There are two other issues that warrant comment.

In various places in their proposed labeling, the sponsor states that there is a therapeutic plasma range for zonisamide, and draws explicit links between a specific range of plasma levels and a specific change in seizure frequency. I have not seen these data analyzed (although Dr. Mahmood has written a brief description of the sponsor's conclusion -see page 9 of his 12/12/97 review), and I have generic objections to the approach the sponsor has likely taken to attempt to establish such a relationship. Nonetheless, a review of this data may be warranted at some point.

The other issue is one that Dr. Burkhart and Dr. Mahmood have commented upon.

The sponsor has submitted the results of a pharmacokinetic study in healthy volunteers in which doses up to 400 mg/day were administered for 35 days. The mean creatinine began to rise by day 8, and reached a peak of between 1.30-1.37 by Day 29 (last on-drug value reported). It began to decrease on Day 38, and essentially returned to baseline levels by Day 56 (see table of findings in Dr. Burkhart's review, page 9). This "finding" is difficult to understand, especially given the development cohort of over 1500 people in which no cases of serious renal injury were noted (of course, the slight increase in mean creatinine in the controlled trials in the zonisamide patients is perhaps more interesting in light of these results). In any event, we should ask the sponsor to discuss the results of this PK study.

RECOMMENDATION

In my opinion, the application can be declared Approvable, but the sponsor must do extensive work to repair the deficiencies in the safety data presentation, as discussed above, and by Dr. Burkhart. Further, they must do additional work to better establish the dosing regimen that should be recommended or described in labeling.

For these reasons, I recommend that the Approvable letter with attached draft labeling included in this package be forwarded to the firm.

APPEARS THIS WAY
ON ORIGINAL

/S/

Russell Katz, M.D.

cc:
NDA 20-789
HFD-120
HFD-120/Katz/Leber/Ware/Sherry/Burkhart
HFD-710/Sahlroot

APPEARS THIS WAY
ON ORIGINAL

APPENDIX I

RESPONSE TO APPROVABLE LETTER

FDA's comments are reproduced below in bold text, followed by our response.

Biopharmaceutics

1. **We ask that the following final dissolution methodology and specification be adopted for zonisamide capsules, 100 mg:**

   Apparatus:
   Agitation:
   Medium:
   Specification:

   We propose to maintain the specification at Q Upon examination of stability data for zonisamide lots 694Z02, 694Z03, and 694Z05, we found that there Recently, Athena manufactured the first commercial scale batch (number 694Z06). In the testing of the bulk capsules, there were This indicates that there is sufficient discrimination in the Q We will continue to monitor the dissolution testing.

2. **In the study entitled, "A Clinical Pharmacokinetic Study of CI-912 (zonisamide) in Patients with Varying Degrees of Renal Function," you indicated that zonisamide is renally secreted. Specifically, the renal clearance of zonisamide is 3.4 mL/min in normal volunteers. This clearance value is much lower than the glomerular filtration rate (GFR), and, therefore, does not support the conclusion that zonisamide is renally excreted *(secreted?)*. Please comment on this finding.**

   Studies with ^{14}C labeled zonisamide have shown that on average about of the administered radioactive dose was excreted in urine and about 3% was excreted in feces indicating that the major route of elimination is by the renal pathway. Linear regression of zonisamide renal clearance and the creatinine clearance indicates correlation between the two variables, but a positive Y-intercept indicates tubular secretion (a phenomenon common with sulfonamides[1], confirmed by co-administration of probenecid and sulphonamides). The renal clearance value of 3.4 mL/min suggests that zonisamide undergoes significant tubular reabsorption, a process documented to occur with some sulfonamides[1]. This reabsorption would negate any impact of renal secretion on the overall excretion of the drug by the kidney.

[1] Vree et. al. "Pharmacokinetics and Mechanism of Renal Excretion of Short Acting Sulfonamides and N_4-Acetylsulphonamide Derivatives in Man" *Eur. J. Clin. Pharmacol.* 20: 283-292 (1981). (Submitted in NDA 20-789, Volume 51, Page297).

Submitted to Dr. Oliver

2.D Reprocessing of Lot 694Z06

The reprocessing of Lot 694Z06 was planned to provide needed clinical supplies and to evaluate the effectiveness of the modified process at producing a uniform blend. Prior [redacted] Lot 694Z06, a [redacted] process evaluation was planned with the following objectives:

1. To evaluate the impact of additional [redacted] on dissolution of capsules resulting from this batch, and its suitability for clinical use.

2. To determine the effectiveness of screening the [redacted] through a [redacted] at [redacted]

Small Scale Process Evaluation

[redacted]

1 pages
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Commercial

COMPLETED FEB 2 2 2000

FEB 18 2000

Zonisamide Capsules (100 mg)
NDA 20-789
Reviewer: Iftekhar Mahmood, Ph. D.
Submission Date:September 27, 1999
Indication: Epilepsy.

Athena Neuroscience/Elan Pharmaceuticals
South San Francisco, CA 94080

The Sponsor Athena Neuroscience/Elan Pharmaceuticals, has responded to the FDA's June 30, 1999 Approvable letter. The dissolution specification for Zonisamide capsules set by the FDA in the Approvable letter was as following:

Dosage Form: Capsules
Strengths:
Apparatus:
Medium:
Speed:

FDA's proposed Specifications: Q
Sponsor's proposed Specifications: Q

In response to the Approvable letter, the Sponsor has submitted dissolution data comparing Based on the data, there Using Q Based on these data the Sponsor requested that a dissolution specification of should be allowed.

Comment 1:

Upon evaluation of the data, it does appear that the Sponsor may need However, a dissolution testing for a particular product does not necessarily mean that the product has failed to meet the dissolution specifications. Since a typical dissolution specification the current proposed Specifications of Q should be used for 100 mg zonisamide capsule dissolution testing.

The Sponsor may propose dissolution time point, media or method which may result in the product dissolution of Until such data become available, the Sponsor should use the dissolution specification of Q

Labeling of ZONISAMIDE

Comment 2:

The Sponsor has responded to the FDA's June 30, 1999 Approvable letter. The Sponsor has incorporated most of the Clinical Pharmacology labeling comments suggested by the Agency. However, the Sponsor is requested to incorporate the following in their labeling.

Under **Pharmacokinetic section please add the following:**
Zonisamide has an eight-fold higher affinity for red blood cells (RBC) than for plasma.

Under **Pharmacokinetic section please replace** the statement that

' by the statement

If indeed the steady state is reached by 10-12 days, please provide the data which support this statement.

Under **Metabolism and Excretion:**
Please add

Recommendation:

Please send comments 1 and 2 to the Sponsor.

/S/ 2/18/2000

Iftekhar Mahmood, Ph. D.
Division of Pharmaceutical Evaluation I

APPEARS THIS WAY
ON ORIGINAL

RD/FT initialed by Chandra Sahajwalla, Ph. D. /S/ 2/15/00

CC: IND HFD-120, HFD-860 (Mahmood, Sahajwalla, Mehta), Biopharm-CDR
(for Drug Files).

7 pages
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hypersynchronization. *In vitro* binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor ionophore complex in an allosteric fashion which does not produce changes in chloride flux. Other *in vitro* studies have demonstrated that zonisamide [redacted] suppresses synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse spinal cord neurons) or neuronal or glial uptake of [^{3}H]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. *In vivo* microdialysis studies demonstrated that zonisamide facilitates both dopaminergic and serotonergic neurotransmission. Zonisamide has weak carbonic anhydrase inhibiting activity, requiring [redacted] higher doses than acetazolamide to achieve equivalent inhibition *in vivo* in rats. This pharmacologic effect is not thought to be a major contributing factor to the antiepilepsy activity of zonisamide.

Pharmacokinetics: Following a 200-400 mg oral zonisamide dose, peak plasma concentrations [redacted] in normal volunteers occur within [redacted] In the presence of food, the time to maximum concentration is delayed, occurring at 4 to 6 hours, but food has no effect on the bioavailability of zonisamide. Zonisamide extensively binds to erythrocytes, resulting in a higher concentration of zonisamide in red blood cells (RBC) than plasma. The pharmacokinetics of zonisamide are dose proportional in the range of 200 – 400 mg; but the C_{max} and AUC increase disproportionately at 800 mg, perhaps due to saturable binding of zonisamide to RBC. The mean plasma elimination half-life is about 60 hours in noninduced subjects after single and multiple doses, thus steady-state is reached following 10 – 12 days of dosing. The elimination half-life of zonisamide in RBC is approximately 105 hours.

The apparent volume of distribution (V/F) of zonisamide is about 1.45 L/kg following a 400 mg oral dose. Zonisamide, at concentrations of [redacted] is approximately 40% bound to human plasma proteins. Protein binding of zonisamide is unaffected in the presence of therapeutic concentrations of phenytoin, phenobarbital or carbamazepine.

