

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40253

CORRESPONDENCE

OCT - 9 1997

Pharmaceutical Associates, Inc.
Attention: Ms. Kaye B. McDonald
P.O. Box 128
Conestee, SC 29636



Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ethosuximide Syrup, 250 mg/5 mL.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'R. N. Patnaik'.

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-253

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
P.O. Box 128
Conestee, SC 29636

|||||

JUN 2 1997

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated May 1, 1997, and your amendment dated May 21, 1997.

NAME OF DRUG: Ethosuximide Syrup ~~USP~~, 250 mg/5 mL

DATE OF APPLICATION: March 26, 1997

DATE OF RECEIPT: March 28, 1997

DATE ACCEPTABLE FOR FILING: May 23, 1997

not a USP product

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/
Jerry Phillips *4/2/97*
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-253

Pharmaceutical Associates, Inc.
Attention: Kaye B. McDonald
P.O. Box 128
Conestee, SC 29636

MAY 1 1997

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated March 26, 1997, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ethosuximide Syrup ~~USR~~ 250 mg/5 mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to include a qualitative and quantitative formulation comparison between your proposed product and the reference listed drug (RLD). This information is necessary to support your request for a request for waiver of *in vivo* bioequivalence under 21 CFR 320.22(b)(3).

The application lacks a letter from the DMF holder, designating the _____ as the U.S. agent with authority to grant access to the DMF.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3) If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Anna Marie H. Weikel
Project Manager
(301) 827-5862

Sincerely yours,

||
/S/ ^ |

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research



December 1, 1999

MAJOR AMENDMENT

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/AC

RE: ANDA 40-253 Ethosuximide Syrup, 250 mg/5 mL

Dear Sirs:

Enclosed please find Form 356h for a major amendment to ANDA 40-253 Ethosuximide Syrup 250mg/5mL. This is in response to the MAJOR DEFICIENCY letter dated October 16, 1998.

Chemistry Deficiencies

1. **Your response regarding pH adjustment, requires either citric acid solution or sodium hydroxide solution to be prepared and used. Master Batch records need to incorporate preparation procedures for both, although they may not be used during production. Also, the components and composition does not include sodium hydroxide (if needed, for pH adjustment). Please address this.**

Steps for preparation of the citric acid and sodium hydroxide solutions, as well as instructions for their use have been added to the Master Batch records. Copies are included on pages 1 - 31. Also, corrected copies of the components and composition, adding "Sodium hydroxide, NF (as needed to adjust pH)" are enclosed on pages 32 - 37.

2. **The packaging/filling records for the product do not indicate an in line filtration system. Wherever appropriate, the records need to reflect what operations are actually carried out.**

As stated in Step of our revised master batch record, Ethosuximide Syrup is screened prior to packaging. The screening apparatus used consists of an outer stainless steel housing with an inner mesh stainless steel screen.

We have added an additional form to our packaging/filling records to better document this operation. A blank sample of this form is included on page 38. This information has been documented in the appropriate equipment logs but is now also included in the batch record.

3. Please provide chromatograms of the placebo, following the assay method and chromatographic impurity method. On page 33 of the amendment you have indicated that excipients elute at RRT (to Ethosuximide) 0.5, 0.8, and at 1.5. Please demonstrate specificity of these methods.

The chromatographic impurity method has been completely revised to improve the sensitivity. The new method is included on pages 39-53. The revised method includes chromatograms of the placebo following the assay method and chromatographic impurity method. Resolution requirements between the ethosuximide, 2-ethyl-2-methylsuccinic acid and the adjacent excipient peak have been established.

4. We further recommend validation of the chromatographic impurity method to address the following: The linearity studies are conducted from _____ % label claim when the limit on 2-ethyl-2-methylsuccinic acid is NMT _____. In this case, linearity studies should be conducted from _____ % of Ethosuximide label claim. Also, a discussion of parameters such as slope, y-intercept, and r^2 should be included. The linearity data provided are not covering the acceptable range. Also, we recommend improving the method to make it more sensitive, to further lower the detection limit. Page 78 of the amendment states that the 2-Ethyl-2-methylsuccinic acid peak is detectable only at _____ %, when _____ % is the limit.

The validation of the revised impurity method is included on pages 54 - 118. Linearity is demonstrated from _____ % of ethosuximide label claim. A discussion of slope, y intercept and r^2 is included on page 60. The revised method is more sensitive with the 2-ethyl-2-methylsuccinic acid detectable at _____ %

5. On page 62 of the amendment response, we are unable to locate a commitment for conducting Antimicrobial Effectiveness Testing on the first three post-approval batches at initial and expiry test stations. Please provide this.

We have enclosed a copy of our commitment to conduct Antimicrobial Effectiveness Testing on the first three post-approval batches at initial and expiry test stations. This statement is included on page 119.

6. We request that you provide all available ambient temperature stability data for the product for the chromatographic impurities test.

The ambient temperature stability data for the product is included on pages 120-127. The impurity testing reported on these pages is using the original method. The revised method was used to test a current lab batch, two retained 90 day accelerated stability and ambient shelf samples which are 36 months old. This data is included on page 128.

7. We request that you lower and propose limits for individual and total limits impurities during stability, based on the ambient data. The results given on page 33-A, for 4 different lots, do not support % total impurities and % single individual impurity limits.

Our stability limits for individual and total impurities were based on results obtained using the original method. Our new method is more sensitive and will likely reveal somewhat higher results. The available data using the new method is included on page 128. The four different lots P381, P382, P383 and P384 are actually different container/closure packaging configurations from the same bulk lot. Our proposed impurity limits are included in our revised specifications on pages 129 - 130.

Labeling Deficiencies

Unit Dose Tray Labeling – 2 × 12 copies of final printed labels incorporating your comments are included on pages 137 - 140.

