CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40253

BIOEQUIVALENCY REVIEW(S)

OCT - 2 1997

Ethosuximide
250 mg/5 ml syrup, USP
ANDA 40-253
Reviewer: Pradeep M. Sathe, Ph.D.
WP #40253W.597

Pharmaceutical Associates, Inc.
Conestee, SC-29636
Submission Date:
May 21, 1997

REVIEW OF A BIO-STUDY WAIVER REQUEST

I.THE DRUG: Ethosuximide is an anti-convulsant succinimide, chemically designated as alpha-ethyl-alpha-methyl-succinimide. Ethosuximide suppresses the paroxysmal three cycle per second spike and wave activity associated with lapses of consciousness which is common in absence (petit mal) seizures. The frequency of the epileptiform attacks is reduced, apparently by depression of the motor cortex and elevation of the threshold of the central nervous system to convulsive stimuli.

The pharmacokinetics of the drug is characterized by a relatively long half-life (approximately 40-50hr). The absorption appears to be complete, with peak concentration occurring in about 3 hours. Ethosuximide is not significantly bound to plasma proteins. The drug is cleared by renal and non-renal routes, the clearance being approximately 0.19 ml/min/kg. Urinary excretion accounts for up to 25%. The remainder is metabolized by hepatic microsomal enzymes. The major metabolite, the hydroxyethyl derivative, accounts for up to 40% of the administered drug, is inactive and is excreted as such and as glucuronide in the urine.

II.THE SUBMISSION : The application consists of a bio-equivalence study waiver request for the test formulation (syrup) of 250 mg/5 ml strength based on 21 CFR 320.22 (b) (3). The orange book lists 'Parke-Davis's Zarontin^{R} as the reference formulation. Besides the reference, there is a generic formulation on the market, implying that, if approved, this will not be the first generic formulation. The formulation, being a solution (syrup) has an 'AA' rating in the orange book, suggesting that it contains active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems.

III.TEST AND REFERENCE FORMULATIONS : The test and reference formulation composition is given in Table 1. **The test formulation may be a proprietary information of the firm and therefore should not be released under the F.O.I.** The exhibit batch size is gallons and the firm is proposing to scale up the batch size to up to gallons.

Table 1

INGREDIENTS	TEST (Per 5 ml) (%w/v)	REFERENCE (Per 5 ml)
Ethosuximide, USP	250 mg	250 mg
Citric Acid, Anhydrous, USP	mg %)	mg
Sodium Citrate, Dihydrate, USP	mg %)	mg
Sodium Benzoate, NF	mg %)	mg
Glycerine, USP	ml % v/v)	ml % v/v)
Saccharin Sodium, USP	mg %)	mg
Sucrose, NF	mg %)	mg
FD & C Red #40		mg
PFC 9908 Respberry Arome	ml %v/v)	ml
PFC 8580, Cheri Beri flavor	ml %)	
		mg
Purified Water, USP Q.S.	ml	ml

IV.COMMENTS:

1. Ethosuximide is the active ingredient. Sucrose is the sugar in the syrup. Saccharin sodium is a sweetener, citric acid/sodium citrate are pH adjusters, sodium benzoate is a preservative, glycerine and water are co-solvents.

2. The test and reference formulations have identical active ingredients in the exact same quantity. Based on the comparative labelling information, the inactive ingredients citric acid and sodium citrate, glycerine and sucrose are qualitatively similar however quantitatively different. Though different in quantity/ml, glycerine and saccharin sodium are within the potency ranges of the currently marketed drug products, based on the 'Inactive Ingredients Guide'. Sucrose percentage is less than that of the reference formulation. The citric acid, anhydrous and sodium citrate, dihydrate are pH adjusters (buffers). Bioavailability of ethosuximide being close to 1 and having primarily an elimination governed kinetics, the slight alterations in the inactive ingredients such as sucrose, , citric acid/sodium citrate concentrations are unlikely to be of major concern with respect to changes in the absorption rates and safety.

3. The strength, route of administration and the end use of the test formulation is identical to the reference formulation.