Metabolism and Excretion: Following oral administration of ^{14}C-zonisamide to healthy volunteers, only zonisamide was detected in plasma. Zonisamide is excreted primarily in urine as parent drug and a glucuronide metabolite. Following multiple dosing, 62% of the ^{14}C dose was recovered in the urine, with 3% in the feces. Zonisamide undergoes acetylation to form N-acetyl zonisamide and reduction to form the open ring metabolite, 2-sulfamoylacetyl phenol (SMAP). Of the excreted dose, 35% was recovered as zonisamide, 15% as N-acetyl zonisamide, and 50% as the glucuronide of SMAP. Reduction of zonisamide to SMAP is mediated by cytochrome P450 isozyme 3A4. Zonisamide does not induce its own metabolism. Plasma clearance of zonisamide is approximately [redacted] in patients not receiving enzyme-inducing antiepilepsy drugs (AEDs). The clearance of zonisamide is increased to 0.5 mL/min/kg in patients concurrently on enzyme-inducing AEDs.

Zonisamide Capsules (100 mg)

NDA 20-789

Teaneck, NJ 07666

Reviewer: Iftekhar Mahmood, Ph. D.

Submission Dates: March 19, 1997; March 27, 1997; July 18, 1997; August 15, 1997; August 26, 1997.

Indication: Adjunct therapy for partial seizures.

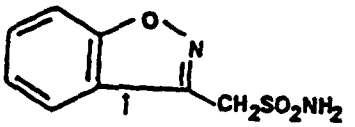
Zonisamide (GR85548) is an antiepilepsy drug in the sulfonamide class. The chemical name of zonisamide is 1,2-benzisoxazole-3-methanesulfonamide. Molecular formula of zonisamide is $C_8HP4508N_2O_3S$ and its molecular weight is 212. Zonisamide is a white powder and is moderately soluble in water (0.80 mg/mL). The pK_a of zonisamide 10.2. Zonisamide possesses no chiral centers.

Zonisamide is absorbed with a T_{max} of 3 to 4 hours in healthy subjects. The relative bioavailability (suspension 50 mg/mL) is about 98% . Following a 200 mg oral dose of zonisamide, the C_{max} is about 3 µg/mL. Food has no effect on the pharmacokinetics of zonisamide capsules. The apparent volume of distribution (V/F) ranges from 1.1 to 1.8 L/kg. Zonisamide is 40% bound to human plasma proteins over the concentration range of 1 to 70 µg/mL. Zonisamide undergoes acetylation to form N-acetyl zonisamide and reduction to form the open ring metabolite, 2-sulfamoylacetyl phenol (SMAP). Of the excreted dose, 35% was recovered as zonisamide, 15% as N-acetyl zonisamide, and 50% as the glucuronide of SMAP. The oral clearance of zonisamide from plasma is 15 mL/min. Renal clearance is about 3.5 mL/min. The elimination half-life of zonisamide in plasma is approximately 63 hours. Zonisamide has high affinity for RBC. Following a 200 mg oral dose of zonisamide, C_{max} and T_{max} in RBC were 12 µg/mL and 6 hours, respectively. The oral clearance of zonisamide from RBC is 2 mL/min. The elimination half-life of zonisamide in RBC is approximately 105 hours.

The pharmacokinetics of zonisamide in patients with impaired liver function have not been adequately studied. Renal impairment (creatinine clearance < 20 mL/min) was associated with an increase in zonisamide AUC by 35% and a decrease of 20% in oral clearance. Age does not have any effect on the pharmacokinetics of zonisamide.

Zonisamide has no significant effect on the steady state plasma concentrations of phenytoin, carbamazepine, or valproate. The half-life of zonisamide following a single 400 mg dose given to patients with epilepsy receiving phenytoin, carbamazepine, valproic acid was 27, 38 and 46 hours, respectively (the half-life in healthy subjects who were not on AEDs was 52 hours). The clearance of zonisamide in patients stabilized on phenytoin, carbamazepine and valproic acid was 0.51, 0.35 and 0.29 mL/min/kg, respectively (the clearance in healthy subjects who were not on AEDs was 0.15 mL/min/kg).

Zonisamide



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ON ORIGINAL

TABLE OF CONTENTS

Total number of studies submitted in this NDA was 34. Total number of studies reviewed were 28.

SUMMARY

Bioavailability and Bioequivalence:

Zonisamide 100, 200 and 300 mg tablets were bioequivalent to 2 x 100 mg and 3 x 100 mg zonisamide capsules. (Studies #1, 2 & 3). The relative bioavailability of 4 x 100 mg zonisamide capsule compared to a 8 mL (50 mg/mL) suspension in 12 healthy subjects was 98% (Study #4).

Absorption:

Following a single 200 mg or 400 mg oral dose of zonisamide, peak plasma concentration was 2.9 ± 0.3 μg/mL and 5.1 ± 0.1 μg/mL, respectively, and the time to reach the peak was between 5 to 6 hours. Following a single 200 mg or 400 mg oral dose of zonisamide, peak concentration in RBC was 12.3 ± 1.9 μg/mL and 19.1 ± 2.1 μg/mL, respectively, and the T_{max} was between 5 to 6 hours (Study #5).

Distribution:

Zonisamide extensively binds to erythrocytes, resulting a higher concentration of zonisamide in RBC than plasma. Following a single 200, 400, and 800 mg oral dose of zonisamide, the mean AUC ratio (RBC/plasma) was 8, 8, and 4, respectively. The uptake of zonisamide into RBC can be described by the summation of a linear process and a nonlinear process. The nonlinear process is attributed to binding of zonisamide to carbonic anhydrase in RBC.

The apparent volume of distribution (V/F) of zonisamide is about 1.47 L/kg following a 400 mg oral dose. Plasma V/F decreased 38% and the RBC and whole blood V/F increased 100% and 65%, respectively, over the dose range of 200 to 800 mg (Study #8). Zonisamide is 40% bound to human plasma proteins over the concentration range of 1 to 70 μg/mL.

Metabolism:

Zonisamide is extensively metabolized in man (Studies #6 & 10). The metabolic disposition of radiolabelled zonisamide (^{14}C-ZNS, 16.7 μCi per 100 mg) was determined after 300 mg oral administration. Six healthy subjects received radiolabelled zonisamide and blood, urine and feces samples were collected up to 9 days after dosing. In human plasma no metabolite could be detected. Approximately 15% of the total dose of zonisamide was recovered in the urine as unchanged drug. By the end of 9 days, 62% of an administered radioactivity was recovered in the urine. Fecal excretion accounted for only

3%. Two metabolites of zonisamide were identified in humans as N-acetyl zonisamide and a glucuronide conjugated open-ring metabolite sulfamoylphenol (SMAP). No study was conducted to identify isozymes responsible for the metabolism of zonisamide .

In-vitro metabolism of zonisamide:

A series of experiments were conducted using various substrates and isozymes to determine the effect of several concentrations of zonisamide (200, 600 or 1000 μM; 200 μM = 40 μg/mL) on the activity of P-450 isozymes. The study indicated that at 200 μM, zonisamide had a less than 10% inhibitory effect on CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 (Study #25). Even at the highest concentration of zonisamide tested, inhibition did not exceed 25% for CYP2D6.

Elimination:

Following 200 mg and 400 mg oral dose of zonisamide, oral clearance was 15 ml/min. Approximately 30% of the dose was excreted unchanged in urine over 15 days at both 200 and 400 mg doses. The elimination half-life of zonisamide was 63 hours in plasma and 105 hours in RBC following 200 mg oral dose of zonisamide (Study #5).

Dose Proportionality:

Dose Proportionality of zonisamide in 12 subject was investigated at doses of 200, 400 and 800 mg (Study #8). Zonisamide concentrations were measured in plasma, whole blood and RBC. The pharmacokinetics of zonisamide was nonlinear over this dose range. This nonlinearity may be due to the saturable binding of zonisamide to RBC.

Food Effect:

The pharmacokinetics of 400 mg oral dose of zonisamide was not modified by food intake in 13 subjects (Study #9). The mean T_{max} occured 2 hours later in fed state as compared to fasting state.

Multiple Dose Kinetics:

Multiple oral doses of 300-mg of zonisamide administered to six healthy subjects resulted in a mean C_{max} plasma concentration of 19.62 μg/mL on Day 15 compared to 3.15 μg/mL on day 1. Mean AUC_{0-24} on Day 15 were at least 7 fold higher than on Day 1. The plasma oral clearance decreased from 22 mL/min to 13 mL/min following multiple dose but half-life was similar between single and multiple dose. A two fold increase in RBC C_{max} and AUC_{0-24} was observed on day 15 as compared to day 1. Oral clearance

of zonisamide from RBC was increased by 3 fold following multiple dosing indicating the saturation of RBC binding (Study #10).

