December 19, 1967

PHARMACOLOGIST REVIEW OF NDA 16-608

Supplement of December 14, 1967

Sponsor: Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502
(AF 25-403)

Drug: Tegretol

The recently revised labeling for Tegretol has been reviewed. We have no objections to this labeling and feel that it accurately summarizes the pharmacology and toxicology of this agent.

T. H. Farber, Ph.D.
Div. of Neuropharmacological Drugs

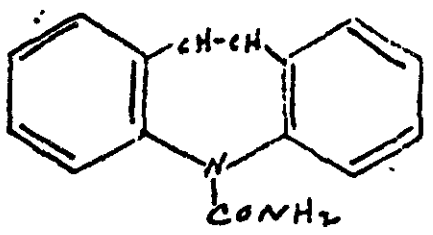
cc:
Orig NDA
Dup NDA
Trip NDA (NY)
M-100 CND
M-120 DND
M-300 CND

DND/THFarber:jc
12/19/67
R/D initialed by DND/Dr. D'Agostino 12/18/67

Pharmacologist Review of NDA 16-608
Supplemental NDA, July 23, 1973

Sponsor: Ciba-Geigy Corporation
Summit, New Jersey 07901

Drug: Tegretol (carbamazepine)
5H-dibenz[b,f] azepine-5-carboxamide



Category: Anticonvulsant- For treatment of epilepsy

Related Drugs: Tofranil - Dilantin

NDA 16-608

Formulation: tablets 200 mg

Previous Reviews:

Previous reviews for . are: March 26, 1964-
November 10, 1964 - October 4, 1966 - November 2, 1966
January 25, 1967 - November 29, 1967 - January 18, 1968
and for NDA 16-608 April 20, 1967 and December 19, 1967

Acute Oral toxicity:

Hazleton Laboratory	Stenger and Roulet report
LD_{50} mg/kg (confidence limits)	LD_{50} mg/kg
Mice 1150 (1020-1300)	3730
Rats 3830 (2390 -6130)	4025
Rabbits approx 1500	2680
Dogs >5620	
Guinea Pigs	920

Labored respiration, depressed righting reflex, depression, clonic and tonic convulsions, coma, pupillary constriction or dilatation and tachycardia were observed.

Subacute and Chronic toxicity:

Rats:

Four weeks- groups of 10 rats given 0, 50, 100, 200, 500 or 1000 mg/kg/day orally. Decreased body weight at all levels, mortality at HD. Increased hepatic fat deposition at 200 mg/kg/day with enlargement of hepatic cells at 500 and 1000 mg/kg/day.

Twelve weeks- groups of 40 rats given 0,50,100 or 200 mg/kg/day orally. Half of each group permitted 1 month recovery period and killed. Slight decrease in body weight at all levels, no mortality. Increased liver weight in HD males at 12 weeks attributed to drug but apparently not seen in animals given 1 month recovery period. At 12 weeks sacrifice a dose-related incidence and severity of hepatic changes were found in all treated groups consisting of cellular and nuclear enlargement, granularity of cells and a few foci of necrosis. Livers of animals on recovery period were comparable to controls.

four weeks-groups of 20 m and 20 F were given 0,50,100,200 mg/kg/day
ge. Mortality occurred at MD and HD. Fatty infiltration of liver
ppeared to be dose related was seen in males and less obvious in
.

wo weeks-groups of 25/sex/level received drug 7 days/week by gavage
,200 or 400 mg/kg/day. High dose rats showed general loss of condition,
degrees of pilo-erection and alopecia. Dosing was followed by
period of either excitability or mild stupor. MD rats showed
signs as HD with females being more susceptible. During the
onth some females showed temporary ataxia after dosing. Growth
ion in both sexes in HD and females in MD which was not correlated
duced food intake. Increased mortality in HD, 6 males 20 females
pared to 5 controls. Urea and SGPT values elevated in male HD rats,
pecially at 26 weeks. Liver and kidney weights were significantly
creased in both sexes of MD and HD rats. Increased heart weights
curred in both sexes of HD and LD females. Liver damage seen in centilobular region in MD and HD, which was dose-related. One third of rviving HD males showed inhibition of spermatogenesis. No significant anges were observed in LD (50 mg/kg) animals.

Dogs:

Fifty two weeks- 4 female mongrel dogs were given 100 mg/kg/day orally 5 day/week. No controls. No changes observed.

