly important is the number of adverse reactions that are so severe as to require discontinuation of the drug.

significant efficacy of the new drug. The 47 major published studies involved 1616 patients with trigeminal neuralgia and the dosage ranged from 100-2000 mg and averaged 400-800 mg. The duration of dosage varied from 2 days to 2½ years. The majority of the patients were treated for periods from 1-6 months. Favorable results, excellent or good were observed in the majority of patients in all 47 studies that were published. The drug was effective in 50-100% of the patients in all studies and in 75-100% of patients in 32 studies. Contrariwise, the published results of the use of the drug in other painful states was not impressive. In fact, it would appear that Tegretol is quite specific in its efficacy in trigeminal neuralgia. The postulated mechanism of action in trigeminal neuralgia (and one which derives support from basic pharmacologic studies) is a blocking of polysynaptic pathways in the central nervous system.

In all the seven controlled studies that were published, Tegretol was superior to the placebo, and in one study was also superior to Dilantin. Two of the studies that were subjected to statistical evaluation showed P less than 0.05. From 63-100% of patients treated had favorable results with an average of 82% compared to 0-26% with an average of 15% on the placebo. In most patients the drug produced rapid complete relief of pain often within 24-48 hours and, in many cases, the patients had been unresponsive to other therapy. A majority of the physicians felt Tegretol was superior to Dilantin in the onset of action, long term effectiveness and overall tolerance. The seven major U.S.A. controlled studies were done by Amols (10 patients), Dalessio (11 patients), Rockcliff (9 patients), Sturman (8 patients), Knighton (27 patients), Saith (11 patients) and Sturman (29 patients). Eighty-three percent of all patients had a good therapeutic response on the drug, while only 14.4% responded to placebo.

As regards uncontrolled major U.S. studies, there were 5 that were published and 33 unpublished. The number of patients in the published study was 148 and the number in the unpublished, 469. Efficacy was shown in 77% of the published group and 80% of the unpublished.

Adverse Reactions: Of 4,490 patients treated with Tegretol, there were 1,083 reactions (24.1%). If one analyzes the reactions by systems, 15.4% of reactions involved the neurologic and sensory system, 4.3% the digestive system, 2.3% skin, 1.2% hemopoietic, .29% genito-urinary, .27% cardiovascular, .16% metabolic, .11% hepatic and .09% other. The most common reported reactions were drowsiness, ataxia, vertigo, dizziness, G.I. disturbances, nausea, rash and leucopenia. Hypotension and abnormal figure liver function were uncommon.

Under these conditions, the usage of the drug must be regarded as a treatment failure. This has occurred in approximately 13% of all treated patients, a relatively low incidence. The reactions which have been most often incriminated are ataxia or unsteadiness, severe dermatitis, vertigo, abnormal gait, persistent somnolence and severe leucopenia.

Abnormal Laboratory Findings:

Hepatic Function Tests:

The tests were broken down according to the duration of treatment. There were 273 tests done on patients treated less than one month, 293 tests on patients treated 1-3 months, 440 tests on patients treated 3-12 months and 216 tests on patients treated 12 months or more. Thus, a total of 1222 liver function tests were done. The number of abnormal tests did not appear to be clearly correlated with the duration of treatment. The tests most often abnormal were alkaline phosphatase and serum bilirubin. There were scattered abnormalities seen in SGOT, SGPT, cephalin flocculation, thymol turbidity, Vandenbergh, bromsulphalein and unspecified tests. Of the liver function tests performed, the range of abnormalities was approximately 12-18% and the abnormalities were not serious, indicating that the drug has a mild hepatotoxic potential which, while not serious, warrants monitoring of the liver function tests during therapy.

Hematologic Tests:

The abnormalities of these tests run higher than with the liver function tests, ranging as high as 55% in the group treated for 12 months or more. However, most of these reactions are self-limited and controllable either by lowering the dosage or are not of sufficient concern to require withdrawal of the drug. The serious reactions are very few and have been previously described.

Renal Function Tests:

Appear to run about 20-30% which show some alteration on microscopic examination, some cases of glycosuria and proteinuria and a mild alteration in the BUN. Again, most of the changes observed were either transient or controlled on lower dosage or had no long-range implications regarding renal damage.

Miscellaneous Tests:

Included blood pressure, pulse, EKG, plasma proteins and non-protein nitrogen tests. Although the percentage of abnormalities of these tests is fairly sizable, the abnormalities themselves qualitatively and from the viewpoint of clinical significance do not appear to be of much concern.

