

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204417Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: November 30, 2018

To: Billy Dunn, MD
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Dhara Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: (Medication Guide (MG))

Drug Name (established name): ELEPSIA XR (levetiracetam) extended-release

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 204417

Applicant: Sun Pharmaceutical Industries, Inc.

1 INTRODUCTION

On May 29, 2012, Sun Pharma Global FZE submitted for the Agency's review a New Drug Application (NDA) for ELEPSIA XR (levetiracetam) extended-release tablets, 1,000mg and 1,500mg.

A Complete Response (CR) letter was issued to the Applicant on March 29, 2013. On September 2, 2014, the Applicant submitted a Class 2 Complete Response in response to the Agency's CR letter. At the same time, the Applicant notified the Agency that they transferred ownership of this NDA to Sun Pharma Advanced Research Company Limited. ELEPSIA XR was approved on March 2, 2015. The approval was then rescinded (due to facility issues) and a Complete Response letter was issued on the same day, September 21, 2015. The Applicant resubmitted their application on September 21, 2016, which included proposed labeling changes as well as a response to address the facility issues. The Agency issued a CR letter on March 22, 2017. The Applicant then resubmitted their application on July 2, 2018.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on July 6, 2018 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ELEPSIA XR (levetiracetam) extended-release tablets.

2 MATERIAL REVIEWED

- Draft ELEPSIA XR (levetiracetam) MG received on July 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 20, 2018.
- Draft ELEPSIA XR (levetiracetam) Prescribing Information (PI) received on July 2, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 20, 2018.
- Approved KEPPRA XR (levetiracetam) comparator labeling dated October 24, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
11/30/2018

DHARA SHAH
12/01/2018

MARCIA B WILLIAMS
12/02/2018

LASHAWN M GRIFFITHS
12/03/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: November 27, 2018

To: Philip Sheridan
Division of Neurology Products (DNP)

LaShawn Dianat, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for ELEPSIA™ XR (levetiracetam) extended-release tablets, for oral use

NDA: 204417

In response to the DNP consult request dated July 26, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for ELEPSIA™ XR (levetiracetam) extended-release tablets, for oral use (Elepsia XR).

PI: OPDP's comments on the proposed labeling are based on the draft PI received from DNP (LaShawn Dianat) on November 20, 2018 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received from DNP (LaShawn Dianat) on November 23, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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/s/

DHARA SHAH
11/27/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 10, 2015
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 204417
Product Name and Strength: Elepsia XR*** (levetiracetam) extended release tablets
1,000 mg and 1,500 mg
Submission Date: February 4, 2015
Applicant/Sponsor Name: SPARC Ltd. (Sun Pharma Advanced Research Company Ltd.)
OSE RCM #: 2014-2061-1
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Associate Director: Irene Z. Chan, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised container labels, prescribing information, and Medication Guide (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container labels, prescribing information, and Medication Guide are acceptable from a medication error perspective.

¹ Harris J. Label and Labeling Review for Elepsia XR*** (NDA 204417). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JAN 21. 11 p. OSE RCM No.: 2014-2061.

3 LIST OF LABELS AND LABELING REVIEWED

We reviewed the following Levetiracetam Extended-Release Tablets labels and labeling submitted by SPARC Ltd. (Sun Pharma Advanced Research Company Ltd.) on February 4, 2015.

- Container labels (Appendix A)
- Medication Guide (no image)
- Prescribing Information (no image)

APPENDIX A. LABEL AND LABELING SUBMITTED ON FEBRUARY 4, 2015

(b) (4)



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/s/

JUSTINE HARRIS
02/10/2015

IRENE Z CHAN
02/12/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

MEMORANDUM

Date: January 30, 2015

To: Taura Holmes, PharmD
Regulatory Project Manager
Division of Neurology Products (DNP)
Office of Drug Evaluation (ODE)-I

From: Melinda McLawhorn, PharmD, BCPS, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, PharmD, RAC
Team Leader, OPDP

Subject: **NDA 204417**
ELEPSIA XR (levetiracetam) extended-release tablets, for oral use

Background

On November 26, 2014, DNP consulted OPDP to review the draft package insert (PI) and Medication Guide (MG) for original NDA submission for ELEPSIA XR (levetiracetam) extended-release tablets, for oral use (Elepsia XR).

OPDP reviewed the draft substantially complete versions of the PI and MG provided by DNP on January 28, 2015. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the MG under a separate cover. Our comments on the PI are provided below.

Thank you for your consult. If you have any questions, please contact Melinda McLawhorn at 6-7559 or at Melinda.McLawhorn@fda.hhs.gov.

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/s/

MELINDA W MCLAWHORN
01/30/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 30, 2015

To: Billy Dunn, M.D.
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Melinda McLawhorn, PharmD, BCPS, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ELEPSIA XR (levetiracetam) extended-release

Dosage Form and Route: Tablets

Application Type/Number: NDA 204-417

Applicant: Sun Pharma Advanced Research Company Limited

1 INTRODUCTION

On May 29, 2012, Sun Pharma Global FZE submitted for the Agency's review a New Drug Application (NDA) for ELEPSIA XR (levetiracetam) extended-release tablets, 1,000mg and 1,500mg.

A Complete Response (CR) letter was issued to the applicant on March 29, 2013. On September 2, 2014, the Applicant submitted a Class 2 Complete Response in response to the Agency's CR letter. At the same time, the applicant notified the Agency that they transferred ownership of this NDA to Sun Pharma Advanced Research Company Limited.

KEPPRA XR (levetiracetam) is currently approved as an extended release tablet available in a 500 mg and 750 mg tablet. The purpose of the submission is to reduce the number of tablets taken daily by developing a higher strength tablet that is intended to be bioequivalent to KEPPRA XR (levetiracetam).

ELEPSIA XR (levetiracetam) extended-release tablets is indicated for the adjunctive therapy in treatment of partial onset seizures in patients 12 years of age and older with epilepsy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on November 27, 2014, and November 26, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) ELEPSIA XR (levetiracetam) extended-release tablets.

2 MATERIAL REVIEWED

- Draft ELEPSIA XR (levetiracetam) MG received on September 2, 2014 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 28, 2015.
- Draft ELEPSIA XR (levetiracetam) Prescribing Information (PI) received on September 2, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 28, 2015.
- Approved KEPPRA XR (levetiracetam) comparator labeling dated August 7, 2014.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
01/30/2015

MELINDA W MCLAWHORN
01/30/2015

MELISSA I HULETT
01/30/2015

LASHAWN M GRIFFITHS
01/30/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 21, 2015
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 204417
Product Name and Strength:	Elepsia XR*** (levetiracetam) extended release tablets 1,000 mg and 1,500 mg
Product Type:	Single Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	SPARC Ltd. (Sun Pharma Advanced Research Company Ltd.)
Submission Date:	October 6, 2014
OSE RCM #:	2014-2061
DMEPA Primary Reviewer:	Justine Harris, RPh
DMEPA Associate Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

This review evaluates the proposed container labels, prescribing information and Medication Guide for Levetiracetam Extended-Release Tablets, 1,000 mg and 1,500 mg (NDA 204417), for areas of vulnerability that can lead to medication errors.

1.1 REGULATORY HISTORY

Sun Pharma Global FZE submitted a 505(b) (2) application for Levetiracetam Extended-Release Tablets with the proposed strengths of 1,000 mg and 1,500 mg on May 24, 2012. Sun developed higher strength tablets in order to reduce the number of tablets to be taken daily. The application utilizes data referenced from Keppra XR (NDA 022285). Due to clinical deficiencies, FDA issued a complete response letter to Sun Pharma Global FZE on March 29, 2013.

There was a transfer of ownership for this NDA from Sun Pharma Global FZE to SPARC Ltd. (Sun Pharma Advanced Research Company Ltd.) on August 20, 2014. SPARC resubmitted NDA 204417 on September 2, 2014 and provided revised proposed labels and labeling on October 6, 2014.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B- N/A
Previous DMEPA Reviews	C
Human Factors Study	D – N/A
ISMP Newsletters	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed labels and labeling for Levetiracetam Extended- Release Tablets, 1,000 mg and 1500 mg to identify vulnerabilities that could lead to medication errors. DMEPA previously completed a label, labeling and packaging review of Levetiracetam Extended-release tablets for the 500 mg, 750 mg, 1,000 mg, and 1,500 mg (OSE Review 2012-1557 and 2012-1558) on February 5, 2013. In this review, a search of the FDA Adverse Event Reporting System (FAERS) revealed that the majority of errors were identified as wrong frequency errors (n= 47) and wrong technique errors (n = 4). Moreover, recommendations for changes to labels and labeling were provided to mitigate these types of errors. We utilized the results of the previous review cases to inform our current review.