Ninety days - groups of 3 dogs/sex/level were given 0,50,100 or 200 mg/kg/day orally 5 days/week. Slight weight loss at HD. No changes in hematology or clinical chemistry or in organ weights. Gross pathology revealed a grey discoloration in urinary bladder in dogs at all dose levels but no histologic indications. Histopathology was similar to controls except for HD dogs, which showed swelling of kidney tubular cells in 1, slight enlargement and vacuolization of hepatic cells in 1, slight to moderate hepatic hematopoiesis in 2, testicular atrophy in 1, and decreased erythropoiesis in the marrow in 1.

Fifty two weeks- groups of 3 dogs/sex/level were started on levels of 0, 50, 150 or 300 mg/kg/day. On day 11 HD reduced to 150 mg/kg/day and MD reduced to 100 mg/kg/day. Toxic signs were sedation, vomiting, ataxia, prostration and rigidity at 300 mg/kg and one death at 300 mg/kg. Sedation was seen at 150 mg/kg. Another dog on 150 mg/kg died after 6 months. Growth inhibition occurred early in study but returned to normal by the sixth month. No eye changes were observed. Slightly higher alk. Phos. in the dosed dogs from the 24th week, however these values were in the range of accepted normality. A brown staining of the urinary bladder mucosa occurred in all dosed dogs. The 300 mg/kg dog that died had necrosis and fatty changes of liver and kidney. The 150 mg/kg dog had a fatty liver. No tissue changes of a drug-related nature was seen in the surviving dogs but a deposition of brown pigment was seen in the urinary bladder.

Reproduction and Teratology Studies:

The following studies were conducted at dosage levels of 0, 48 or 192 mg/kg via diet.

Rats:

1) Ten males and 20 females. Males treated for nine weeks and females for two weeks prior to mating. Six or seven females from each group were killed on day 14 or 15 of gestation and remainder allowed to litter normally.

2) Ten males and 20 females. Drug was administered from day 6 through day 15 of gestation. Females were killed on day 19 or 20 of gestation. Visceral and skeletal examination of fetuses were done.

3) Ten males and 20 females. Drug was administered from day 15 of gestation to weaning of the pups. A 21 day lactation period was allowed.

Mice:

Seventeen males and 17 females. Drug administration was from day 6 through day 15. Females were killed on day 18 of gestation. Fetuses were examined for external, visceral and skeletal defects.

"Administration of 0, 48 or 192 mg/kg/day had little effect on the reproductive process in the rat or mouse except that in the case of the rat, the high dose caused a decrease in the body weight gain of the pups during lactation and the low dose had the same effect in the mouse studies." (Pharmacologist review of IND 1250, November 29, 1967)

Additional studies at higher dosage levels.

Rats:

1) Groups of 7 and 16 females were given 250 and 500 mg/kg/day orally on days 7 through 16 of gestation. Bilateral kinking of ribs was seen in 2 newborn of the 250 mg/kg/day group.

2) Groups of 10-20 females were given 300-650 mg/kg/day orally for 4-14 days during pregnancy. Increased number of abortions occurred at 400 mg/kg and higher. Cataracts and doubtful eyes were seen at 500 mg/kg and higher. Unspecified microscopic malformations occurred in the 650 mg/kg groups.

Mice:

1) Females were given oral doses of 300-650 mg/kg for 3-14 days. Decreased fertility, decreased numbers of fetuses and increased resorptions occurred at 400 mg/kg and higher. Fetal anomalies were seen at 450 mg/kg and higher doses.

2) Females were given 300-450 mg/kg I.M. for 2-4 days in early pregnancy. Decreased fertility and a slight increase in resorptions were seen at all levels with fetal anomalies at 450 mg/kg.

Rabbits:

Rabbits were given the drug at 225-450 mg/kg at either the 5th or 6th day of pregnancy and continued through the 12th day. No malformations were seen, however, decreased numbers of fetuses, increased resorptions and decreased fertility was seen in all groups. The 450 mg/kg level was toxic.

Evaluation:

Tegretol is an approved drug for treatment of pain associated with trigeminal neuralgia. This supplemental application is for the treatment of epilepsy.

Summaries of the acute, subacute and chronic toxicity, reproduction and teratology studies are in this review. Chronic toxicity studies of 1 year duration in rats at dosage levels of 50, 200 and 400 mg/kg/day and in dogs at 50, 100 and 150 mg/kg/day were conducted. In rats increased mortality occurred at 400 mg/kg/day and at 200 and 400 mg/kg/day the
imals growth was depressed, showed periods of excitability or mild
ipor, pilo-erection and alopecia and a dose-related damage in the
itrilobular region of the liver. No significant changes were observed
rats receiving tegretol for one year at 50 mg/kg/day. Sedation,
niting, ataxia and prostration was exhitited in dogs receiving 300
/kg/day. One dog died on each level of 150 and 300 mg/kg/day. No
ig related tissue changes were seen in surving dogs that received
ily doses up to 150 mg/kg/day for one year. Dogs at all levels showed
a lipofuscin like pigment in the urinary bladder.