Two groups of healthy subjects received 400-mg daily doses of zonisamide for 35 days in an open-label, parallel group, dose-escalation study. One group (N=11) received 200-mg dose twice daily from Days 15 through 35, and the other group (N=4) received a single 400-mg dose once daily (QD) from Days 15 through 35. Steady state was reached by day 28. At steady-state, mean maximum plasma concentrations of 30.3 (BID group) and 28.0 μg/mL (QD group) were reached in 2.1 (BID group) and 1.8 hours (QD group), respectively. AUC_{0-12} values for both dosing groups were similar. However, the bioavailability of the QD regimen (400 mg) was estimated to be 84% of that achieved with the BID dosing regimen (200 mg). The oral clearance was about 10 mL/min and half-life was about 63 hours following 400 mg dose administered as QD or BID. zonisamide administration was associated with an increase in serum creatinine concentrations which returned to normal values after discontinuation of zonisamide (Study #11).

SPECIAL POPULATION:

Hepatic Impairment:

The pharmacokinetics of zonisamide were investigated in 2 subjects with alcoholic cirrhosis (determined by biopsy) compared with 5 healthy subjects. Each subject received a 300 mg single dose of zonisamide. This inconclusive study indicated that there is no difference in zonisamide pharmacokinetics between healthy subjects and alcoholic cirrhosis (Study #12).

Renal Impairment:

The pharmacokinetics of zonisamide were investigated in a single dose study in 23 subjects (17 males and 6 females) with varying degrees of renal function. The subjects were divided into 3 groups. Group 1 (n =8) was healthy group with a creatinine clearance ranging from 70 to 152 mL/min. Group II (n =8) and Group III (n = 7) had creatinine clearance ranging from 14.5 to 59 mL/min and 10 to 20 mL/min, respectively. Each group received a single dose of 300 mg zonisamide. Renal impairment (creatinine clearance < 20 mL/min) was associated with an increase in zonisamide AUC by 35% and a decrease of 20% in oral clearance (Study #13).

Age:

Eleven healthy elderly subjects (aged 65-71 years) and eleven healthy young subjects (aged 21-40 years) received a single dose of 300 mg zonisamide. The mean C_{max} (3.12 vs 4.13 μg/mL) and $AUC_{0\text{-}inf}$ (251 vs 275 μg.hr/mL) were 30% and 10% higher in the elderly compared to young. The elimination half life was 52 hours in the elederly as compared to 66 hours in the young (Study #14). Overall, age does not seem to have any effect on the pharmacokinetics of zonisamide.

Gender and Race:

The information on the effect of gender and race on the pharmacokinetics of zonisamide is not available.

Pharmacokinetics of Zonisamide in patients with epilepsy:

Following a single 400-mg dose of zonisamide administered to 12 patients with epilepsy (medically refractory patients) receiving at least one but not more than three anticonvulsants (phenytoin, carbamazepine, phenobarbital, valproic acid, clonazepam and methsuximide) resulted in a mean C_{max} of 5.9 μg/mL which was reached in 3.3 hours and a mean AUC of 213 μg/mL*hr. Concomitant antiepilepsy drugs (AED) therapy enhanced the plasma clearance (0.32 mL/min/kg without AED vs 0.51 mL/min/kg with AED) and decreased the half-life (23 hours with AED vs 52 hours without AED) of zonisamide (Study #15).

A single 400-mg dose of zonisamide administered to 11 epileptic patients (medically refractory patients with partial seizures) receiving other AEDs (phenytoin, carbamazepine, phenobarbital, valproic acid, clonazepam, methsuximide and primidone) resulted in a mean C_{max} of 5.5 μg/mL which was reached in 2.8 hours and a mean AUC of 194 μg/mL*hr (Study # 16). The plasma clearance and half-life were 0.51 mL/min/kg and 25 hours, respectively. As seen in the previous study (study #15), concomitant AED therapy enhanced the plasma clearance and decreased the half-life of zonisamide (Study #16).

Fourteen medically refractory epileptic patients were given zonisamide twice a day (dose ranging from 1.23 mg/kg/day to 12.69 mg/kg/day). Six patients were maintained on phenytoin therapy and eight patients were on carbamazepine therapy prior to the start of zonisamide therapy. The mean steady state zonisamide clearance was 0.3 mL/min/kg for concomitant phenytoin therapy and 0.2 mL/min/kg for carbamazepine therapy. Plasma protein binding of phenytoin and carbamazepine was not affected by zonisamide administration (Study #17).

Drug Interactions:

Effect of phenytoin, carbamazepine, valproic acid and phenobarbital on zonisamide pharmacokinetics:

The half-life of zonisamide following a single 400 mg dose given to patients with epilepsy receiving phenytoin, carbamazepine, valproic acid was 27, 38 and 46 hours, respectively (the half-life in healthy subjects who were not on AEDs was 52 hours). The clearance of zonisamide in patients stabilized on phenytoin, carbamazepine and valproic acid was 0.51, 0.35 and 0.29 mL/min/kg, respectively (the clearance in healthy subjects who were not on AEDs was 0.152 mL/min/kg). The half-life of 300 mg dose of zonisamide in patients given repeated doses of phenobarbital was 38 hours, whereas clearance of zonisamide was 0.40 mL/min /kg (Studies #19-23).

Interaction with cimetidine:

In eight healthy volunteers, pharmacokinetics of zonisamide (300 mg dose) was investigated before and after a 12-day regimen of cimetidine (300 mg four times a day) a known inhibitor of cytochrome P-450. zonisamide single dose pharmacokinetic parameters were not affected by cimetidine (Study #18).

Pharmacodynamics:

In a long term safety and efficacy evaluation of zonisamide, 208 medically refractory patients with or without secondary generalization, or of generalized seizures were enrolled in this trial. The trial was a multicenter, open label, outpatient clinical trial. The trial started with an initial screening for patient selection, and was followed by a 4-week dose-introduction phase, a 20-week continued treatment phase and a long term therapy phase up to a total of 24 months. The patients received at least one but not more than two concurrent AEDs upon entering the dose-introduction phase. During the first 4 weeks, zonisamide dose was increased gradually to 400 mg/day. The primary measure of efficacy was percent reduction in baseline seizure frequency by 50%. One hundred forty six subjects withdrew from the study either due to lack of efficacy of zonisamide or adverse events. In the group of responders, it was noted that a serum concentration of zonisamide ranging between [redacted] produces the maximum effect (Study #24).

Analytical Method:

[redacted]

Dissolution:

The Sponsor's proposed Dissolution Method and Specifications for zonisamide capsules are as follows:

Dosage Form: Capsules

Strengths:

Apparatus:

Medium:

Speed:

[redacted]

Sponsor's proposed Specifications: Q =

FDA's proposed Specifications: Q =

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ON ORIGINAL

4 pages redacted

DRAFT LABELING

Comments to the Medical Reviewer

1. In study #11, the subjects were given doses of zonisamide ranging from 100 mg daily to 400 mg daily for 35 days. By day 15 elevation of creatinine concentration was observed and remained elevated by day 35. After discontinuation of zonisamide, creatinine concentrations came back to normal values by day 56. The medical reviewer is requested to evaluate if increase in creatinine conconcentrations has also been observed in clinical trials. Increase in creatinine concentrations may be suggestive of kidney impairment.

2. The drug is extensively metabolized, therefore a conclusive study in hepatic impaired patients should be conducted by the Sponsor. Until these data are available it is recommended that label cautions the use of zonisamide in hepatic impaired population.

3. In different pharmacodynamic studies, many subjects (75%) withdrew from the study which resulted in small sample size making any meaningful conclusion impossible. The reasons for withdrawl of subjects from these studies was given as lack of efficacy or toxicity of zonisamide.

Comments

1. The mass balance study is inconclusive. Less than 70% of drug has been accounted for (Study #7).

2. Food seems to delay the absorption of zonisamide. On average T_{max} was prolonged by 2 hours in fed state mainly due to prolongation of T_{max} in 2 subjects (10 and 15 hours). Data also suggest that there is a probability of prolonged T_{max} in some subjects (Study # 9).

3. In the study entitled:'A clinical pharmacokinetic study of CI-912 (zonisamide) in patients with varying degrees of renal function', the Sponsor indicates that zonisamide is renally secreted. The renal clearance of zonisamide is only 3.4 mL/min in normal volunteers which is much lower than the GFR. Therefore, the conclusion that zonisamide is renally secreted is not supported by the results of the study.

4. The drug is extensively metabolized, therefore a conclusive study in hepatic impaired patients should be conducted by the Sponsor.