Since the first review cycle for this proposed product, Sun has conducted a bioavailability study and concluded that there is no clinically meaningful impact for dosing in the fed or fasted states; therefore, our previous concerns regarding the risk for administering with food no longer applies. However, we note that the proposed container labels (b) (4) (b) (4). This statement can be removed as it no longer applies.

We identified areas of the insert labeling, container labels and Medication Guide that can be revised to increase clarity, improve readability, and increase prominence of important information to the labels and labeling.

The proposed insert labeling includes dosage and administration instructions that the tablets should be swallowed whole, however, this information is not stated in the Highlights of Prescribing Information or Section 2.1 General Dosing Information of the Full Prescribing Information. Additionally this information is on the side panel of the container label where it might be overlooked. Since this is an extended-release formulation and there have been cases where patients have split or crushed tablets with other currently marketed extended-release formulations of levetiracetam, this important information should be prominently placed in these areas.

In addition, we note that Section 2.1 of the insert labeling states that (b) (4) (b) (4) (b) (4) The statement should be revised (b) (4) (b) (4)

Furthermore, there is lack of clarity regarding the frequency of administration in the Medication Guide. Under the “How should I take levetiracetam extended-release tablets?” section of the Medication Guide, it is stated that “(b) (4) (b) (4) To provide clarity we recommend deleting the word “usually” in the sentence.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that changes are needed to the prescribing information, Medication Guide labeling and container labels in order to promote safe use of this product. We recommend the following revisions are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information

1. Include the statement “tablets should be taken whole; do not split or cut tablets” in the Dosage and Administration section to help to prevent wrong technique errors as this is important information that may be overlooked.
2. Replace Levetiracetam extended release tablet where applicable with the conditionally acceptable name “Elepsia XR.”

B. Full Prescribing Information

1. In Section 2.1 General Dosing Recommendations, include the statement “tablets should be taken whole; do not split or cut tablets”
2. See A.2 above.
3. In Section 2.2 Adult Patients with Impaired Renal Function, it states (b) (4)

(b) (4) . We recommend that the statement be revised (b) (4)

4. The symbols (b) (4) utilized in Section 2 Table 1 of the prescribing information (b) (4)

can be misinterpreted (b) (4)
(b) (4). We recommend that (b) (4) > be replaced with 'greater than' in Table 1.

5. In Section 16.2 *Storage* revise "Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) to include "C" and "F" after each number such as 15°C and 30°F (59°C and 86°F).

C. Medication Guide

1. Under the "How should I take levetiracetam extended-release tablets?" section, delete the word "usually" in the sentence that reads (b) (4)
(b) (4) to help provide clarity that the medication should only be taken once a day and not multiple times per day.

4.2 RECOMMENDATIONS FOR SPARC LTD

We recommend the following be implemented prior to approval of this NDA 204417:

A. Container Labels

1. Include the conditionally acceptable name "Elepsia XR."
2. Remove the statement (b) (4)
(b) (4).
3. To decrease clutter and improve readability, consider removing (b) (4)
(b) (4) from the side panel as this information appears in the strength presentation on the principle display panel and is redundant.
4. Revise the Storage statement "Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) to include units of "C" and "F" after each number.
5. Move the statement (b) (4)
(b) (4) to the Principle Display Panel (PDP), to avoid this important information from being overlooked..

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Elepsia XR that SPARC Ltd. submitted on October 6, 2014, and the reference listed drug.

Table 2. Relevant Product Information for Elepsia XR and the Reference Listed Drug Keppra XR		
Product Name	Elepsia XR	Keppra XR
Initial Approval Date	N/A	500 mg approved September 12, 2008 750 mg approved February 12, 2009
Active Ingredient	levetiracetam	levetiracetam
Indication	Indicated as adjunctive therapy in the treatment of partial onset seizures in patients ≥ 12 years of age with epilepsy	Indicated as adjunctive therapy in the treatment of partial onset seizures in patients ≥ 12 years of age with epilepsy
Route of Administration	oral	oral
Dosage Form	extended release tablets	extended release tablets
Strength	1,000 mg and 1,500 mg	500 mg and 750 mg
Dose and Frequency	Initiate with a dose of 1,000 mg once daily. The once daily dosage may be adjusted in increments of 1,000 mg every 2 weeks to a maximum recommended once daily dose of 3,000 mg. o For patients with mild renal impairment (Creatinine Clearance: 50 mL/min to 80 mL/min), the recommended dosing adjustment is 1,000 mg to 2,000 mg every 24 hours	Initiate with a dose of 1,000 mg once daily. The once daily dosage may be adjusted in increments of 1,000 mg every 2 weeks to a maximum recommended once daily dose of 3,000 mg. o For patients with mild renal impairment (Creatinine Clearance: 50 mL/min to 80 mL/min), the recommended dosing adjustment is 1,000 mg to 2,000 mg every 24 hours o For patients with moderate renal impairment (Creatinine Clearance: 30 mL/min to 50 mL/min), the recommended

	(b) (4)	dosing adjustment is 500 mg to 1,500 mg every 24 hours o For patients with severe renal impairment (Creatinine Clearance less than 30 mL/min), the recommended dosing adjustment is 500 mg to 1,000 mg every 24 hours
How Supplied	bottles of 30, 100 and 500 tablets	white HDPE bottles containing 60 tablets
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]; Dispensed in tight, light-resistant	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure	The 30 count and 100 count bottles have child resistant caps; The 500 count bottles have non-child resistant cap.	

APPENDIX B. Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive and AIMS on October 16, 2014 using the terms, levetiracetam to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified one previous label and labeling review¹. We confirmed that most of the recommendations from the previous review have been implemented, but have additional recommendations to promote safe use of the product.

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on December 10, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Levetiracetam extended-release

E.2 Results

Our search resulted in no cases.

¹ Neshiewat, J. Label, and Labeling Review for Levetiracetam Extended-release Tablets (NDA (b) (4) and ANDA 203059). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 FEB 5. 17 p. OSE RCM No.: 2012-1557 and 2012-1558.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Levetiracetam Extended-Release Tablets labels and labeling submitted by SPARC Ltd. (Sun Pharma Advanced Research Company Ltd.) on October 6, 2014.

- Container labels (Appendix G.2)
- Medication Guide (no image)
- Prescribing Information (no image)

G.2 Label and Labeling Images



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² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE HARRIS
01/21/2015

IRENE Z CHAN
01/21/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 21, 2014

TO: William H. Dunn, M.D.
Director
Division of Neurology Products
Office of New Drugs

FROM: Himanshu Gupta, Ph.D.
Staff Fellow, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Acting Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Recommendation to accept data for NDA 204417,
Levetiracetam Extended Release (1000 mg and 1500 mg)
sponsored by Sun Pharma Advanced Research Company,
Ltd.India, without on-site inspection of the clinical
and bioanalytical sites

The Division of Bioequivalence and GLP Compliance (DBGLPC) recommends accepting study data for **NDA 204417**, which includes study PKD_14_049 without on-site inspections of the clinical site, Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara - 390020, Gujarat, India and analytical site, (b) (4)

(b) (4)
(b) (4). This memo provides the rationale for this recommendation and explains why DBGLPC is declining to inspect the clinical and analytical sites.

Background

The Division of Neurology Products requested routine inspections of the clinical and analytical sites for the following study:

PKD_14_049: A Randomized, Open Label, Two Treatment, Two Period, Two Sequence, Multiple Dose, Crossover, Switchover Relative Bioavailability Study Of Levetiracetam 1500 Mg Extended Release Tablets Of Sun Pharma Advanced Research Company Limited And Keppra Xrtm (Levetiracetam) 750 Mg (2 X 750 Mg Dose) Extended Release Tablets Of Ucb, Inc., In 36 Healthy Human Adult Subjects.

The clinical portion of this study was conducted at the following site:

Clinical Site: Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara, Gujarat, India

The Office of Regulatory Affairs (ORA) inspected Sun Pharmaceutical Industries Vadodara, Gujarat, India, three times in the last four years (b) (4)

(b) (4) covering clinical study portions of three applications. The following table lists applications with studies audited during those inspections, the studies audited, and the dates of conduct of the trials.

Application	Study Number	Study trial dates
NON-RESPONSIVE		
NDA 204417	PKD_10_130 (Fasted)	5/3/2010-5/14/2010
	PKD_10_272 (Fed)	8/30/2010-9/10/2010
NON-RESPONSIVE		

Each inspection included a thorough review of all records including the informed consent process, the clinical facility, all ethics committee reviews and approvals, data collection and integrity, qualifications and training of study personnel, correspondence with the sponsor, adverse event reporting, and adherence to the study protocols and schedules. Reserve samples were also collected. One of the previous inspections assessed study PKD-10-130 (fasted) and PKD-10-272 (Fed) from the same

application (NDA 204417). **None of these inspections resulted in issuance of Form FDA 483, and all final classifications were NAI.**

The previous inspections and similar protocols provide reasonable assurance that Sun Pharmaceutical Industries Ltd., conducted study PKD_14_049 without significant irregularities.