Reproduction studies at dosage levels of 48 or 192 mg/kg caused a decrease in the body weight gain of pups during lactation at 192 mg/kg in rats and in mice at 48 mg/kg. Bilateral kinking of ribs was seen in 2 newborn rats at dosage levels of 250 mg/kg, increased number of abortions at 400 mg/kg. A dose related decrease in fertility was observed in rabbits.

Metabolic studies of tegretol have lead to the identification of a 10-11 epoxide derivative in urine of rats and man. It has been postulated that expoxides are responsible for carcinogenic activity of parent hydrocarbons. See attached memo.

Sponsor has submitted references to support their contention that the tegretol epoxide is not carcinogenic. Among the references were two pertaining to mutagenic tests in the mouse and hamster. In a dominant lethal study, mice were given single oral doses of either 0,600 or 1200 mg/kg of tegretol and then mated to different groups of untreated females for 7 consecutive weeks. Only effects observed was on low dose at mating weeks # 1 and 7 which showed a high incidence of embryonic deaths. Chinese Hamsters were given oral doses of tegretol at either 400, 800, 1600 or 3200 mg/kg for 2 consecutive days followed by 10 mg/kg IP of colcemid. No chromatid-type or chromosome-type aberrations were observed on the somatic cells.

The chemical reasons why sponsor believes that this epoxide is not carcinogenic is that in order to be carcinogenic the epoxide must be capable of functioning like an alkylating agent. When the tegretol epoxide is heated in hydroxylic solvents it can be recovered unchanged, therefore, it is a stable compound and does not change into an alkylating like agent.

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In our opinion, there are no short term tests for predicting carcinogenecity at the present time. Also, it has not been established that the dominant lethal or other mutagenic tests are reliable to predict the carcinogenic potential of a compound.

Sponsor's proposed use of tegretol for the treatment of epilepsy would involve long term use of the drug and also probable use early in life. Duration of animal studies have been for only one year. A one year study in rats is not sufficient exposure to determine the carcinogenic potential of tegretol. Since 1966 the preclinical guidelines have recommended 18 month studies in rodents. The current thinking is for 2 years plus or lifetime studies in rodents.

Recommendations:

Since tegretol is now proposed for chronic administration for treatment of epilepsy this NDA is deficient in that the one year rat study submitted is not sufficient to determine if tegretol or its epoxide metabolite has carcinogenic potential.

Walter H. Hansen

cc:
Orig
Dup
BD-100
BD-120
BD-120/WHansen 11-2-73
Trip
FT.cld/11-29-73
Init:VGlocklin/11-27-73

Walter H. Hansen
Marc.. 20, 1974

PHARMACOLOGIST REVIEW OF NDA 16-608
Addendum to review of November 2, 1973

SPONSOR: Ciba-Geigy Corporation
Summit, New Jersey 07901

DRUG: Tegretol (carbamazepine)

CATEGORY: Anticonvulsant - for treatment of epilepsy

PREVICUS REVIEW: November 2, 1973

PERTINENT MEMOS/TELEPHONE CONVERSATION:

Memo of Dr. Barrett Scoville's to Acting Director, OSE, March 19, 1974.

Telephone conversation of March 18, 1974 - Mr. Walter H. Hansen to Dr. James Sontag.

EVALUATION:

In view of the above mentioned memo and telephone conversation with Dr. James Sontag of the National Cancer Institute the preclinical data for this NDA was reviewed again.

The one year chronic toxicity rat study was re-evaluated with particular emphasis on tumor incidence. There was no evidence to indicate that carbamazepine elicited any carcinogenic potential in this study. By present standards one year studies in rodents are not adequate to detect weak carcinogens, however, changes would have been observed by one year if compounds are potent carcinogens.

During the metabolism of carbamazepine an epoxide derivative is formed. It has been postulated that these epoxides may play an important role in carcinogenesis. No further information is available; however, the National Cancer Institute is not interested in funding any money to study either the metabolism or long term carcinogenic studies with carbamazepine.

RECOMMENDATIONS:

Since carbamazepine showed no remarkable carcinogenic potential in the one year rat study and recommendations have been made to limit its use to an adult population, the preclinical data can be considered adequate for approval of this NDA for a new indication for an already marketed drug.

Walter H. Hansen

Orig
Dup
HFD-100
HFD-120
HFD-102:D'Aguanno
HFD-120:WHansen:3/20/74
[illegible]
FT:cm:3/20/74