5. The Sponsor should evaluate the role of N-acetyl transferase in the metabolism of zonisamide. Furthermore, the Sponsor is requested to assess if zonisamide is metabolized by any cytochrome P-450 enzymes.

6. A drug interaction study between oral contraceptives and zonisamide should be conducted.

7. It is suggested that the Sponsor adopt the following dissolution specifications:

Dosage Form: Capsules
Strengths:
Apparatus:
Medium:
Speed:

Sponsor's proposed Specifications: Q
FDA's proposed Specifications: Q =

Recommendation:

From a pharmacokinetic point of view this NDA is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Please convey labeling Comments and Comments 3-7 to the Sponsor.

Iftekhar Mahmood, Ph.D. /S/ 12/12/97

FT initialed by Chandra Sahajwalla, Ph.D. /S/ 12/12/97

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CPB Briefing:

CC: NDA 20-789, HFD-120, HFD-860 (Mahmood, Sahajwalla, Malinowski), HFD-340 (Viswanathan), CDR (Barbara Murphy) and FOI (HFD-19) files.

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ON ORIGINAL

Dainippon Pharmaceutical
U.S.A. Corporation
Glenpointe Centre East, 300 Frank W. Burr Blvd., Teaneck, NJ 07666
Tel: (201) 692-9090 Fax: (201) 692-8388

PATENT AND EXCLUSIVITY INFORMATION ON PRODUCT OF DAINIPPON PHARMACEUTICAL CO., LTD. OSAKA, JAPAN

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

1. Active Ingredient(s): Zonisamide

2. Strength(s) 100mg

3. Trade Name: (Not yet established)

4. Dosage Form: Capsules

5. IND Number: [redacted]

6. Approval Date: (Not yet approved)

7. Applicable patent number and expiration date:

   Patent No.: 4,172,896
   Expires: June 5, 1998

8. Pursuant to Section 505(j)(4)(D)(ii) and Section 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetic Act, we are requesting a five-year period of marketing exclusivity from the date of approval of this NDA for zonisamide capsules.

   This request for exclusivity is based upon the following:

   (a) No active ingredient in zonisamide capsules has ever been approved in another drug product in the United States either as a single entity or as a part of a combination product; and

   (b) No active ingredient of the drug product has ever been previously marketed in a drug product in the United States.

K. Tsuchihashi

Kenshi Tsuchihashi, President
Dainippon Pharmaceutical U.S.A. Corporation

4172896

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

Whereas, THERE HAS BEEN PRESENTED TO THE

Commissioner of Patents and Trademarks

A PETITION PRAYING FOR THE GRANT OF LETTERS PATENT FOR AN ALLEGED NEW AND USEFUL INVENTION THE TITLE AND DESCRIPTION OF WHICH ARE CONTAINED IN THE SPECIFICATIONS OF WHICH A COPY IS HEREUNTO ANNEXED AND MADE A PART HEREOF, AND THE VARIOUS REQUIREMENTS OF LAW IN SUCH CASES MADE AND PROVIDED HAVE BEEN COMPLIED WITH, AND THE TITLE THERETO IS, FROM THE RECORDS OF THE PATENT AND TRADEMARK OFFICE IN THE CLAIMANT(S) INDICATED IN THE SAID COPY, AND WHEREAS, UPON DUE EXAMINATION MADE, THE SAID CLAIMANT(S) IS (ARE) ADJUDGED TO BE ENTITLED TO A PATENT UNDER THE LAW.

NOW, THEREFORE, THESE Letters Patent ARE TO GRANT UNTO THE SAID CLAIMANT(S) AND THE SUCCESSORS, HEIRS OR ASSIGNS OF THE SAID CLAIMANT(S) FOR THE TERM OF SEVENTEEN YEARS FROM THE DATE OF THIS GRANT, SUBJECT TO THE PAYMENT OF ISSUE FEES AS PROVIDED BY LAW, THE RIGHT TO EXCLUDE OTHERS FROM MAKING, USING OR SELLING THE SAID INVENTION THROUGHOUT THE UNITED STATES.

In testimony whereof *I have hereunto set my hand and caused the seal of the* **Patent and Trademark Office** *to be affixed at the City of Washington this thirtieth day of October in the year of our Lord one thousand nine hundred and seventy-nine, and of the Independence of the United States of America the two hundred and fourth.*

Attest:
Ruth M. Wray
Attesting Officer.

Sarah F. Parker
Acting Commissioner of Patents and Trademarks.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,172,896

DATED : October 30, 1979

INVENTOR(S) : Hitoshi Uno et al

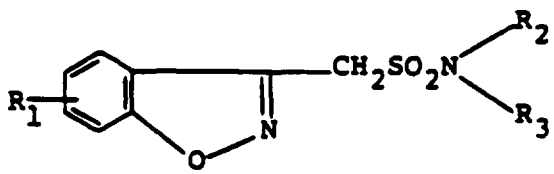
It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In col. 2, line 58, "basis" should be --basic--.

In col. 3, line 2, "ing" should be --ed--.

In col. 7, line 4, after "8.0" there should be --g--.

In Claim 2, line 2; Claim 14, line 4; and Claim 20, line 3, the formula should read as follows:



In Claim 18, line 2, "14" should be --15--.

Signed and Sealed this

Eighth Day of April 1980

Attest:

Ruth C. Mason

Attesting Officer

Sidney A. Diamond

SIDNEY A. DIAMOND

Commissioner of Patents and Trademarks

United States Patent [19]

Uno et al.

[54] **METHANE-SULFONAMIDE DERIVATIVES, THE PREPARATION THEREOF AND COMPOSITION COMPRISING THE SAME**

[75] **Inventors:** Hitoshi Uno, Takatsuki; Mikio Kurokawa, Kobe; Yoshinobu Maeda, Hirakata, all of Japan

[73] **Assignee:** Dainippon Pharmaceutical Co., Ltd., Osaka, Japan

[21] **Appl. No.:** 912,857

[22] **Filed:** Jun. 5, 1978

[51] **Int. Cl.**[3] A61K 31/42; C07D 261/20; C07D 263/56

[52] **U.S. Cl.** 424/272; 548/217; 548/241

[58] **Field of Search** ..... 260/307 D, 307 DA; 424/272

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,833,608 9/1974 Rooney et al. ..... 260/326.12 R

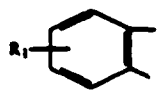
OTHER PUBLICATIONS

Noller—"Chemistry of Organic Compounds"—W. B. Saunders Company—(1965), pp. 314–315.

Primary Examiner—R
Attorney, Agent, or Fir
Mosher

[57]

Methane-sulfonamide



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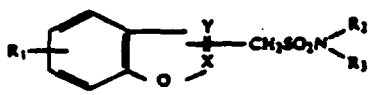
METHANE-SULFONAMIDE DERIVATIVES, THE PREPARATION THEREOF AND COMPOSITION COMPRISING THE SAME

The present invention relates to novel methane-sulfonamide derivatives, more particularly, to compounds of the formula:

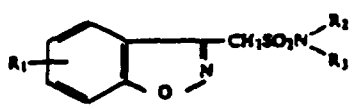


(I)

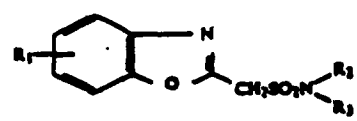
wherein R_1 is hydrogen or a halogen atom, R_2 and R_3 are the same or different and are each hydrogen or an alkyl having 1 to 3 carbon atoms, and one of X and Y is a carbon atom and another is a nitrogen atom, provided that the group: $-CH_2SO_2NR_2R_3$ is bonded to the carbon atom of either of X and Y,
and an alkali metal salt thereof when either one or both of R_2 and R_3 are hydrogen atoms, and further relates to a process for the preparation of said methane-sulfonamide derivatives and also to a pharmaceutical composition containing said compounds as the essential active ingredient.

The term "halogen atom" denotes fluorine, chlorine and bromine atoms, and "alkyl" denotes a straight or branched alkyl having 1 to 3 carbon atoms, such as methyl, ethyl, propyl and isopropyl. "Alkali metal salt" includes sodium salt and potassium salt.

The compounds of the formula (I) include the following two types of compounds:



(I')



(I'')

In the course of intensive studies on sulfamoyl-alkyl derivatives of various benzenoles, the present inventors have found that when sulfamoylmethyl group is introduced at the 3-position of 1,2-benzisoxazoles or at the 2-position of benzoxazoles, the resulting compounds show an excellent anticonvulsant activity.

Although some 3-sulfamoylmethylindole derivatives are disclosed in U.S. Pat. No. 3,833,608, the compounds of the formula (I) in the present invention are clearly different from these indole derivatives disclosed in the U.S. patent in the chemical structure and also in the pharmacological properties.