V.RECOMMENDATION:

The Division of Bioequivalence agrees that the information submitted by Pharmaceutical Associates, Inc. on its Ethosuximide syrup 250 mg/ 5 ml falls under 21 CFR 320.22 (b) (3) of the Bioavailability/Bioequivalence regulations. The waiver of *in-vivo* bioequivalence study for the test product 250 mg/5 ml Ethosuximide syrup is granted. From the bioequivalence point of view, the test product Ethosuximide syrup 5 mg/ 5 ml (Pharmaceutical Associates, Inc.) is deemed bioequivalent to Zarontin^{R} syrup manufactured by 'Parke Davis'.

/S/

9/4/97

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch I.

RD INITIALED BY YCHUANG /S/
FT INITIALED BY YCHUANG 10/2/97

Concur: /S/ Date: 10/2/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 40-253 (original, duplicate), HFD-650 (Director), HFD-652 (Huang, Sathe), Division File, Drug File.

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:40-253 APPLICANT: Pharmaceutical Associates Inc.

DRUG PRODUCT: Ethosuximide 250mg/5ml syrup

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Ethosuximide
250 mg/5 ml syrup, USP
ANDA 40-253
Reviewer: Pradeep M. Sathe, Ph.D.
W #40253O.900

Pharmaceutical Associates, Inc.
Conestee, SC-29636
Submission Date:
~~September 7, 2000~~
September 11, 2000

ADDENDUM TO THE REVIEW

I.BACKGROUND:

The review of the above product Ethosuximide syrup 250mg/5 ml (ANDA 40-253) was finalized by the Division on October 2, 1997. Since the reference drug product is listed in the 'Orange Bok' with an 'AA' category, a bio-study waiver was granted based on CFR 320.22(b). In the syrup, the firm is using Cheri Beri flavor (PFC 8580), ml or % v/v. Based on the label information, children of the ages 3 and above, are the potential users of the drug product. Pursuant on the current OGD policy on the safety and efficacy of the flavors, it was therefore decided that a detailed composition information on the Cheri Beri flavor, ml or % v/v may be necessary for the adequate assessment of safety of the flavor. Subsequent to the Division request, in a fax amendment dated 09/11/00, Foote & Jenks Corporation, the manufacturers of Cheri Beri flavor, provided detailed composition of the flavor (Attachment I).

II.TEST AND REFERENCE FORMULATIONS:

The test and reference product composition is given in Table 1. The exhibit batch size of the syrup is gallons. The firm is proposing to scale up the batch size to up to gallons. Table 2 gives composition of the Cheri Beri flavor constituents namely 2440 CFX Raspberry and F-9503 Vogue Sweet Cherry. Table 3 gives the percentages of the sub-constituents of these two components.

Note: **The test formulation may be a proprietary information of the firm and therefore should not be released under the F.O.I.**

Table 1: Product Composition

INGREDIENTS	TEST Syrup (Per 5 ml)	REFERENCE, Zarontin by Parke-Davis (Per 5 ml)
Ethosuximide, USP	250 mg	250 mg
Citric Acid, Anhydrous, USP	mg (% w/v)	mg
Sodium Citrate, Dihydrate, USP	mg % w/v)	mg
Sodium Benzoate, NF	mg % w/v)	mg
Glycerine, USP	ml % v/v)	ml (% v/v)
Saccharin Sodium, USP	mg % w/v)	mg
Sucrose, NF	mg (% w/v)	mg
	mg % w/v)	mg
FD & C Red #40	----------	mg
PFC 9908 Respberry Arome	ml % v/v)	ml
PFC 8580, Cheri Beri flavor*	ml % v/v)	
		mg
Purified Water, USP Q.S.	ml	ml

* Table 2: Cheri Beri flavor, PFC 8580 intermediates:

Ingredient	Amount gallons	Amount ml
F-9503 Vogue Sweet Cherry	*lbs*	*mg*
2444 CXC Raspberry	*lbs*	*mg*
Total Yield	**gallons**	**ml**

Table 3: Composition of the Sub-Constituents of the 'Cheri Beri' flavor Intermediates