Geigy has submitted a report from Dr. [redacted] of Geigy Co. in Canada which tells of 20 epileptic patients who had received Tegretol and who had examination of the eyes for possible changes. Nine of the 20 are reported to have some abnormalities, e.g., clouding or opacities of the lens, cornea and some degenerative changes in the retinal pigment layer. There were no baseline eye examinations, no controls and the patients were on multiple drugs, including phenothiazines so that the linkage of the observed findings to the treatment with Tegretol was most fragile. Nonetheless, because of this and because of incomplete chemical controls and stability data, it has been decided to declare the application incomplete and to request additional data on chemical controls and additional examinations of the eyes of approximately 100 patients and a comparable number of controls to rule out the damaging effects of Tegretol on the eyes. At the moment, there appears little evidence to suggest that the drug is damaging to the eye and in animals pathologic studies of the eyes revealed no abnormalities. Epileptic populations representing groups of people treated with multiple drugs for many years are impure ones and difficult to evaluate.

VIII. Literature Reviewed:

Many papers from the more than 100 articles referred to were reviewed and practically all investigators reached a similar conclusion that Tegretol was a remarkably significant new drug for the treatment of trigeminal neuralgia, far better than any drug previously available. Moreover, the effects were longer lasting than with phenytoin and, after chronic administration, anywhere from 10 to 60% of patients were still receiving benefit from the drug. It was apparent that the investigators felt that it was particularly useful in the elderly population and that any patient should be tried on the drug prior to trying the more radical surgical approach, results of which were far from perfect. Adverse reactions reported in the articles read were similar to those delineated above.

IX. Labeling Evaluation:

Because of the incomplete letter which will issue in the near future, all comments regarding labels and labeling are premature and will have to await the arrival and evaluation of the additional data requested in the incomplete letter. At that time we will go into the labeling information in considerable detail.

X. See Volume I for copies of conferences, telephone conversations, etc. related to this New Drug Application.

XI. Summary and Conclusions:

In my opinion, the development of Tegretol for the treatment of trigeminal neuralgia represents a significant breakthrough drug in a field where no truly effective medication existed before. It has been estimated by various clinical investigators to whom I spoke, including Dr. [redacted] of the [redacted], that this drug is at least five times as effective as Diphenylhydantoin (Dilantin). Several investigators have stated that there are fewer side effects with Tegretol than Dilantin.

To evaluate an outstanding drug such as Tegretol for efficacy is a relatively simple matter. We find that statistical manipulations or extensive double-blind controlled studies are unnecessary when the efficacy of the drug is so clearly superior to placebo and where the medication so far exceeds any previously known. Such sophisticated studies become increasingly necessary as the degree of efficacy decreases. To detect a small superiority of a new drug over the placebo is, indeed, a difficult task. The amount of data presented by Geigy in support of the efficacy of the drug in trigeminal neuralgia is, in my opinion, both enormous and substantial.

As regards the safety of the drug, it is no more toxic than other anticonvulsive drugs and, in fact, may be less toxic than Dilantin and many of the others. This has been stated by many of the investigators. The most serious side reaction has been discussed above, namely, the fatal aplastic anemia and it is felt that this occurs rarely and, in many instances, can be prevented by a carefully worded special warning in the labeling. This would include pre-treatment blood and platelet counts so that patients with thrombocytopenia or leucopenia or severe anemia would not be treated with the drug. In addition, it would be clearly stated that complete blood counts and platelet counts at regular intervals were mandatory to preclude severe

or fatal bone marrow injury and that if thrombocytopenia, severe anemia or severe leucopenia developed, the drug should be stopped. In addition, the physicians should be instructed to inform their patients about the hazardous signs of early aplastic anemia, including tongue ulcers, sore throat, ecchymoses of the gums, lips or skin, easy bruising, purpuric spots, tarry stools or frank hemorrhage from any site. In the event of the occurrence of any of the latter symptoms, the patient will be instructed to stop the drug at once and to notify the physician immediately. Finally, the physician should be warned that the drug should not be given concomitantly with any known agent causing bone marrow injury, for example, radiation or drugs known to be toxic to the bone marrow. As regards the other toxic reactions, these have been delineated above and 13% will require withdrawal of the drug and the remainder can be handled by either lowering the dosage or by adaptation to the drug.

Tic douloureux, a disease which is characterized by stabbing, burning or lightning-like pain in the region of the fifth cranial nerve, is one that causes immense suffering for the victim who finds life converted into a nightmare of continuous unpredictable attacks. Any medication that is effective in this disease, even for a short duration, is a significant advance. In the case of Tegretol, it appears that a sizable number of patients will be helped for long periods of time.

Patients treated with Tegretol fall into one of the following groups:

1. The pain is totally controlled and the patient goes into a remission.

2. The pain is totally controlled but the patient requires continuous drug therapy.

3. Pain is incompletely controlled on the drug.

4. Pain is controlled initially and then there is escape with recurrence of pain.

5. Patient is a therapeutic failure.

6. Drug is discontinued because of severe and continuing adverse reactions.

More data are needed to fill the gaps in our knowledge regarding the precise incidence of each of the above reactions. However, this information, while of considerable scientific interest is not essential for the approval of the New Drug Application. There is more than ample data indicating superior efficacy in the treatment of tic douloureux.