It is an object of the present invention to provide novel methane-sulfonamide derivatives and their alkali metal salts having an excellent anticonvulsant activity.

Another object of the invention is to provide a process for the preparation of the methane-sulfonamide derivatives and their alkali metal salts.

A further object of the invention is to provide a method of controlling convulsions and seizures in patients with epilepsy which comprises administering an effective amount of the methane-sulfonamide derivatives or their alkali metal salts.

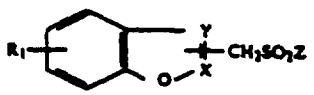
A still further object of the invention is to provide a pharmaceutical composition comprising the methane-sulfonamide derivatives or their alkali metal salts as an active ingredient.

These and other objects will be apparent from the description hereinafter.

Preferred compounds of the present invention are the compounds of the formula (I) wherein R_1 is hydrogen or 5- or 6-halogen atom and R_2 and R_3 are the same or different and are each hydrogen or methyl. Particularly preferred compounds are the compounds of the formula (I) wherein R_1 is hydrogen or 5- or 6-halogen and R_2 and R_3 are both hydrogen. Suitable examples are as follows, among of which the first three compounds are particularly suitable.

3-Sulfamoylmethyl-1,2-benzisoxazole
5-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole
2-Sulfamoylmethylbenzoxazole
5-Chloro-3-sulfamoylmethyl-1,2-benzisoxazole
5-Bromo-3-sulfamoylmethyl-1,2-benzisoxazole
6-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole

The compounds of the formula (I) can be prepared by reacting a compound of the formula:



(II)

wherein R_1, X and Y are as defined above, and Z is a halogen atom (e.g. chlorine, bromine), with an amine of the formula:

(III)

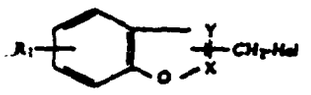
wherein R_2 and R_3 are as defined above.

The reaction of the compound of the formula (II) with the amine of the formula (III) may be carried out in the absence of a solvent, but may preferably be carried out in the presence of an inert solvent. The inert solvent includes water, alcohols (e.g. ethanol, isopropanol), aromatic hydrocarbons (e.g. toluene, xylene), ethers (e.g. diethyl ether, tetrahydrofuran, dioxane), esters (e.g. ethyl acetate), or the like, which may be used alone or in a mixture of two or more thereof. Suitable solvents are ethers and esters.

The reaction is preferably carried out in the presence of a basic substance as a dehydrohalogenating agent. The basic substance includes alkali metal hydrogen carbonates (e.g. sodium hydrogen carbonate, potassium hydrogen carbonate), alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), organic amines (e.g. triethylamine), or the like. Instead of using a specific basic substance, there may be used an excess amount of the amine of the formula (III) which acts as a reactant and also as a dehydrohalogenating agent.

The amine of the formula (III) is usually used in an amount of 1 to 4 moles to 1 mole of the compound of the formula (II), but may be used in a large excess amount. The reaction temperature is not critical, but the reaction is usually carried out at a temperature of from about 0° C. to about 35° C. The desired compound of the formula (I) can be isolated from the reaction mixture and purified in a conventional manner.

The starting compound of the formula (II) is preparing by reacting a halogenomethyl derivative of the formula:



(IV)

wherein R_1, X and Y are as defined above, and Hal is a halogen atom (e.g. chlorine, bromine, iodine), which is prepared by the similar process to that as disclosed in Chem. Pharm. Bull. (Tokyo), Vol. 24, page 632 (1976) and Belgian Pat. No. 624,463, with sodium sulfite in an inert solvent (e.g. aqueous methanol or aqueous ethanol) at a temperature of from 40° C. to 80° C. to give a sodium methanesulfonate of the formula:

(V)

wherein R_1, X and Y are as defined above, and then reacting the resulting sodium methanesulfonate of the formula (V) with a halogenating agent (e.g. phosphorus oxychloride, phosphorus oxybromide).

The compound of the formula (I) wherein either one or both of R_2 and R_3 are hydrogen may be reacted with an alkali metal compound in a conventional manner to give an alkali metal salt of the compound of the formula (I). The alkali metal compound includes alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide), alkali metal alcoholates (e.g. sodium ethylate), or the like.

The compounds of the formula (I) and their alkali metal salts of the present invention have an excellent anticonvulsant activity. The pharmacological test data of the representative compounds of the present invention are shown below together with the data of commercially available anticonvulsants.

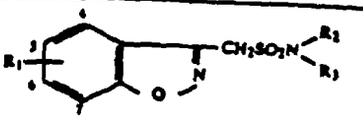
(1) Anti-maximal electroshock seizure activity in mice

Male mice of STD-ddY strain were used. The test compounds were orally administered to the test animals (each group: 10 mice) in the form of a homogeneous suspension in a 0.5% tragacanth solution.

Maximal electroshock seizures (MES) were induced by the method of Swinyard [cf. J. Amer. Pharm. Assoc., Vol. 38, page 201 (1949)]. The animals were subjected to 60 Hz current of 25 mA for 0.2 second delivered through corneal electrodes after administration of the test compounds. Median effective dose (ED_{50}), i.e. the dose which prevents hindlimb tonic extensor components of seizures in 50% of animals, was calculated by the method of Litchfield and Wilcoxon [cf. J. Pharmacol. Exp. Ther., Vol. 96, page 99 (1947)].

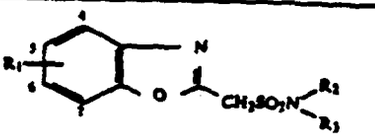
The ED_{50} at peak effect time of the compounds is shown in Tables 1a and 1b.

Table 1a



Test compound No.	R_1	R_2	R_3	ED_{50} (mg/kg, p.o.)
1	H	H	H	19.6
2	H	H	CH_3	22.3
3	H	H	C_2H_5	38.9
4	H	H	$CH(CH_3)_2$	56.0
5	H	CH_3	CH_3	37.2
6	5,6-□	H	H	14.2
7	5,6-□	H	CH_3	ca. 20
8	5,6-□	H	C_2H_5	21.3
9	5,6-□	CH_3	CH_3	36.2
10	5-F	H	H	14.5
11	5-F	H	CH_3	34.5
12	5-F	H	C_2H_5	31.6
13	5-F	CH_3	CH_3	32.0
14	5-Br	H	H	13.5
15	5-Br	H	CH_3	15.0
16	5-Br	H	C_2H_5	18.3
17	5-Br	H	$CH(CH_3)_2$	23.3
18	6-F	H	H	18.9

Table 1b



Test compound No.	R_1	R_2	R_3	ED_{50} (mg/kg, p.o.)
19	H	H	H	12.0
20	H	H	CH_3	17.2
21	H	CH_3	CH_3	34.0
22	H	H	$(CH_3)_2CH_3$	31.2
23	5-Cl	H	H	30.3
Diphenylhydantoin				7.8
Carbamazepine				13.2
Primidone				21.7
Phenacemide				61.2

(Note)
Diphenylhydantoin: 5,5-diphenyl-2,4-imidazolidinedione
Carbamazepine: 5H-dibenz[b,f]azepine-5-carboxamide
Primidone: 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione
Phenacemide: phenylacetylurea

The anti-MES activities of the compounds of this invention were more potent than that of phenacemide, while less than that of diphenylhydantoin. The activities of some compounds of this invention were almost equal to or more potent than those of carbamazepine and primidone.

(2) Effect on coordinated motor movements in mice

Mice trained to continue coordinated motor movements for 100 seconds or more on a rotarod apparatus (2.5 cm in diameter at 11 RPM) were used [J. Amer. Pharm. Assoc., Sci. Ed., Vol 46, page 208 (1957)]. Impairment of coordinated motor movements was defined as the inability of the animals to retain on the rotarod for a 100 second test period. After oral administration of the test compounds rotarod performance was tested at intervals of 1 hour for 6 hours. Median neurotoxic dose (NTD_{50}), i.e. the dose which causes fall from rotarod in 50% of animals, was calculated by the method of Litchfield and Wilcoxon.

The NTD_{50} at peak effect time of the test compounds is shown in Table 2. The protective indices (NTD_{50}/ED_{50} of anti-MES) of the test compounds were calculated and are also shown in the same table.

Table 2

Test compound*1	NTD_{50} (mg/kg, p.o)	Protective index
1	292 (2)*2	14.9
10	134 (2)	10.6
19	168 (2)	14.0
Diphenylhydantoin	72 (6)	9.5
Carbamazepine	141 (1)	10.7

(Note)
*1The test compounds 1, 10 and 19 are as defined in Tables 1a and 1b.
*2Figures in parentheses represent peak effect time in hours.