Ingredient	mg/5ml of flavor	mg/5ml of syrup*	Percent (w/v) in the Syrup	Conclusion
CXC Raspberry 2444				
Arome Artificial Raspberry Flavor				Less than %, acceptable
Alcohol	1373	10.725	0.22	within the limits of IIG
Ethyl Butyrate	17	0.133	0.003	Less than 0.1%, acceptable
Ethyl Acetate	14	0.109	0.002	Less than 0.1%, acceptable
Isolate Orange 2218	35	0.273	0.006	Less than 0.1%, acceptable
Water	2873	22.44	0.46	-------
Total Weight	4720	36.87		
F-9503 Vogue Sweet Cherry				
Benzaldehyde	102	0.267	0.005	Less than 0.1%, acceptable
F-5511 F&J Oil Pistachio	6.2	0.016	0.0003	Less than 0.1%, acceptable
Ethyl Vanillin	1.8	0.0047	0.00009	Less than 0.1%, acceptable
Propylene Glycol	3109	8.134	0.163	within the limits of IIG
Water	1999	5.222	0.105	-------
2515 F&J Red color	10.2	0.027	0.0005	Less than 0.1%, acceptable
Caramel Color 2X	0.7	0.0018	0.00003	Less than 0.1%, acceptable
Total Weight	5228.9	13.68		

* Weight normalized for the actual weight portions of the raspberry and cherry components

III. Comment:

Table 3 indicates that at the given level of dose i.e. 250mg (5 ml) or 500mg (10ml) per day, the individual inactive ingredient levels are below the Agency recommended safe limit of 0.1%. The Cheri-Beri flavor used in the current concentration is therefore deemed within the safety limit.

IV. Recommendations:

1. The Cheri-Beri flavor used in the product is deemed safe at the current safety level. The Recommendations made in the previous review dated 10/2/97 (Application date May 21, 1997) are still valid.

2. The Division of Bioequivalence agrees that the information submitted by Pharmaceutical Associates, Inc. on its Ethosuximide syrup 250 mg/ 5 ml falls under 21 CFR 320.22 (b) (3) of the Bioavailability/Bioequivalence regulations. The waiver of *in-vivo* bioequivalence study for the test product 250 mg/5 ml Ethosuximide syrup is granted. From the bioequivalence point of view, the test product Ethosuximide syrup 5 mg/ 5 ml (Pharmaceutical Associates, Inc.) is deemed bioequivalent to Zarontin[R] syrup manufactured by 'Parke Davis'.

Pradeep M. Sathe, Ph.D.
Division of Bioequivalence,
Review Branch II

/S/ 10/17/2000

RD INITIALED BY SGNerurkar
FT INITIALED BY SGNerurkar

Concur: /S/ Date: 10/27/00
for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA 40-253 (original, duplicate), HFD-650 (Director), HFD-655 (Nerurkar, Sathe), Division File, Drug File.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 40-253 SPONSOR: Pharmaceutical Associates Inc.

DRUG AND DOSAGE FORM: **Ethosuximide Syrup**

STRENGTH(S): **250mg/5ml**

TYPES OF STUDIES: n/a

CLINICAL STUDY SITE(S): n/a

ANALYTICAL SITE(S): n/a

SUMMARY: 'AA' category reference. Flavor found safe. Bio-Waiver request granted.

DISSOLUTION: n/a

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic No New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Pradeep M. Sathe, Ph.D. BRANCH: II

INITIAL: /S/ DATE: 10/18/00

TEAM LEADER: Shrinivas G. Nerurkar, Ph.D. BRANCH: II

INITIAL: /S/ DATE: 10/18/2000

for DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: /S/ DATE: 10/27/00

KAC

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 40253 SPONSOR : Pharmaceutical Associates Inc.

DRUG & DOSAGE FORM : Ethosuximide Syrup

STRENGTH (s) : 250 mg/5 ml

TYPE OF STUDY:N/A Waiver Request

SUMMARY :

1. The test and reference formulations have identical active ingredient in the exact same quantity. The inactive ingredients are qualitatively similar. Though different in quantity/ml, glycerine, and saccharin sodium are within the potency ranges of the currently marketed drug products, based on the 'Inactive Ingredients Guide'. Citric acid and Sodium citrate are for pH adjustment.

2. The strength, route of administration and end use of the test product is identical to the reference product.

3. For the reasons outlined in 1 and 2, the bio-study waiver is granted.

PRIMARY REVIEWER :Pradeep M. Sathe, Ph.D. BRANCH : I

INITIAL : /S/ DATE : 1/20/98

Team Leader : Yih Chain Huang, Ph.D. BRANCH : I

INITIAL : /S/ DATE : 1/20/98

DIRECTOR : Dale Conner, Pharm.D.
DIVISION OF BIOEQUIVALENCE

INITIAL : /S/ DATE : 1/20/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL : _____ DATE : _____