It is felt that neither of the requests contained in the incomplete letter soon to be written is sufficiently strong to act as a serious barrier to the approval of this New Drug Application. Assuming the requisite chemical control information is supplied and the eye studies in humans show no serious adverse reactions, the prosector strongly recommends approval of a significantly new drug in the treatment of trigeminal neuralgia. The drug has already been approved in 14 other countries, beginning in 1963, and none of these countries has seen fit to remove it from the market because of toxic reactions. It seems to me that Tegretol will become the standard reference drug in the treatment of trigeminal neuralgia in the future. FDA should assume leadership in the rapid processing and approval of this extraordinary new drug.

Morris A. Weinberger

Morris A. Weinberger, M.D.

cc:
Dup NDA
Trip NDA
OND
DND
ODS
DND/MAWeinberger/smr
4/20/67

October 25, 1967

MEDICAL OFFICER REVIEW OF NDA 16-608

Supplement

Vols. 48.1 and 48.2

The submission is dated October 10, 1967 and includes the following material relative to the NDA: an introduction and background discussion of the eye cases, a summary of the findings in treated patients and controls, individual case reports on treated patients and controls in trigeminal neuralgia and epilepsy and, finally, revised prescribing information. The latter changes were in conformity with suggestions made at a meeting here at FDA attended by Drs. T. P. S. Watts and McKeon on April 12, 1967.

The data submitted were summarized case by case per investigator and with a separation of treated cases (trigeminal neuralgia and epilepsy) and controls. In essence, the submission summary consists of raw data with no analysis of the incidence of the various lesions, that is, the abnormal findings in the treated groups as compared to the control group. This study was referred to Dr. Howard Bernstein who is an ophthalmologist with experience in abnormalities of the eye caused by drugs. Dr. Bernstein analyzed the abnormalities and separated them into the treated and control groups. The data were compiled on 83 patients who were treated for trigeminal neuralgia, 52 patients who were treated for epilepsy and 91 controls. This makes a total of 226 patients. The table that follows lists the abnormalities encountered and indicates the incidence in the treated and control groups.

Abnormal Observation	Treated	Controls
1. Hyperemia	7	1
2. Blepharitis	4	0
3. Corneal opacities	9	1
4. Cataracts:		
a. Nuclear sclerosis	19	6
b. Posterior subcapsular	5	1
c. Incipient cataracts	3	0
5. Macular mottling or stippling	7	0
6. Peripheral retinal degeneration	4	1
7. Vascular attenuation or arteriosclerotic changes	7	3

Dr. Bernstein noted that the other observations were either too few in number or equally divided among the control and treated groups. His conclusions were as follows:

1. All observations are consistent with naturally occurring ocular abnormalities. There does not appear to be any obvious qualitatively unique drug-related abnormality.

2. There is a higher incidence of the observations noted under "Results" in the treated group than in the control group and this appears to be higher than the ratio of treated and control patients.

I might add at this point, however, that a graph of the population distribution of treated and control groups reveals dissimilar age characteristics with the treated groups skewed toward the higher age groups and the control groups skewed toward the younger age groups. I discussed this matter with Dr. Bernstein and he agrees that this could account for some of the differences that were noted in treated and control groups. In other words, with the higher incidence of older people one would expect more lesions than in a younger age group as seen in the controls. Dr. Bernstein concluded that the differences were probably not significant, but that the type of study done would not allow an unequivocal decision regarding this. He stated that it would have been more desirable to have done a study in which the patients received pretreatment baseline eye examinations and examinations at suitable intervals after treatment began and that these examinations should be done double blind and with a control group.

I am in agreement with Dr. Bernstein's conclusions. The evidence available does not support a conclusion that the drug has induced any eye abnormalities and therefore the question originally raised by Dr. [redacted] study in Canada seems to be resolved.

Applicant has submitted revised prescribing information as discussed at the conference of April 12, 1967. We plan to recommend some additions and alterations. The most important addition to be recommended is an important boxed warning to precede the first paragraph of the package insert in which the fatalities from aplastic anemia are cited and the recommendation made that frequent complete blood and platelet counts should be done in order to detect serious bone marrow injury <u>early</u>. We are also going to request applicant to augment the description of the pharmacologic and toxicologic findings in the animal studies and we also will recommend that a paragraph be added on therapeutic responses to Tegretol in tic doloureux clinically. These responses include:

1. Complete symptomatic relief while on the drug.

2. Partial symptomatic relief while on the drug.

3. Complete remission which continued after cessation of drug therapy.

4. Partial or complete symptomatic relief initially with relapse with time.

5. No response.

6. Drug withdrawal because of toxicity.

A meeting has been arranged with the applicant for Wednesday, October 25, 1967 at 2:00 pm and it will be attended by Dr. McKeon and Watts of Geigy and members of the staff of the Division of Neuropharmacologic Drugs.

Morris A. Weinberger, M.D.

cc:
NDA Dup., Thlp.
M-100
M-120
M-300
M-120/MWeinberger/smr
10/25/67