Neurotoxic effects of the compounds of this invention were about one-half to about one-fourth as potent as that induced by diphenylhydantoin. The protective indices of the compounds of this invention were higher than that of diphenylhydantoin and were almost equal to or higher than that of carbamazepine. Therefore, the compounds of this invention have a wide separability of therapeutic effects from acute neurotoxic effects.

(3) Acute toxicity in mice

Male mice of STD-ddY strain weighing 20–22 g were used. The test compounds were orally administered to the test animals (each group: 10 mice) in the form of a homogeneous suspension in 0.5% tragacanth solution. The mortality was observed for 7 days. Median lethal dose (LD_{50}), i.e. the dose which causes death in 50% of animals, was calculated by Probit method.

The LD_{50} of the test compound is shown in Table 3. The safety index (LD_{50}/ED_{50} of anti-MES) of each compound was calculated and is also shown in the same table.

Table 3

Test compound*	LD_{50} (mg/kg, p.o)	Safety index
1	1829	93.3
10	1257	86.7
19	ca.1800	—
Diphenylhydantoin	343	47.8
Carbamazepine	1700	129

(Note)
*The test compounds 1, 10 and 19 are as defined in Tables 1a and 1b.

Acute lethal toxicities of the compounds of this invention were considerably weak compared with that of diphenylhydantoin. The safety indices of the compounds of this invention were about twice as high as that of diphenylhydantoin, while their indices were somewhat lower than that of carbamazepine. The compounds of this invention have large safety margins of therapeutic effects from acute lethal toxicities compared with diphenylhydantoin.

As is clear from the above test results, the compounds of the formula (I) and their alkali metal salts of the present invention have an excellent anticonvulsant activity and have a low toxicity, and hence, these compounds are useful as anticonvulsants for controlling convulsions and seizures in patients with epilepsy.

These compounds of the present invention can be administered by an oral, parenteral or intrarectal route. The dosage of these compounds may vary in accordance with the kinds of the compounds, the administration manner, the age of the patient and the degree of the therapeutic effect desired, but is usually in the range of 1 to 100 mg/kg/day, preferably 3 to 30 mg/kg/day, which may be administered at a time or in divided doses.

The compounds of the present invention are usually administered in the form of a pharmaceutical composition which contains them in admixture with a pharmaceutical carrier. The pharmaceutical composition may be in the dosage forms such as tablets, capsules, granules, fine granules, powders, syrups, suppositories, injections, or the like. These preparations can be prepared by conventional methods.

The carriers useful for these preparations include all organic or inorganic carrier materials which are usually used for the pharmaceutical preparations and are inert to the active ingredient. Examples of the carriers suitable for the preparation of tablets, capsules, granules and fine granules are diluents such as lactose, starch, sucrose, D-mannitol, calcium sulfate, or microcrystalline cellulose; disintegrators such as sodium carboxymethylcellulose, modified starch, or calcium carboxymethylcellulose; binders such as methylcellulose, gelatin, acacia, ethylcellulose, hydroxypropylcellulose, or polyvinylpyrrolidone; lubricants such as light anhydrous silicic acid, magnesium stearate, talc, or hydrogenated oil; or the like. When formed into tablets, they may be coated in a conventional manner by using the conventional coating agents such as calcium phosphate, carnauba wax, hydroxypropyl methylcellulose, macrogol, hydroxypropyl methylphthalate, cellulose acetate phthalate, titanium dioxide, sorbitan fatty acid ester, or the like.

Examples of the carriers suitable for the preparation of syrups are sweetening agents such as sucrose, glucose, fructose, or D-sorbitol; suspending agents such as acacia, tragacanth, sodium carboxymethylcellulose, methylcellulose, sodium alginate, microcrystalline cellulose, or veegum; dispersing agents such as sorbitan fatty acid ester, sodium lauryl sulfate, or polysorbate 80; or the like. When formed into syrups, the conventional flavoring agents, aromatic substances, preservatives, or the like may optionally be added thereto. The syrups may be in the form of a dry syrup which is dissolved or suspended before use.

Examples of bases used for the preparation of suppositories are cacao butter, glycerin saturated fatty acid ester, glycerogelatin, macrogol, or the like. When formed into suppositories, the conventional surface active agents, preservatives or the like may optionally be admixed.

When formed into injections, the alkali metal salt of the compound is dissolved in distilled water for injection, to which may optionally be added the conventional solubilizers, buffering or pH adjusting agents, isotonic agents, preservatives and other suitable substances. The injections may be in the solid dry preparations which are dissolved before use.

These pharmaceutical compositions usually contain the compounds of the formula (I) or their alkali metal salts as the active ingredient in an amount of 0.5% by weight or more, preferably 10 to 70% by weight, based on the total weight of the composition. These compositions may optionally contain other therapeutically active compounds.

The present invention is illustrated by the following Examples, but is not limited thereto. In Examples, the compounds were identified by elementary analysis, mass spectrum, IR spectrum, NMR spectrum, or the like.

EXAMPLE 1

1,2-Benzisoxazole-3-methanesulfonyl chloride:

To a solution of 8.0 g of 3-bromomethyl-1,2-benzisoxazole (m.p. 64°–66° C.) in 130 ml of methanol was added a solution of 8.1 g of sodium sulfite in 130 ml of water. The mixture was heated with stirring at 50° C. for 4 hours and concentrated under reduced pressure. The crystalline residue was dissolved in 250 ml of methanol with warming and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure and the crystalline residue was washed with diethyl ether to give crude sodium 1,2-benzisoxazole-3-methanesulfonate (10.5 g).

To 100 ml of phosphorus oxychloride was added 10.5 g of the above-mentioned sodium salt and the mixture was heated under reflux for 3 hours. The excess of phosphorus oxychloride was distilled off under reduced pressure. The residue was dissolved in 200 ml of ethyl acetate and the removal of the insoluble material by filtration gave the solution of the desired product.

EXAMPLE 2

The following compounds were prepared in substantially the same manner as in Example 1:

5-Fluoro-1,2-benzisoxazole-3-methanesulfonyl chloride;

5-Chloro-1,2-benzisoxazole-3-methanesulfonyl chloride;

5-Bromo-1,2-benzisoxazole-3-methanesulfonyl chloride;

6-Fluoro-1,2-benzisoxazole-3-methanesulfonyl chloride.

EXAMPLE 3

3-Sulfamoylmethyl-1,2-benzisoxazole:

The solution of 1,2-benzisoxazole-3-methanesulfonyl chloride in ethyl acetate, which was prepared in Example 1, was cooled on an ice bath, saturated with dry ammonia gas, and allowed to stand at room temperature for one hour. After the removal of the insoluble material by filtration, the filtrate was concentrated to yield a crystalline solid, which was washed with a small amount of ethyl acetate and recrystallized from ethyl acetate to give the desired product (5.2 g), m.p. 160°–163° C.

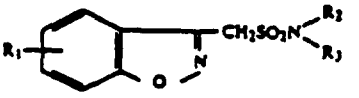
EXAMPLE 4

5-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole:

Sixty six grams of sodium 5-fluoro-1,2-benzisoxazole-3-sulfonate, which was prepared in substantially the same manner as described in the first paragraph of Example 1, was dissolved in 300 ml of phosphorus oxychloride and the solution was heated under reflux for 4 hours. After the removal of the remaining phosphorus oxychloride by distillation, the residue was dissolved in 500 ml of benzene and then filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in 900 ml of diethyl ether. The resulting solution was saturated with dry ammonia gas under cooling on an ice bath and allowed to stand at room temperature for 30 minutes. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate. The ethyl acetate layer was concentrated to a volume of about 100 ml under reduced pressure. The crystalline precipitate was collected and washed with benzene to give the desired product (32 g), m.p. 182°–185° C.

EXAMPLE 5

Various compounds of the formula:



as listed in the following Table 4 were prepared in substantially the same manner as in Examples 3 and 4.

Table 4

R_1	R_2	R_3	Melting point (°C.)
H	H	CH_3	113–115
H	H	C_2H_5	76–78
H	H	$(CH_2)_2CH_3$	86–88
H	H	$CH(CH_3)_2$	114–117
H	CH_3	CH_3	105–107
5-F	H	CH_3	141–144
5-F	H	C_2H_5	114–117
5-F	H	$CH(CH_3)_2$	127–130
5-F	CH_3	CH_3	145–148
6-F	H	H	187–190
5-Cl	H	H	192–195
5-Cl	H	CH_3	148–151
5-Cl	H	C_2H_5	150–152
5-Cl	H	$CH(CH_3)_2$	114–116
5-Cl	CH_3	CH_3	176–179
5-Br	H	H	221–225
5-Br	H	CH_3	152–154
5-Br	H	C_2H_5	144–147
5-Br	H	$CH(CH_3)_2$	95–97
5-Br	CH_3	CH_3	183–185

EXAMPLE 6

Benzoxazole-2-methanesulfonyl chloride:

To a solution of 3.0 g of 2-bromomethylbenzoxazole [prepared according to the procedures described in Belgian Pat. No. 624,463] in 40 ml of methanol was added a solution of 1.9 g of sodium sulfite in 40 ml of water. The mixture was heated with stirring at 60° C. for 6 hours and concentrated under reduced pressure to give crude sodium benzoxazole-2-methanesulfonate (4.5 g). To the sodium salt was added 15 ml of phosphorus oxychloride and the mixture was heated under reflux for one hour. The removal of the remaining phosphorus oxychloride by distillation under reduced pressure gave the desired product as an oil.