The bioanalytical portion of this study was conducted at the following site:

Analytical Site:

(b) (4)

OSI-DBGLPC inspected the analytical site two times in the last two years, covering three applications. The following table lists applications with studies audited during those inspections, the dates of bioanalyses, and the analytical methods for study sample analyses.

Application	Analytical Method	Bioanalysis dates
NDA 204417	LC-MS/MS	PKD-10-130: (b) (4)
		PKD-10-272: (b) (4)
	NON-RESPONSIVE	

Each inspection included a thorough review of all records associated with the studies and method validations, correspondence with the sponsors and the clinical sites, records of subject sample receipt and storage, notebooks and electronic records, standard operating procedures (SOPs), as well as examination of facilities, and interviews and discussions with the firm's management and staff.

NON-RESPONSIVE

The inspection for [REDACTED] NON-RESPONSIVE and **NDA 204417** (PKD_10_130 (Fasted) & PKD_10_272 (Fed)) found no objectionable conditions. **No Form FDA 483 was issued.** OSI recommended that study data from [REDACTED] NON-RESPONSIVE and **NDA 204417** be accepted for review.

Studies PKD_10_130 (Fasted) & PKD_10_272 (Fed) in **NDA 204417** were conducted at [REDACTED] (b) (4), relying on the similar method validation used in previous inspected study. DBGLPC considers that the inspectional outcomes from recent inspections with methodology representative of that used in the [REDACTED] (b) (4) [REDACTED] (b) (4) [REDACTED] (b) (4) conducted study PKD-14-049 without significant irregularities.

DBGLPC recommends that analytical data for study PKD-14-049 is acceptable for review without an on-site inspection.

Conclusion:

Based on the satisfactory inspections in recent years and the similarity of the methodologies and processes in studies **PKD_10_130** (Fasted) & **PKD_10_272** (Fed), the study data are acceptable for Agency review without an on-site inspection.

Page 5 - NDA 204417, Levetiracetam Extended Release Tablet,
sponsored by Sun Pharma Advanced Research Company, Ltd.
India

Himanshu Gupta, Ph.D.
Staff Fellow, GLP Branch, DBGLPC, OSI

DARRTS cc:

OSI/Kassim/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Dejernet
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Draft: HG 10/08/2014
Edit: AD 10/08/2014 10/09/2014; CRB 10/16/2014

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program
/Analytical Sites/ (b) (4)

(b) (4) /NDA 204-417 2nd inspection
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program
/Clinical Sites/Sun Pharmaceutical Industries Ltd.-Clinical
Pharmacology Unit, Vadodara, India/NDA 204-417

File: BE6763(NDA 204417)

FACTS: NA

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/s/

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10/22/2014

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10/23/2014

**SAFETY REVIEW: COMPARATIVE SAFETY OF
ANTIEPILEPTIC DRUGS DURING PREGNANCY IN THE
NORTH AMERICAN AED PREGNANCY REGISTRY –
2012 DATA**

Application Type	Postmarketing Safety Review: Literature Publication
Application Number(s)	Multiple
Priority or Standard	Standard
Submit Date(s)	Publication May 2012
Received Date(s)	Publication May 2012
Division / Office	Division of Neurology Products Office of New Drugs (OND)
Reviewer Name(s)	M. Lisa Jones, MD MPH
Review Completion Date	July 3, 2013
Established Name	Lamotrigine, Phenobarbital, Valproate, Topiramate, Carbamazepine, Levetiracetam, Phenytoin
(Proposed) Trade Name	Multiple
Therapeutic Class	Antiepileptic Drugs
Applicant	Multiple
Formulation(s)	Multiple
Dosing Regimen	Varies
Indication(s)	Epilepsy
Intended Population(s)	Patients treated with AEDs for multiple indications

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1. INTRODUCTION

1.1 Review Content – Executive Summary

This review addresses the findings of the North American Anti-Epileptic (NAAED) Pregnancy Registry from 1997 to 2011 as published in *Neurology*, May 2012¹. The registry examined the risk of major malformations in infants with first trimester prenatal exposure to one of the following AED monotherapies: valproate, topiramate, phenytoin, phenobarbital, levetiracetam, carbamazepine or lamotrigine.

The NAAED registry collected information on AED use and maternal characteristics through phone interviews at enrollment, at seven months' gestation and postpartum. Malformations were confirmed by medical records. The study found the following risk of major malformations:

- Valproate: 9.3% (30 of 323)
- Phenobarbital: 5.5% (11 of 199)
- Topiramate: 4.2% (15 of 359)
- Carbamazepine: 3.0% (31 of 1,033)
- Phenytoin: 2.9% (12 of 416)
- Levetiracetam: 2.4% (11 of 450)
- Lamotrigine: 2.0% (31 of 1,562)

The publication reported that the relative risk (compared to registry enrollees treated with lamotrigine) was:

- 5.1 (95% CI 3.0–8.5) for valproate
- 2.9 (1.4–5.8) for phenobarbital
- 2.2 (1.2–4.0) for topiramate

The authors found that the proportion of women with epilepsy with seizures during pregnancy ranged from 23% for valproate to 31% for lamotrigine. Valproate was associated with a higher risk of neural tube defects, hypospadias, cardiac defects, and oral clefts while phenobarbital was linked to a higher risk of cardiac defects and oral clefts; five infants exposed to topiramate (1.4%) had a cleft lip. Topiramate was associated with an increased risk of cleft lip compared with a reference population (an external population of 206,224 births from the Brigham and Women's Hospital in Boston).

Reviewer comment: *As noted elsewhere in the review, the Division has previously (2011) changed the label and prepared a Drug Safety Communication to inform patients and prescribers of cases of oral clefts following prenatal topiramate exposure within the NAAED registry.*

¹ Hernandez-Diaz, Smith CR, Shen A et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012; 78: 1692-1699.

This review concludes that the results of the NAAED registry data through 2011 did not find evidence of malformations or adverse events that are not currently addressed in the labels of the respective AEDs. The registry does provide support for previously detected adverse events, particularly for oral clefts during topiramate use. However, since both the prior FDA decision and this publication utilize data from the NAAED registry, this publication does not represent an independent confirmation of this finding.

1.2 Documents Used in this Review

1.1.1 Literature Documents

1. Hernandez-Diaz S, Smith CR, Shen A et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012; 78: 1692-1699.

1.1.2 FDA Documents

1. Topiramate (Topamax ®) NDA 020-505, 020-844. Safety Review: Topiramate Use During Pregnancy. Prepared by M. Lisa Jones, MTD MPH. Dated March 3, 2010.
2. Lamotrigine (Lamictal ®) NDA 20-241, 20-764. Safety Review: Pregnancy Registry Data of an Increased Risk of Oral Clefts with Prenatal Lamotrigine Exposure. Prepared by the M. Lisa Jones, MD MPH. Dated January 19, 2007.

2. NORTH AMERICAN AED PREGNANCY REGISTRY: 2012 RESULTS

2.1 Registry Methods

2.1.1 Patient Enrollment

The North American AED (NAAED) Pregnancy Registry is “an ongoing surveillance system of pregnant women who are taking an AED for any reason.” The women tracked by the registry self-enrolled by calling a toll-free telephone number. To be eligible, a woman must be pregnant and have taken AEDs at some point during her pregnancy.

Reviewer comment: *The units of analysis were pregnancies, and malformations in one or more fetuses in twins were considered as one outcome. In addition, although women could enroll if they had taken AEDs at any point during the pregnancy, the primary analyses only examined women with first-trimester usage of AED monotherapies.*

Of note, although some analyses were limited to women with epilepsy, the NAAED registry enrolled women treated with AEDs for any indication. However, the majority (approximately 90%) of women in the NAAED registry were receiving AEDs for epilepsy, and as discussed in Section 2.1.5, a number of analyses were limited to women with epilepsy.

2.1.2 AED Exposure

The authors reported that women were considered exposed if they used any AED, as monotherapy, during the first 4 months after the last menstrual period.

Reviewer comment: *The Methods section of the publication specifically stated that “Women could have added or switched to different AEDs after the first trimester.”*

The authors stated that the publication presented findings for the first trimester monotherapy-exposed groups for which there were 50 or more women eligible for analysis.

2.1.3 Data Collection

The authors stated that data was collected from the women participating in the registry by interview at enrollment, at 7 months’ gestation and at 8 to 12 weeks after the expected date of delivery. The computer-assisted interviews include questions on start and stop dates of each AED taken, dose, frequency, changes in medication, indication, and, if epilepsy, number and type of seizures during pregnancy; demographic characteristics; habits, such as cigarette smoking, alcohol intake, and use of illicit drugs; medical conditions; use of other medications; family history; and results of any prenatal testing (Hernandez-Diaz et al., pg. 1693).