Insert – 2 × 12 copies of final print incorporating your comments are included on pages 134 - 136.

A side-by-side comparison of the inserts is included on pages 131 - 133.

We have answered all of your questions to the best of our knowledge. If you have any further questions, please let us know.

Sincerely yours,

PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs

AMENDMENT

ORIG AMENDMENT

N/AF

September 7, 2000

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 40-253, Ethosuximide Syrup, 250 mg/5 mL

Dear Sirs,

Please find enclosed form 356h in response to your telephone call on September 7, 2000 concerning ANDA 40-253, Ethosuximide Syrup.

You will find 12 copies of the final print insert on pages 1 – 4.

We have answered all of your questions to the best of our knowledge and ability. Should you require additional information, please do not hesitate to contact us.

Sincerely yours,
PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs



noted 1/8/00
6/15/00

June 8, 2000

MINOR AMENDMENT

ORIG AMENDMENT

NTAM

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 40-253 Ethosuximide Syrup, 250 mg/5mL

Dear Sirs,

Enclosed, please find form 356h for a minor amendment to ANDA 40-253 Ethosuximide Syrup 250 mg/5 mL. This is in response to the MINOR DEFICIENCY letter dated May 24, 2000.

Chemistry Deficiencies

1. **Please tighten your in-process and finished product assay limits for Ethosuximide.**

We have tightened our in-process and finished product assay limits for Ethosuximide to % for bulk and finished product and % for stability. The revised monograph and specification sheet are on pages 1 - 18.

2. **Please demonstrate precision at the limit of detection for the revised chromatographic impurities method.**

We have demonstrated precision at the limit of detection for the revised chromatographic impurities method, the data is on pages 19 69.



3. Please revise your room temperature stability testing frequency to 0, 3, 6, 9, 12, and 18 months for product with an 18 month expiration period, and 0, 3, 6, 9, 12, 18, and 24 months for product with a 24 month expiration period.

We have revised our room temperature stability testing frequency to 0, 3, 6, 9, 12, and 18 months for product with an 18 month expiration period and 0, 3, 9, 12, 18, and 24 months for product with a 24 month expiration period. The revised Stability Protocol is on pages 70 - 71.

4. Please tighten the upper limit of your stability assay limit for Ethosuximide.

We have tightened upper limit of our stability assay limit for Ethosuximide to %. The revised monograph is on pages 1 - 18, and the revised Stability Protocol is on pages 70 - 71.

Acknowledgments

1. Please acknowledge that DMF for Cheri Beri PFC 8580 has been found not acceptable. The DMF holder has been informed of the deficiencies.

We acknowledge that DMF for Cheri Beri PFC 8580 has been found not acceptable.

2. Please acknowledge that a satisfactory methods evaluation and validation for the chromatographic impurity method used to analyze the drug product is required to support the ANDA.

We acknowledge that a satisfactory methods evaluation and validation for the chromatographic impurity method used to analyze the drug product is required to support the ANDA.



Labeling Deficiencies

We have incorporated the changes for the product insert that you requested. You will find the revised insert on pages 72 - 75.

We have answered all of your questions to the best of our knowledge. If you have any further questions, please let me know.

Sincerely yours,

PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs



505(j)(2)(a)(ok)
Anna Marie H. Weikel
5/27/97

May 21, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/C

AMENDMENT

RE: ANDA 40-253 Ethosuximide Syrup USP 250mg/5mL (Response to Refusal to File Letter)

Dear Sir:

Enclosed please find form 356h to requesting an amendment to our ANDA 40-253 Ethosuximide Syrup, USP 250 mg/5 mL. This letter is in response to your refusal to file letter dated May 1, 1997.

On May 13, 1997 we spoke with Anna Marie H. Weikel concerning the qualitative and quantitative formulation comparison between our proposed product and the reference listed drug. A qualitative comparison is included with this amendment. Our proposed product contains the active drug ingredient in the same concentration and dosage form as the reference listed drug and contains the same inactives. We believe this is adequate for an oral solution or syrup.

A letter form the DMF holder, _____ designating the _____ as the US agent with authority to grant access to the DMF is included with this amendment.

Sincerely,

PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Director of Scientific Affairs

RECEIVED

MAY 23 1997

GENERIC DRUGS



*Refuse to File
4/29/97
Oma M*

March 26, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA Ethosuximide Syrup, USP 250mg/5mL

Dear Sir:

Enclosed is the abbreviated new drug application for the drug product Ethosuximide Syrup, USP 250mg/5mL in 5 mL Unit Dose Cups, 16 oz PET, and 16 oz HDPE containers.

We have answered comprehensively, responsibly, and to the best of our ability all required items on Form FDA 356h and have to the best of our knowledge replied to the requirements of 21 CFR Section 314.50 and 314.94 where applicable.

The Table of Contents explains the organization of the application which consists of two volumes. Volume 1 consists of Sections I-XIV and Volume 2 consists of Sections XV-XXI. Each separate section of the ANDA is split off by labeled dividers that contain both the section number of that section and brief description of the section's subject matter (e.g., I. Basis). These dividers correspond to the sections listed in the Table of Contents.

Pharmaceutical Associates, Inc. is filing an archival copy (in blue folder) that contains all the information required in the ANDA and a technical review copy (in red folder) which contains all the information in the archival copy. In addition, we are also providing, in black folders, three additional copies of the methods validation portion of the ANDA.

I certify that a true copy of this application has been provided to the Atlanta District Office.

Thank you for your consideration in this matter.

Sincerely yours,

PHARMACEUTICAL ASSOCIATES, INC.

Kaye B. McDonald

Kaye B. McDonald
Scientific Affairs Manager

RECEIVED

MAR 28 1997

GENERIC DRUGS