EXAMPLE 7

2-Sulfamoylmethylbenzoxazole:

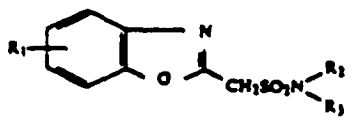
The benzoxazole-2-methanesulfonyl chloride, which was prepared in Example 6, was dissolved in 100 ml of ethyl acetate, saturated with dry ammonia gas under cooling on an ice bath, and allowed to stand at room temperature for 30 minutes. Evaporation of the solvent under reduced pressure gave an oily residue, which was chromatographed on silica gel with 3% methanol-chloroform as eluent. The eluate was concentrated to dryness and the crystalline residue was recrystallized from ethyl acetate to give the desired product (0.4 g), m.p. 166°–169° C.

EXAMPLE 8

5-Chlorobenzoxazole-2-methanesulfonyl chloride was prepared in substantially the same manner as in Example 6.

EXAMPLE 9

Various compounds of the formula:



as listed in the following Table 5 were prepared in substantially the same manner as in Example 7.

Table 5

R_1	R_2	R_3	Melting point (°C.)
H	H	CH_3	139–142
H	CH_3	CH_3	109–111
H	H	$(CH_2)_2CH_3$	146–149
5-Cl	H	H	188–191

EXAMPLE 10

Sodium salt of 3-sulfamoylmethyl-1,2-benzisoxazole:

To a solution of 7.0 g of 3-sulfamoylmethyl-1,2-benzisoxazole in 300 ml of ethanol was added a solution of sodium ethylate which was prepared from 0.76 g of sodium and 40 ml of ethanol. The mixture was allowed to stand at room temperature for a while and evaporated to one-fifth of its original volume under reduced pressure. The concentrated solution was cooled and the crystalline precipitate was collected, washed with ethanol and dried to give the desired product (6.5 g), m.p. 225°–230° C. (decomposition).

EXAMPLE 11

The following compounds were prepared in substantially the same manner as in Example 10:

Sodium salt of 5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole, m.p. 240°–243° C. (decomposition);

Sodium salt of 2-sulfamoylmethylbenzoxazole, m.p. 265°–267° C. (decomposition).

EXAMPLE 12

	per 1,000 tablets
3-Sulfamoylmethyl-1,2-benzisoxazole	100 g
Lactose	35 g
Corn starch	17 g
Microcrystalline cellulose	40 g
Polyvinylpyrrolidone	4 g
Light anhydrous silicic acid	1 g
Magnesium stearate	1 g

The above components were blended, granulated and made into tablets by a conventional method. 1,000 tablets each weighing 200 mg were formed.

EXAMPLE 13

3-Sulfamoylmethyl-1,2-benzisoxazole	200 g
Lactose	779 g
Hydroxypropylcellulose	20 g
Light anhydrous silicic acid	1 g

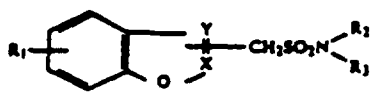
The above components were blended and made into fine granules by a conventional method.

EXAMPLE 14

The same procedures as in Examples 12 and 13 were repeated except that 5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or 2-sulfamoylmethylbenzoxazole was used instead of 3-sulfamoylmethyl-1,2-benzisoxazole. Thus, tablets and fine granules of each compound were prepared respectively.

What is claimed is:

1. A compound of the formula:

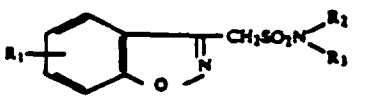


(I)

wherein R_1 is hydrogen or a halogen atom, R_2 and R_3 are the same or different and are each hydrogen or an alkyl having 1 to 3 carbon atoms, and one of X and Y is carbon atom and another is nitrogen atom, provided that the group:

$-CH_2SO_2NR_2R_3$ is bonded to the carbon atom of either of X and Y, or an alkali metal salt thereof.

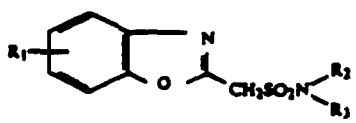
2. A compound of the formula:



(I')

wherein R_1 is hydrogen or a halogen atom, and R_2 and R_3 are the same or different and are each hydrogen or an alkyl having 1 to 3 carbon atoms, or an alkali metal salt thereof.

3. A compound of the formula:



(I'')

wherein R_1 is hydrogen or a halogen atom, and R_2 and R_3 are the same or different and are each hydrogen or an alkyl having 1 to 3 carbon atoms, or an alkali metal salt thereof.

4. A compound according to claim 1, 2 or 3, wherein R_1 is hydrogen or 5- or 6-halogen, or an alkali metal salt thereof.

5. A compound according to claim 4, wherein R_2 and R_3 are the same or different and are each hydrogen or methyl, or an alkali metal salt thereof.

6. A compound according to claim 5, wherein R_2 and R_3 are both hydrogen, or an alkali metal salt thereof.

7. 3-Sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

8. 5-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

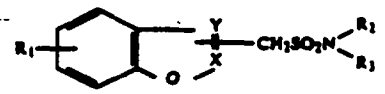
9. 5-Chloro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

10. 5-Bromo-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

11. 6-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

12. 2-Sulfamoylmethylbenzoxazole or an alkali metal salt thereof.

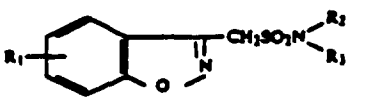
13. A pharmaceutical composition comprising as an active ingredient a compound of the formula:



(I)

wherein R_1 is hydrogen or a halogen atom, R_2 and R_3 are the same or different and are each hydrogen or an alkyl group having 1 to 3 carbon atoms, and one of X and Y is carbon atom and another is nitrogen atom, provided that the group: $-CH_2SO_2NR_2R_3$ is bonded to the carbon atom of either of X and Y, or an alkali metal salt thereof and a pharmaceutically acceptable carrier.

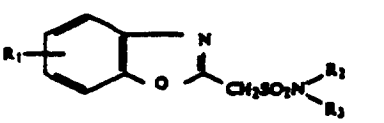
14. A pharmaceutical composition according to claim 13, wherein the active ingredient is a compound of the formula:



(I')

wherein R_1 is hydrogen or a halogen atom, and R_2 and R_3 are the same or different and are each hydrogen or an alkyl group having 1 to 3 carbon atoms, or an alkali metal salt thereof.

15. A pharmaceutical composition according to claim 13, wherein the active ingredient is a compound of the formula:



(I'')

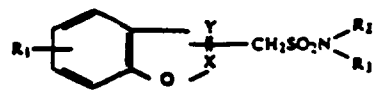
wherein R_1 is hydrogen or a halogen atom, and R_2 and R_3 are the same or different and are each hydrogen or an alkyl having 1 to 3 carbon atoms, or an alkali metal salt thereof.

16. A pharmaceutical composition according to claim 13 or 14, wherein the active ingredient is 3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

17. A pharmaceutical composition according to claim 13 or 14, wherein the active ingredient is 5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

18. A pharmaceutical composition according to claim 13 or 14, wherein the active ingredient is 2-sulfamoylmethylbenzoxazole or an alkali metal salt thereof.

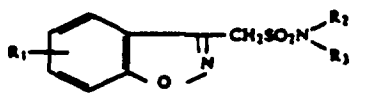
19. A method for controlling convulsions and seizures in patients with epilepsy which comprises administering an effective amount of a compound of the formula:



(I)

wherein R_1 is hydrogen or a halogen atom, R_2 and R_3 are the same or different and are each hydrogen or an alkyl having 1 to 3 carbon atoms, and one of X and Y is carbon atom and another is nitrogen atom, provided that the group: $-CH_2SO_2NR_2R_3$ is bonded to the carbon atom of either of X and Y, or an alkali metal salt thereof to said patients.

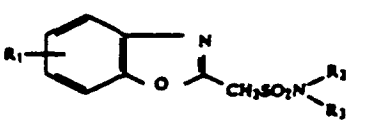
20. A method according to claim 19, wherein said compound is a compound of the formula:



(I')

wherein R_1 is hydrogen or a halogen atom, and R_2 and R_3 are the same or different and are each hydrogen or an alkyl group having 1 to 3 carbon atoms, or an alkali metal salt thereof.