2.1.4 Outcome Identification

The registry’s “outcomes of interest” were major congenital malformations diagnosed within “12 completed weeks after birth.” The protocol defined a major malformation as “a structural abnormality with surgical, medical, or cosmetic importance. The registry excluded the following as outcomes: minor anomalies, birth marks, deformations, anatomic findings by ultrasound studies in pregnancy that were not identified by the examining pediatrician, complications of prematurity, genetic disorders, and chromosome abnormalities (Hernandez-Diaz, pg. 1693).

The publication summarized that outcomes were identified during the postnatal interview by asking the mother about the birth status, including whether any health problems were found. The mother was asked to complete a medical record release form, and medical records of examination findings through the first 12 weeks of life were requested from the infant’s physicians (both primary care and specialists when applicable). These medical records were reviewed by the registry’s teratologist, who was blinded to exposure status, to determine via the registry’s inclusion or exclusion criteria whether an adverse event had occurred.

Reviewer comment: *As discussed further in the Registry Analysis section of this review below (Section 2.1.5), the publication stated that the outcomes from pregnancies that resulted in spontaneous abortions were not included in their analysis.*

2.1.5 Registry Comparator Groups

As one of the reference groups for their analysis, the authors selected lamotrigine-treated patients within the registry. The authors asserted that use of AED-treated patients as the reference group (i.e., specific AEDs vs lamotrigine) minimized confounding by indication (epilepsy). The lamotrigine-treated patient cohort was chosen because lamotrigine was the most frequently reported AED in the registry. In addition, the authors stated that they believed this approach best addressed “the most clinically relevant question: which AED is safest?” (Hernandez-Diaz et al., pg. 1693).

The registry also used a secondary internal reference group consisting of pregnant women from the general population who were not exposed to an AED. The authors stated that these patients were recruited from the friends and families of registry participants and were tracked by the same protocol used for AED-exposed pregnancies.

The authors stated that for the calculation of expected risk regarding specific malformations, the registry used an external reference group of 206,224 infants born at Brigham and Women’s Hospital in Boston. Information on these pregnancies were tracked using the same inclusion/exclusion criteria for outcomes as the registry with the exception that only malformations or other outcomes identified in the first five days after birth were included, compared to outcomes identified up to 12 weeks after birth in the NAAED registry. The authors stated for the analyses using this external comparator group, malformations identified in the registry after five days of life were excluded.

Reviewer comment: *The comparators used for the different analyses presented are specified in Section 2.2 of this review (Study Results).*

2.1.6 Registry Analysis

The authors stated that registry participants were eligible for analysis if they had a liveborn infant, a stillborn infant, or a pregnancy terminated because of a fetal abnormality and were ineligible if they had a spontaneous abortion, withdrew from the registry, or were lost to follow-up.

Reviewer comment: *It is likely that some percentage of spontaneous abortions were caused by or occurred in conjunction with underlying congenital malformations. Although the NAAED registry has previously included data on any malformations identified in pregnancies ending in spontaneous abortions (as discussed in a prior DNP Safety Team review²), in the analysis described in this publication pregnancies resulting in spontaneous abortions were not analyzed.*

The authors stated that their analysis examined the following factors as potential confounders: maternal age, race, education, alcohol use, cigarette smoking,

² Lamotrigine (Lamictal ®) NDA 20-241, 20-764. Safety Review: Pregnancy Registry Data of an Increased Risk of Oral Clefts with Prenatal Lamotrigine Exposure. Prepared by the M. Lisa Jones, MD MPH. Dated January 19, 2007.

periconceptional folic acid supplementation, illicit drug use, chronic diseases (e.g., insulin-dependent diabetes), and calendar year.

The publication noted that “although women are encouraged to enroll before they have had any prenatal testing, they are enrolled throughout pregnancy.” The registry therefore used the differing terminology below based upon their knowledge of the fetus’ health status:

- **“Pure Prospective” Enrollees:** Women who, at enrollment, have no knowledge of the health status of their unborn infant. Enrollment is considered pure prospective if subjects enroll without having had, for example, a nuchal translucency screening test, chorionic villus sampling, amniocentesis, ultrasound or maternal serum screening.
- **“Traditional” Enrollees:** Women who, at enrollment, have had prenatal screening, such as ultrasound or the tests listed for the pure prospective enrollment, that could have identified a fetal abnormality.

The authors reported performing the following sub-analyses:

- Within women with epilepsy, the authors also examined the risk of seizures during pregnancy among AED-exposed groups.
- To assess the role of indication, the authors restricted the comparisons to women with epilepsy. To assess the impact of gestational time at enrollment, the analysis was restricted to pure prospective subjects.
- To assess the accuracy of maternal AED report, the authors repeated the analyses using only AED use information from medical records.

2.2 Registry Results

2.2.1 Enrollment Results

The authors stated that from February 1997 to June 2011, a total of 7,370 AED-exposed and 479 AED-unexposed women (internal comparison group) were enrolled in the registry. From these total numbers:

- Of 5,667 women taking an AED as mono- therapy during the first trimester, 4,899 were eligible for analysis.
- From the unexposed internal comparison group, 442 subjects were eligible for analysis.

The authors noted that in 2011, the most commonly reported AED monotherapies during the first trimester were lamotrigine, levetiracetam, and topiramate. AEDs were used for epilepsy (92%), mood disorders (6%), migraine (1%), and other conditions.

Reviewer comment: *Although the registry enrolled some women receiving AED treatment for indications other than epilepsy, the authors commented that “the AED pregnancy registry does not reflect the indications in the general population because it targets women with epilepsy (Hernandez-Diaz et al., pg. 1695).” As noted previously in*

this review, the majority of women enrolled in the registry were receiving treatment with the medications for the indication of epilepsy.

2.2.2 Patient Demographics

The publication summarized the demographic characteristics of the women enrolled in the registry in the table below:

FDA Table 1: Summary of NAAED Registry Enrollee Characteristics: 1997 to 2011
(Adapted from Publication Table 1, Hernandez-Diaz, pg. 1693)

1694

Monotherapy for May 2012

Table 1 Characteristics of the study subjects either unexposed or exposed to AEDs in monotherapy during the first trimester: North America AED Pregnancy Registry 1997-2011

Categories*	Unexposed (n = 442) ^b	Lamotrigine (n = 1,562)	Carbamazepine (n = 1,033)	Levetiracetam (n = 450)	Phenytoin (n = 416)	Topiramate (n = 359)	Valproate (n = 323)	Phenobarbital (n = 199)	Oxcarbazepine (n = 182)	Gabapentin (n = 145)	Zonisamide (n = 90)	Clonazepam (n = 64)
Maternal age, y, mean (SD)	31.5 (4.2)	30.24 (5.0)	29.9 (5.5)	29.6 (5.1)	29.8 (5.3)	28.81 (5.5)	28.6 (6.0)	31.1 (5.2)	30.4 (5.5)	31.12 (5.4)	27.4 (5.5)	33.4 (4.4)
Mother's education, n (%)												
< Grade 12	17 (3.9)	181 (11.6)	81 (16.1)	73 (16.3)	30 (18.4)	98 (28.7)	37 (23.1)	7 (8.2)	21 (11.6)	17 (20.5)	19 (21.1)	0 (0.0)
Junior college graduate (2-y)	59 (13.4)	284 (19.7)	109 (21.7)	100 (22.3)	46 (28.2)	98 (28.7)	46 (28.8)	20 (23.5)	50 (27.6)	18 (21.7)	22 (24.4)	9 (24.3)
College graduate (4-y)	177 (40.2)	582 (40.4)	193 (38.5)	170 (37.9)	56 (34.4)	99 (29.0)	50 (31.3)	32 (37.7)	67 (37.0)	23 (27.7)	32 (35.6)	16 (43.2)
Postcollege	187 (42.5)	393 (27.3)	119 (23.7)	106 (23.6)	31 (19.0)	47 (13.7)	27 (16.9)	26 (30.6)	43 (23.8)	25 (30.1)	17 (18.9)	12 (32.4)
Married, n (%)	417 (94.8)	1,289 (89.5)	414 (83.1)	375 (83.9)	133 (81.6)	252 (73.9)	108 (67.9)	78 (82.9)	155 (85.2)	69 (83.1)	64 (71.1)	27 (73.0)
Mother Caucasian, n (%)	401 (90.9)	1,381 (88.4)	903 (87.4)	377 (83.8)	344 (82.7)	325 (90.5)	277 (85.8)	176 (88.4)	155 (85.2)	136 (93.8)	76 (84.4)	60 (93.8)
Father Caucasian, n (%)	394 (89.3)	1,330 (85.3)	882 (85.6)	366 (81.5)	335 (80.5)	295 (82.2)	258 (80.1)	171 (85.9)	149 (81.9)	124 (85.5)	68 (75.6)	59 (92.2)
Primiparity, n (%)	146 (33.0)	663 (42.5)	374 (36.2)	180 (40.0)	135 (32.5)	151 (42.0)	124 (38.4)	51 (25.6)	81 (44.5)	55 (37.9)	50 (55.6)	25 (39.1)
Folic acid supplement at LMP, n (%)	305 (69.0)	1,229 (78.7)	684 (66.2)	358 (79.6)	232 (55.8)	216 (60.2)	209 (64.7)	126 (63.3)	142 (78.0)	82 (56.6)	57 (63.3)	27 (42.2)
Cigarette smoking, n (%)												
None	414 (93.9)	1,422 (91.2)	904 (87.8)	403 (89.6)	352 (85.0)	297 (82.7)	240 (74.3)	174 (87.4)	168 (92.8)	114 (78.6)	78 (88.6)	47 (73.4)
> None, <1/2 pack	16 (3.6)	57 (3.7)	48 (4.7)	26 (5.8)	19 (4.6)	20 (5.6)	35 (10.8)	10 (5.0)	5 (2.8)	7 (4.8)	4 (4.6)	5 (7.8)
>1/2 pack, <1 pack	6 (1.4)	37 (2.4)	27 (2.6)	13 (2.9)	16 (3.9)	22 (6.1)	20 (6.2)	5 (2.5)	5 (2.8)	12 (8.3)	4 (4.6)	5 (7.8)
>1 pack	3 (0.7)	34 (2.2)	41 (4.0)	7 (1.6)	24 (5.8)	15 (4.2)	22 (6.8)	10 (5.0)	2 (1.1)	10 (6.9)	2 (2.3)	6 (9.4)
Yes, but unknown	2 (0.5)	9 (0.6)	10 (1.0)	1 (0.2)	3 (0.7)	5 (1.4)	6 (1.9)	0 (0.0)	1 (0.6)	2 (1.4)	0 (0.0)	1 (1.6)
Alcohol, n (%)												
None	308 (70.0)	1,186 (76.2)	726 (70.4)	347 (77.1)	299 (72.2)	283 (79.1)	222 (68.7)	132 (67.0)	147 (80.8)	102 (70.3)	75 (83.3)	39 (60.9)
Moderate (1-5 drinks/wk)	103 (24.4)	323 (20.8)	265 (25.7)	80 (17.8)	99 (23.9)	62 (17.3)	81 (25.1)	58 (29.4)	29 (15.9)	38 (26.2)	13 (14.4)	23 (35.9)
>5 drinks/wk	20 (4.6)	24 (1.5)	17 (1.7)	16 (3.6)	3 (0.7)	7 (2.0)	8 (2.5)	4 (2.0)	3 (1.7)	1 (0.7)	1 (1.1)	1 (1.6)
Yes, but unknown	9 (2.1)	23 (1.5)	23 (2.2)	7 (1.6)	13 (3.1)	6 (1.7)	12 (3.7)	3 (1.5)	3 (1.7)	4 (2.8)	1 (1.1)	1 (1.6)
Indication epilepsy, n (%)	NA	1,366 (87.5)	1,021 (98.8)	447 (99.3)	416 (100)	302 (84.1)	296 (91.6)	198 (99.5)	179 (98.4)	105 (72.4)	89 (98.9)	19 (29.7)
Age first seizure, y, mean (SD) ^c	NA	17.9 (8.5)	16.6 (8.7)	18.1 (8.7)	18.2 (8.6)	17.09 (8.6)	13.3 (6.3)	14.7 (8.2)	18.8 (9.1)	19.1 (10.0)	13.4 (8.0)	12.4 (6.6)
Seizures during pregnancy, n (%) ^c	NA	424 (31.0)	283 (27.7)	138 (30.9)	113 (27.2)	100 (33.1)	69 (23.3)	40 (20.2)	78 (43.6)	47 (44.8)	21 (23.6)	5 (26.3)

Abbreviations: AED = antiepileptic drug; LMP = last menstrual period.

^a Numbers in columns might not add to the total because of missing values.

^b The unexposed internal comparison group were pregnant women, not taking an AED, who were recruited from among the friends and family members of the enrolled women taking an AED.

^c Among subjects with epilepsy.

2.2.3 Overall Malformations

The authors reported that the overall risk of major malformations associated with first-trimester exposure to specific AEDs ranged from 9.3% for valproate to 2.0% for lamotrigine.

FDA Table 2: Risk of major malformations by first trimester exposure to AEDs within the NAAED Registry compared to unexposed and lamotrigine-treated pregnancies (Adapted from Publication Table 2, Hernandez-Diaz et al., pg. 1695)

Table 2 Risk of major malformations identified among infants who had been exposed to a specific AED in monotherapy during the first trimester and among the internal comparison group of unexposed infants and relative risk of major malformations compared with both unexposed and lamotrigine groups: North America AED Pregnancy Registry 1997-2011

	Unexposed (n = 442) ^b	Lamotrigine (n = 1,562)	Carbamazepine (n = 1,033)	Phenytoin (n = 416)	Levetiracetam (n = 450)	Topiramate (n = 359)	Valproate (n = 323)	Phenobarbital (n = 199)	Oxcarbazepine (n = 182)	Gabapentin (n = 145)	Zonisamide (n = 90)	Clonazepam (n = 64)
Major congenital malformations^a												
No. (%)	5 (1.1)	31 (2.0)	31 (3.0)	12 (2.9)	11 (2.4)	15 (4.2)	30 (9.3)	11 (5.5)	4 (2.2)	1 (0.7)	0 (0)	2 (3.1)
95% CI	(0.37-2.6)	(1.4-2.8)	(2.1-4.2)	(1.5-5.0)	(1.2-4.3)	(2.4-6.8)	(6.4-13.0)	(2.8-9.7)	(0.6-5.5)	(0.02-3.8)	(0.0-3.3)	(0.4-10.8)
Unexposed reference												
Relative risk	Reference	1.8	2.7	2.6	2.2	3.8	9.0	5.1	2.0	0.6	NA	2.8
95% CI		(0.7-4.6)	(1.0-7.0)	(0.9-7.4)	(0.8-6.4)	(1.4-10.6)	(3.4-23.3)	(1.8-14.9)	(0.5-7.4)	(0.07-5.2)		(0.5-14.8)
Exposed reference												
Relative risk		Reference	1.5	1.5	1.2	2.2	5.1	2.9	1.1	0.3	NA	1.6
95% CI			(0.9-2.5)	(0.7-2.9)	(0.6-2.5)	(1.2-4.0)	(3.0-8.5)	(1.4-5.8)	(0.4-3.2)	(0.05-2.5)		(0.4-6.8)
Exposed reference restricted to pure prospective participants												
Relative risk		Reference	1.1	1.4	0.8	2.5	4.2	2.5	1.5	0.5	NA	1.3
95% CI			(0.6-2.2)	(0.6-3.4)	(0.3-2.1)	(1.2-5.2)	(2.1-8.3)	(0.9-6.8)	(0.5-4.6)	(0.07-4.1)		(0.2-10.1)

Abbreviations: AED = antiepileptic drug; CI = confidence interval.

^a Diagnosed during pregnancy or before 12 weeks after birth. Confirmed by review of medical records.

^b The unexposed internal comparison group were pregnant women not taking an AED, who were recruited from among the friends and family members of the enrolled women taking an AED.

The authors noted that, compared to lamotrigine-exposed pregnancies, the relative risk of major malformations was 1.2 (95% 95% C.I. 0.6–2.5) for levetiracetam and 2.2 (1.2–4.0) for topiramate. The authors further stated that “neither restriction to pure prospective enrollees, nor adjustment for potential confounders, nor restriction to women with epilepsy, nor use of AED information from medical records (data not shown) changed the results significantly.” For example, compared with lamotrigine, the relative risk for topiramate was (Hernandez-Diaz et al., pg. 1695):

- 2.5 (1.2–5.2) after restriction to pure prospective enrollees,
- 2.2 (1.2– 4.2) after adjustment for potential confounders,
- 2.4 (1.2– 4.6) after restriction to nonsmokers, 3.1 (1.6 –5.9) after restriction to women with epilepsy,
- 2.2 (1.2– 4.1) based on AED information from medical records

Compared with the unexposed reference group, the relative risk of major malformations was 2.2 (0.8–6.4) for levetiracetam and 3.8 (1.4 –10.6) for topiramate.