21. A method according to claim 19, wherein said compound is a compound of the formula:



(I'')

wherein R_1 is hydrogen or a halogen atom, and R_2 and R_3 are the same or different and are each hydrogen or an alkyl group having 1 to 3 carbon atoms, or an alkali metal salt thereof.

22. A method according to claim 19 or 20, wherein said compound is 3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

23. A method according to claim 19 or 20, wherein said compound is 5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

24. A method according to claim 19 or 21, wherein said compound is 2-sulfamoylmethylbenzoxazole or an alkali metal salt thereof.

* * * * *

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

\IBLA # ***NDA 20-789*** Supplement Circle one: SE1 SE2 SE3 SE4 SE5 SEE

HFD-120 Trade and generic name/dosage form: ***Zonisamide Capsules, 100mg*** Action: AP AE NA

Applicant: ***Athena Neurosciences for Dainippon*** Therapeutic Class: ***Anticonvulsant***

Indication(s) previously approved: ***None.***

Pediatric information in labeling of approved indication(s) is adequate ____ inadequate __X__

Proposed indication in this application: ***Adjunctive Therapy of Partial Seizures in Adults with epilepsy.***

ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? __X__ Yes (Continue with questions) ____ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

____ Neonates(Birth-1month) __X__ Infants (1month-2yrs) __X__ Children (2-12yrs) __X__ Adolescents (12-16yrs)

____ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

____ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

____ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

____ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

____ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

____ c. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing,

____ (2) Protocols were submitted and approved.

____ (3) Protocols were submitted and are under review.

____ (4) If no protocol has been submitted, attach memo describing status of discussions.

____ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__X__ 5. If none of the above apply, attach an explanation, as necessary. ***In the approvable letter for this NDA, the Division has strongly urged the firm to perform adequate and well controlled investigations in children with epilepsy at the earliest possible time. We have asked the firm to respond to this request as part of their response to our approvable letter.***

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ____ Yes __X__ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from /S/ (e.g., medical review, medical officer, team leader)

/S/ Robert Baker DMD

Signature of Preparer and Title

3/16/98

Date

Orig NDA/BLA# 20-789
HFD-120 Div File
NDA/BLA Action Package
HFD-006/KRoberts

(revised 10120197)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Dainippon Pharmaceutical
U.S.A. Corporation
Glenpointe Centre East, 300 Frank W. Burr Blvd., Teaneck, NJ 07666
Tel: (201) 692-9090 Fax: (201) 692-8388

DEBARMENT CERTIFICATION

Dainippon Pharmaceutical U.S.A. Corporation hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306(a) or (b), in connection with this application.

K. Tsuchihashi

Kenshi Tsuchihashi, President
Dainippon Pharmaceutical U.S.A. Corporation

Feb. 21, 1997

Date

APPEARS THIS WAY
ON ORIGINAL

Printed by Jackie Ware

Electronic Mail Message

S.. .vity: COMPANY CONFIDENTIAL

Date: 05-May-1997 04:18pm
From: Jackie Ware

Dept:
Tel No:

TO: Michael Klein

Subject: Clarification regarding NDA 20-789 (Zonisamide)

Mike,

I received your fax on Friday, 5/2/97, of the abuse liability guidelines. I will pass them along to the firm as you requested. However, I am not clear on what our expectations are at this point.

What would we like for the firm to do with these guidelines? Or will we explain our expectations to them in the sponor meeting that you suggested? Or should I relay the deficiencies described in your initial review (which you emailed)?

Sorry for my confusion. I just want to deliver a clear message to the sponsor and want to make sure you get what you need for your review.

Thanks,
J- -ie

870

SEP 11 1997

REQUEST FOR PROPRIETARY/ESTABLISHED NAME REVIEW

To: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D., Chair
HFD-530
9201 Corporate Blvd, Room N461

From: HFD-120 - Division of Neuropharmacological Drug Products
Paul Leber, M.D., Director /S/

Date: September 10, 1997

RECEIVED JAN 30 1998

Application Status (IND/NDA/ANDA): NDA 20-789

Proposed Proprietary Name: see attachment

Trademark registration status/Countries registered(if known): none

Company tradename: **Athena Neurosciences**

Other proprietary names by same firm for companion products: none

United States Adopted Name, dosage form, strength and dosing schedule:
Zonisamide, Capsules, 100 mg, twice daily

Indication for use: Adjunct therapy of partial seizures with and without secondary generalization in adults.

Comments from submitter (concerns, observations, etc.):
Note: The firm has submitted three proposed proprietary names for review.

Meetings of the Committee are scheduled for the 4th Tuesday of each month. Please submit this form at least one week before the meeting. Responses will be as timely as possible.
Rev. 2/97

cc
NDA 20-789
HFD-120/Division File
HFD-120/CSO/JWare
/S/ 9/10/97

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE 870

athena neurosciences

Athena Neurosciences, Inc.
800 Gateway Boulevard
South San Francisco, CA 94080
Tel 415 877 0900 Fax 415 877 8370

August 22, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
Woodmont Two Building 4th Floor
HFM-99, Room 200N
1451 Rockville Pike
Rockville, MD 20852

Attn.: Paul D. Leber, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

NEW CORRESP

RE: Zonisamide Capsules
NDA 20-789

Dear Dr. Leber:

The following three tradenames are proposed by Athena for zonisamide capsules, in order of preference:

1) Zonegran
2) ——
3) ——

Athena is currently conducting a trademark search on these names. They are being submitted now to maximize the time available for Nomenclature Committee review.

If you have any questions or comments, please contact me at (415) 794-5709 or Larry Rosania at (415) 877-7457. Alternatively, we can be reached by facsimile at (415) 877-7699.

Sincerely,

Louise C. Johnson

Louise C. Johnson
Associate Director, Regulatory Affairs

Consult #870 (HFD-120)

ZONEGRAN

zonisamide capsules

There were no look-alike/sound-alike conflicts noted with all three name candidates nor were there any misleading aspects found with ZONEGRAN or ——. However, the committee felt that ——, communicated the impression of "prompt control" and was therefore potentially misleading.

Overall, the committee found ZONEGRAN and —— acceptable and —— unacceptable.

/S/ 1/28/98, Chair
CDER Labeling and Nomenclature Committee

Exclusivity Summary for NDA 20-789

Exclusivity Summary Form

Trade Name: **Zonegran** Generic Name: **zonisamide capsules**

Applicant Name: **Elan Pharmaceuticals, Inc.**

HFD#: **HFD-120** Approval Date If Known: 3/27/00

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 question about the submission.*

a) Is it an original NDA? YES /_X_/ NO/___/

b) Is it an effectiveness supplement? YES /__/ NO/_X_/
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 /_X_/ 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.

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/_X_/

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

e) Has pediatric exclusivity been granted for this Active Moiety? NO

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? (Rx to OTC switches should be answered NO-please indicate as such) YES /___/ NO/_X_/

If yes, NDA #_____. Drug Name _____.

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

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cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

3. Is this drug product or indication a DESI upgrade? YES /___/ NO/_X_/

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 /_X_/

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

2. Combination product – **not applicable**

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# _____ _____

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.

APPEARS THIS WAY
ON ORIGINAL

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.

(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:

Exclusivity Summary for NDA 20-789

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /___/

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

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 /___/

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

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"):

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 /___/

If no, explain: _____

Investigation #2 IND # _____ YES /___/ NO /___/

If no, explain: _____

Form OGD-011347 Revised 10/13/98
cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

Exclusivity Summary for NDA 20-789

(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 IND # YES /___/ NO /___/

If no, explain: _____

Investigation #2 IND # _____ YES /___/ NO /___/

If 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: _____

Signature: /S/ *Date:* 3/14/00

Title: Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

Signature of Office/Division Director

Signature: /S/ *Date:* 3/29/00

Russell Katz, M.D., Director, HFD-120

APPEARS THIS WAY
ON ORIGINAL

Form OGD-011347 Revised 10/13/98
cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20789	**Trade Name:**	ZONISAMIDE 100 MG CAPSULES
Supplement Number:		**Generic Name:**	ZONISAMIDE 100 MG CAPSULES
Supplement Type:		**Dosage Form:**	Capsule; Oral
Regulatory Action:	PN	**Proposed Indication:**	Adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication, but is inadequate to support pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

___NeoNates (0-30 Days) _X_ Children (25 months-12 Years)

_X_ Infants (1-24 Months) _X_ Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	NEW FORMULATION needed. Applicant in NEGOTIATIONS with FDA
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Sponsor is working on a pediatric development plan and will submit for Agency comment once plan is well defined.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JACKIE WARE

/S/ March 14, 2000

Signature Date