2.2.4 Specific Malformations

The publication summarized the frequency of specific malformations for each AED in the tables below.

FDA Table 3: Specific malformations diagnosed before 5 days of age among infants exposed to the AED monotherapies in the North America AED Pregnancy Registry 1997–2011 and among an external reference population from Brigham and Women’s Hospital in Boston (Adapted from Publication Table 3, Hernandez-Diaz et al., pg. 1697)

Table 3 Prevalence of most common specific malformations diagnosed before 5 days of age among infants exposed to the AED monotherapies most commonly reported in the North America AED Pregnancy Registry 1997–2011 and among an external reference population from Brigham and Women’s Hospital in Boston								
Major congenital anomaly ^a	Lamotrigine (n = 1,562)	Carbamazepine (n = 1,033)	Phenytoin (n = 416)	Levetiracetam (n = 450)	Topiramate (n = 359)	Valproate (n = 323)	Phenobarbital (n = 199)	External reference, % ^b
Hypospadias^c								
No. (%)	0	1 (0.19)	0	0	2 (1.1)	5 (3.1)	1 (0.97)	0.04
95% CI		(0.01–0.93)			(0.19–3.6)	(1.1–6.7)	(0.05–4.7)	
Neural tube defects								
No. (%)	2 (0.13)	3 (0.29)	0	1 (0.22)	0	4 (1.2)	0	0.12
95% CI	(0.02–0.42)	(0.07–0.79)		(0.01–1.1)		(0.39–3.0)		
Cardiovascular anomalies								
No. (%)	3 (0.19)	3 (0.29)	4 (0.96)	1 (0.22)	1 (0.28)	8 (2.5)	5 (2.5)	0.33
95% CI	(0.05–0.52)	(0.07–0.79)	(0.31–2.4)	(0.01–1.1)	(0.01–1.4)	(0.12–4.6)	(0.93–5.5)	
Oral clefts								
No. (%)	7 (0.45)	5 (0.48)	2 (0.48)	0	5 (1.4)	4 (1.2)	4 (2.0)	0.11
95% CI	(0.20–0.88)	(0.18–1.1)	(0.08–1.6)		(0.51–3.1)	(0.39–3.0)	(0.64–4.8)	

Abbreviations: AED = antiepileptic drug; CI = confidence interval.

^a Restricted for malformations diagnosed before 5 days of age, including elective terminations, to be comparable with the external reference population. Confirmed by review of medical records. Some infants had more than one defect.

^b Prevalence among 206,224 births, including stillbirths and elective terminations surveyed for anomalies at Brigham and Women’s Hospital in Boston.

^c Excludes mild glandular hypospadias. Restricted to male infants.

In a comparison of the lower bound of the risk estimates with the risk in the external reference population, the authors noted that valproate was associated with an increased risk of neural tube defects, hypospadias, and cardiovascular malformations, and phenobarbital was associated with a higher risk of cardiovascular malformations. The risk of oral clefts was higher among infants exposed to phenobarbital, valproate, and topiramate. Among the topiramate-exposed infants, there were five infants with cleft lip.

Reviewer comment: *As the result of a prior DNP safety review, the labeling for topiramate notes an elevated risk of oral clefts following prenatal exposure.*³

For topiramate, based on 5 events among 359 women exposed in monotherapy during the first trimester, the authors found a risk of cleft lip of **14 per 1,000 pregnancies**. The lower bound of the 95% CI was 5.1 per 1,000, which the authors stated was still higher than the expected risk in the background population. Another registry from the United Kingdom has reported a risk of oral clefts of 29 (95% CI 5–91) per 1,000 (among 70 topiramate monotherapy users), more than 10 times their background risk. A recent study from Denmark has reported 1 case among 108 women exposed during the first trimester, corresponding to a risk of 9.3 cases (95% CI 0.5– 45) per 1,000 compared with 1.7 per 1,000 in their unexposed population (Hernandez-Diaz et al., pg. 1697).

Reviewer comment: *The DNP has previously reviewed the information on topiramate and oral clefts described above⁴ and has included this data in the topiramate label (See Section 5.1 for the FDA Drug Safety Communication on the issue). Section 8.1 PREGNANCY of the Topamax label includes the following information:*

Human Data

Data from the NAAED Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.2% compared to a prevalence of 0.39% - 0.46% in infants exposed to other AEDs, and a prevalence of 0.12% in infants of mothers without epilepsy or treatment with other AEDs. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral clefts in the United States and found a similar background rate of 0.17%. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 9.6 (95% Confidence Interval = CI 3.6 – 25.7) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts of 3.2% among infants exposed to topiramate monotherapy. The observed rate of oral clefts was 16 times higher than the background rate in the UK, which is approximately 0.2%.

³ Topiramate (Topamax ®) NDA 020-505, 020-844. Safety Review: Topiramate Use During Pregnancy. Prepared by M. Lisa Jones, MTD MPH. Dated March 3, 2010.

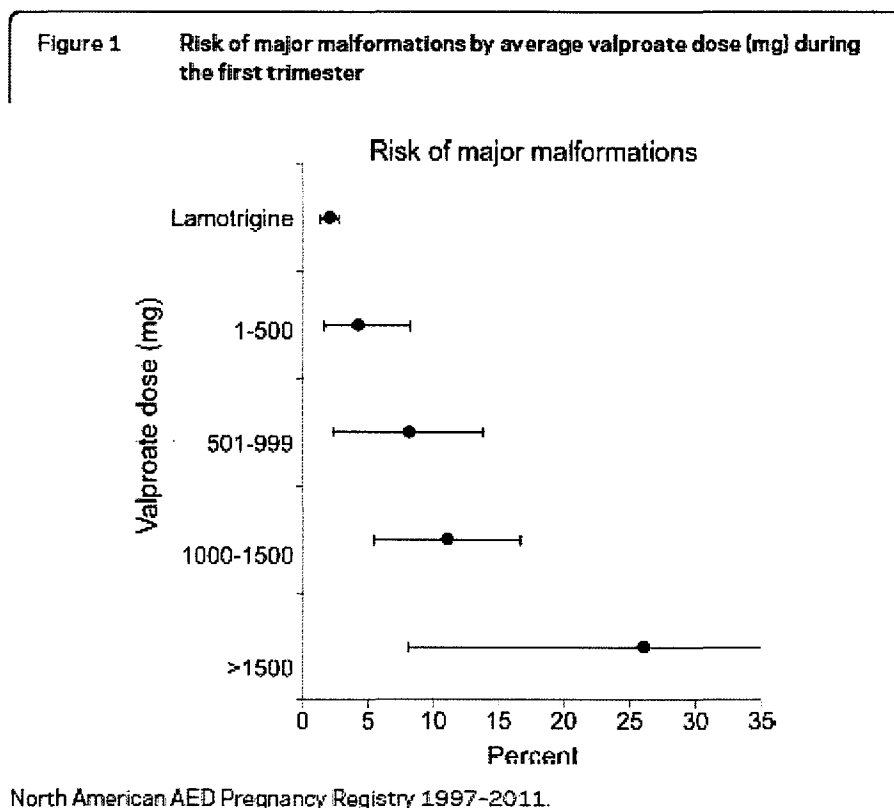
⁴ Topiramate (Topamax ®) NDA 020-505, 020-844. Safety Review: Topiramate Use During Pregnancy. Prepared by M. Lisa Jones, MTD MPH. Dated March 3, 2010

2.2.5 Other Analyses: Dose

As shown in the figure below, the authors found that the risk of major malformations increased with valproate dose, with the median average daily dose during the first trimester was 1,000 mg for pregnancies with malformations and 750 mg for those without malformations. The publication reported that no apparent dose trend was found for other AEDs (Hernandez-Diaz, pg. 1695).

Reviewer comment: *The valproate labeling already contains information on the risk of congenital malformations in multiple sections, including the following in the Boxed Warning: “Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida).”*

FDA Figure 1: Major malformation risk by average dose of valproate during the first trimester (Publication Figure 1, Hernandez-Diaz et al., pg. 1696)

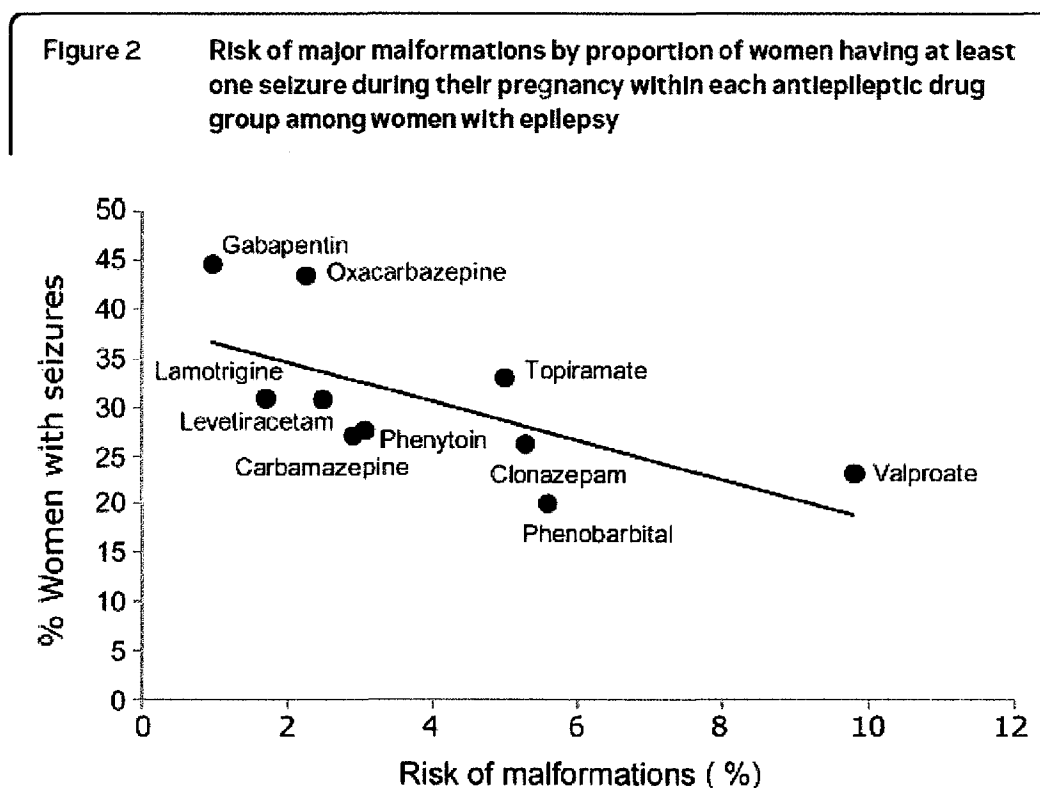


2.2.6 Other Analyses: Seizures

The publication reported that in the registry, the proportion of women with epilepsy who reported seizures during pregnancy varied among AED, as shown in the figure below. The authors found that, contrary to the hypothesis that seizures could contribute to fetal

harm and malformations, in the registry the AED groups with a higher frequency of seizures generally had a lower risk of major malformations.

FDA Figure 2: Risk of major malformations by proportion of epileptic women with at least one seizure during pregnancy by antiepileptic drug group (Publication Figure 2, Hernandez-Diaz et al., pg. 1696)



North American AED Pregnancy Registry 1997-2011.

The authors stated that when the analysis is restricted to valproate and phenobarbital users, women without seizures during pregnancy had a numerically higher risk of malformations (10.6% and 6.3%, respectively) than women with seizures (7.3% and 2.5%), and such a difference was not explained by AED dose. The authors cautioned that these analyses were based on small numbers and should be considered exploratory.

Reviewer comment: Further information on the relationship between maternal seizure frequency and infant adverse outcomes is presented in Section 3 of this review (Sponsor Conclusions).

3. SPONSOR CONCLUSIONS

In their conclusions, the publication discussed the following issues:

- ***Confounding by Indication:*** The authors noted that the evaluation of the teratogenic effects of AEDs is complicated by the fact that epilepsy itself could potentially increase the risk of birth defects. However, the authors stated that several lines of evidence suggest that the type of epilepsy and the number of seizures during pregnancy do not appear to affect the risk of malformations. The authors asserted that the risk of malformations was higher in the infants of women taking AEDs than in those with untreated epilepsy during pregnancy, and women with a history of epilepsy but taking no AED do not have an increased risk of having children with major malformations. However, the authors acknowledged that the latter observations might also reflect an effect of disease severity, because epilepsy “can seldom remain untreated, and untreated women are likely not comparable to women taking AEDs.”
- ***Effect of Analysis Comparator Group and Other Subanalyses:*** In addition to the lamotrigine-exposed reference group, the registry used two unexposed comparison groups, one external and the other internal. The authors stated that “it was reassuring to see that there was no qualitative difference in the main conclusions from either of these comparisons. Results were also similar when restricting the sample to pure prospective enrollees, when using evidence of AED prescriptions in medical records, when adjusting for potential confounders, or when restricting the sample to women with epilepsy.
- ***Medical Record Release Compliance:*** The authors stated that over 70% of the enrolled mothers provided medical records release forms. Medical records were received from the neurologist or psychiatrist who prescribed the AED for 65% of the mothers and from the pediatrician for 59% of the infants. In a validation study, the authors found a 99% agreement between the mother’s verbal report and the doctors’ records for the infants whose mothers had provided permission. However, authors reported that the sensitivity of maternal report might be lower for women who did not provide permission.
- ***Generalization of Registry Results:*** The authors attributed the low risk of malformations in this study, relative to that in other reports, to the registry’s strict outcome inclusion criteria. The risk of oral clefts is similar to that included in the currently approved labeling.
- ***Effect of Seizures on Fetal Outcomes:*** In the absence of randomization, the authors speculated that the differences in effectiveness observed among the drugs may be due to the underlying indication. For example, clinicians might continue valproate or phenobarbital treatment for women of childbearing age when their epilepsy is well controlled and be reluctant to switch drugs and risk seizure recurrence. Conversely, newer AEDs could have been prescribed to patients whose epilepsy was not responding to traditional drugs. Another important factor is the pharmacokinetic changes during pregnancy due to increased clearance, which may be particularly pronounced for specific AEDs and can increase the risk of seizures.

4. DISCUSSION AND RECOMMENDATIONS

4.1 Discussion

This review addresses the findings of the North American Anti-Epileptic (NAAED) Pregnancy Registry from 1997 to 2011 as published in *Neurology*, May 2012⁵. The registry examined the risk of major malformations in infants with first trimester prenatal exposure to one of the following AED monotherapies: valproate, topiramate, phenytoin, phenobarbital, levetiracetam, carbamazepine or lamotrigine.

The NAAED registry collected information on AED use and maternal characteristics through phone interviews at enrollment, at 7 months' gestation and postpartum. Malformations were confirmed by medical records. The study found the following risk of major malformations:

- Valproate: 9.3% (30 of 323)
- Phenobarbital: 5.5% (11 of 199)
- Topiramate: 4.2% (15 of 359)
- Carbamazepine: 3.0% (31 of 1,033)
- Phenytoin: 2.9% (12 of 416)
- Levetiracetam: 2.4% (11 of 450)
- Lamotrigine: 2.0% (31 of 1,562)

The publication reported that the relative risk (compared to registry enrollees treated with lamotrigine) was:

- 5.1 (95% CI 3.0–8.5) for valproate
- 2.9 (1.4–5.8) for phenobarbital
- 2.2 (1.2–4.0) for topiramate

The authors found that the proportion of women with epilepsy who had seizures during pregnancy ranged from 23% for valproate to 31% for lamotrigine. Valproate was associated with a higher risk of neural tube defects, hypospadias, cardiac defects, and oral clefts and phenobarbital with a higher risk of cardiac defects and oral clefts; 5 infants exposed to topiramate (1.4%) had a cleft lip. Topiramate was associated with an increased risk of cleft lip compared with that of a reference population (an external population of 206,224 births from the Brigham and Women's Hospital in Boston).

Reviewer comment: As noted elsewhere in the review, the Division has previously (2011) changed the label and prepared a Drug Safety Communication to inform patients and prescribers of cases of oral clefts following prenatal topiramate exposure within the NAAED registry.

⁵ Hernandez-Diaz, Smith CR, Shen A et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012; 78: 1692-1699.

This review concludes that the results of the NAAED registry through 2011 did not find evidence of malformations or adverse events that are not currently addressed in the labels of the respective AEDs. The registry does provide support for previously detected adverse events, particularly for oral clefts during topiramate use. However, since both the prior FDA decision and this publication utilize data from the NAAED registry, this publication does not represent an independent confirmation of this finding.

4.2 Recommendations

This review concludes that the registry confirms prior DNP review of the teratogenic potential of individual AEDs, particularly the risk of oral cleft defects with prenatal exposure to topiramate. The current labeling adequately describes this risk. The Division should continue to monitor data from the NAAED registry for potential emerging signals for safety issues related to prenatal AED exposure.

5. ATTACHMENTS

5.1 Drug Safety Communication for Oral Clefts following Prenatal Exposure to Topiramate

FDA Drug Safety Communication: Risk of oral clefts in children born to mothers taking Topamax (topiramate)

(Taken from <http://www.fda.gov/Drugs/DrugSafety/ucm245085.htm>)

Safety Announcement

Additional Information for Patients

Additional Information for Healthcare Professionals

Data Summary

Safety Announcement

[03-04-2011] The U.S. Food and Drug Administration (FDA) is informing the public of new data that show that there is an increased risk for the development of cleft lip and/or cleft palate (oral clefts) in infants born to women treated with topiramate (Topamax and generic products) during pregnancy.

The benefits and the risks of topiramate should be carefully weighed when prescribing this drug to women of childbearing age, particularly for conditions not usually associated with permanent injury or death. Alternative medications that have a lower risk of oral clefts and other adverse birth outcomes should be considered for these patients. If the decision is made to use topiramate in women of childbearing age, effective birth control should be used. Oral clefts occur in the first trimester of pregnancy before many women know they are pregnant.

Topiramate was previously classified as a Pregnancy Category C drug, which means that data from animal studies suggested potential fetal risks, but no adequate data from human clinical trials or studies were available at the time of approval. However, because of new human data that show an increased risk for oral clefts, topiramate is being placed in Pregnancy Category D.

Pregnancy Category D means there is positive evidence of human fetal risk based on

Facts about Topiramate

- An anticonvulsant medication FDA-approved for use alone or with other medications to treat patients with epilepsy who have certain types of seizures.
- FDA-approved for use to prevent migraine headaches, but not to relieve the pain of migraine headaches when they occur.¹
- Has been used off-label (for unapproved uses) for other conditions, some of which may not be considered serious.
- From January 2007 through December 2010, approximately 32.3 million topiramate prescriptions were dispensed and approximately 4.3 million patients filled topiramate prescriptions from the outpatient retail pharmacies in the U.S.²

human data but the potential benefits from use of the drug in pregnant women may be acceptable in certain situations despite its risks.

(see [Data Summary](#))

Additional Information for Patients

- If you take topiramate during pregnancy, there is a higher risk that your baby will develop a cleft lip and/or cleft palate. Oral clefts happen early in pregnancy, before many women even know they are pregnant. For this reason, women of childbearing age should talk to their healthcare professionals about other treatment options.
- Women of childbearing age who do decide to take topiramate and are not planning a pregnancy should use effective birth control (contraception) while taking topiramate. Women should talk to their healthcare professionals about the best kind of birth control to use while taking topiramate.
- Before you start topiramate, you should tell your healthcare professional if you are pregnant or are planning to become pregnant. Healthcare professionals may discuss other treatment options with you.
- You should tell your healthcare professional right away if you become pregnant while taking topiramate. You and your healthcare provider should decide if you will continue to take topiramate while you are pregnant.
- Topiramate should not be stopped without talking to a healthcare professional, even in pregnant women. Stopping topiramate suddenly can cause serious problems. Not treating epilepsy during pregnancy can be harmful to women and their developing babies.
- If you become pregnant while taking topiramate, you should talk to your healthcare professional about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect additional information about the safety of antiepileptic drugs during pregnancy. Information about the North American Drug Pregnancy Registry can be found at <http://www.massgeneral.org/aed/>¹.
- Topiramate passes into breast milk, but its effects on developing babies remain unknown. You should talk to your healthcare professional about the best way to feed your baby if you take topiramate.
- You should report any side effects you experience to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of the page.
- You should read the Medication Guide when picking up a prescription for topiramate. It will help you understand the potential risks and benefits of this medication.

Additional Information for Healthcare Professionals

- You should inform women of childbearing age of the increased risk for oral clefts when topiramate is used in the first trimester of pregnancy.

- You should weigh the benefits and risks of topiramate when prescribing this drug to women of childbearing age, particularly when treating a condition not usually associated with permanent injury or death. Alternative medications that have a lower risk of oral clefts and other adverse birth outcomes should be considered. Healthcare professionals should discuss the relative risks and benefits of appropriate alternative therapies.
- If the decision is made to prescribe topiramate to women of childbearing age, healthcare professionals should recommend use of effective contraception for women who are not planning a pregnancy, keeping in mind the potential for a decrease in hormonal exposure and a possible decrease in contraceptive efficacy when using estrogen-containing birth control with topiramate.
- You should inform patients of the North American Antiepileptic Drug (NAAED) Pregnancy Registry and encourage patients who become pregnant to enroll by calling 1-888-233-2334.
- You should report adverse events involving topiramate to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

Data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.4% compared to a prevalence of 0.38% - 0.55% in infants exposed to other antiepileptic drugs (AEDs), and a prevalence of 0.07 % in infants of mothers without epilepsy or treatment with other AEDs. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 21.3 as compared to the risk in a background population of untreated women (95% Confidence Interval: 7.9 – 57.1). The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts (3.2 %) among infants exposed to topiramate monotherapy, a 16-fold increase in risk compared to the risk in their background population (0.2%).

The benefits and the risks of topiramate should be carefully weighed when prescribing this drug for women of childbearing age, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. Appropriate alternative treatment should be considered. Inform women of childbearing age of the increased risk for having a baby with an oral cleft if they become pregnant while using topiramate.

Cleft lip and cleft palate range from a small notch in the lip to a groove that runs into the roof of the mouth and nose, possibly leading to problems with eating, talking and ear infections. Surgery is often used to close the lip and palate. With treatment, most children with cleft lip or palate do well.³

1. U.S. National Library of Medicine. National Institutes of Health. Topiramate monograph. Available at

- <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a697012.html>². Accessed January 6, 2011.
2. SDI, Vector One[®]: National (VONA) and Total Patient Tracker (TPT). January 2007-December 2010. Data extracted 2-9-11
 3. U.S. National Library of Medicine. National Institutes of Health. Cleft Lip and Palate health topic. Available at <http://www.nlm.nih.gov/medlineplus/cleftlipandpalate.html>³. Accessed January 6, 2011.

Related Information

- [Questions and Answers: Risk of oral clefts \(cleft lip and/or palate\) in infants born to mothers taking Topamax \(Topiramate\)](#)⁴
- [FDA Drug Safety Podcast for Healthcare Professionals: Risk of oral clefts in children born to mothers taking Topamax \(topiramate\)](#)⁵
- [FDA: Risk of oral birth defects in children born to mothers taking topiramate](#)⁶
Press Release
- [Topiramate \(marketed as Topamax\) Information](#)⁷

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/s/

MARION L JONES
07/03/2013

SALLY U YASUDA
07/03/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 15, 2013

TO: Russell Katz
Director
Division of Neurology Products

FROM: Gopa Biswas, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 204417, Levetiracetam
Extended Release Tablets, 1000mg and 1500 mg,
sponsored by Sun Pharma Advanced Research Company,
Ltd. (SPARC Ltd.)

At the request of the Division of Neurology Products (DNP), the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted an inspection of the clinical and analytical portions of the following bioequivalence studies:

Study # 1: PKD_10_130
Study Title: "A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Levetiracetam 1500 Mg Extended Release Tablets of Sun Pharmaceutical Industries Ltd, India and KEPPRA XR™ (Levetiracetam) 750 mg (2x 750mg dose) Extended Release Tablets of Ucb, Inc., Smyrna, GA 30080 in

18 healthy human adult subjects, under fasting conditions."

Study # 2: PKD_10_272

Study Title: "A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Levetiracetam 1500 mg Extended Release Tablets of Sun Pharmaceutical Industries Ltd, India and KEPPRA XR™ (Levetiracetam) 750 mg (2 X 750 mg Dose) Extended Release Tablets of Ucb, Inc., Smyrna, GA 30080 in 24 healthy human adult subjects, under fed conditions."

The inspection was conducted

(b) (4)

(b) (4)

by ORA Investigator Allen Hall and DBGLPC scientist Gopa Biswas. The audit included a thorough review of study records, examination of facilities, equipment, interviews and discussions with the firm's management and staff.

At the conclusion of the inspection, no objectionable conditions were observed and no Form FDA-483 was issued.

Conclusions:

Following review of the above inspection, the DBGLPC reviewer recommends that data from studies PKD_10_130 and PKD_10_272 be accepted for further agency review.

Gopa Biswas, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Page 3 - NDA 204417, Levetiracetam Extended Release Tablets,
1000mg and 1500 mg

Final Classification:

NAI: Sun Pharmaceutical Industries Ltd. (SPIL)
FEI#: 3004520113

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Dejernet

DBGLPC/BeB/Haidar/Cho/Biswas

OND/ODEI/DNP/Lana Y Chen/Russell Katz/Rusinowitz, Martin

CDER/OCP/DCPI/Dimova, Hristina

ORA/ (b) (4) /Allen Hall

Draft: GB 1/15/2013

Edit: JSC 1/16/2013; SHH 1/18/2013; WHT 1/18/2013

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ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/Electronic Archive/BEB

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GOPA BISWAS
01/18/2013

SAM H HAIDAR
01/18/2013

WILLIAM H TAYLOR
01/18/2013