Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 28, 2011
To:	Thomas P. Laughren, M.D. Director, Division of Psychiatry Products
Through:	Solomon Iyasu, MD, MPH, Director, Division of Epidemiology I (DEPI-I) Tarek A. Hammad, MD, PhD, MSc, MS Deputy Division Director, DEPI-I
From:	Andrew D. Mosholder, M.D., M.P.H. Medical Officer, DEPI-II
Subject:	Addendum to 9-1-11 review of FDA / AHRQ-sponsored observational studies of cardiovascular events with drugs for Attention Deficit Hyperactivity Disorder (ADHD)
Drug Name(s):	Amphetamine products, methylphenidate products, atomoxetine
Tracked Safety Issue Number:	TSI #114
Applicant/sponsor:	multiple
OSE RCM #:	2006-536

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1 INTRODUCTION

The purpose of this memo is to provide an update to the 9-1-11 Division of Epidemiology review of FDA / AHRQ-sponsored observational studies of cardiovascular events with drugs for Attention Deficit Hyperactivity Disorder (ADHD). Please refer to that review for a description of these observational studies. This memo will discuss certain revisions that the investigators made to the youth study and the combined adult studies pursuant to journal peer review of manuscripts describing the studies. The updated Child ADHD study report has been posted on the AHRQ website.

2 MATERIAL REVIEWED

1. Attention Deficit Hyperactivity Disorder Medications and Risk of Serious Cardiovascular Disease in Children and Youth, updated study report dated 10-25-11
2. "Summary of Changes to Child ADHD Report" provided by Dr. William Cooper, received 11-14-11
3. Revised manuscript for Journal of the American Medical Association (JAMA), Habel et al., ADHD Medications and Risk of Serious Cardiovascular Events In Young and Middle-Aged Adults, received 11-4-11
4. Letter dated 11-4-11, from Dr. Laurel Habel to JAMA editors, responding to peer review comments

3 DISCUSSION

1. Updates to child ADHD report

The main change from the previous study report was to remove four transient ischemic attacks which had been inappropriately included in the numerators for the analysis. Before the 9-1-11 DEPI review was finalized, the investigators noted this error and supplied the corrected results, which were included in the 9-1-11 DEPI/OSE review. The other changes outlined in the "Summary of Changes to Child ADHD Report" principally involved data that were not presented in the 9-1-11 DEPI review. Appendix 12 was added to address comments from FDA regarding the heterogeneity of event rates by type of insurance (Medicaid versus private); this issue was noted in the 9-1-11 review. Also, as pointed out in the Statistical Safety Review and Evaluation Addendum by Dr. Bradley McEvoy, dated 11-3-11, the revised report omits some materials previously included in the original study report; the interested reader may refer to Dr. McEvoy's review for details.

On balance, the changes do not materially affect the previous review and interpretation of the child ADHD study findings. Accordingly, no revisions to the DEPI review of the child ADHD report are needed based on the updated study report.

2. Updates to adult ADHD studies

The manuscript for the adult ADHD study includes some additional data displays and figures that were not included in the study reports. Below is a summary of some additional data pertaining to the issue of site heterogeneity. The tables below display rates of events and rate ratios by site.

Table 1. Endpoints per 1000 person years, by site, standardized to age and gender distribution of all sites combined (source: eTable 8 in manuscript).

Site	Sudden cardiac death	MI	Stroke
OptumInsight (Ingenix)	0.25	1.26	0.50
Kaiser California	0.27	1.23	0.65
TN Medicaid	1.34	4.20	1.82
HMORN	0.10	1.12	0.44

Table 2. Rate ratios, current use/nonuse, and 95% confidence intervals by site (source: eTable 10 in manuscript). Adjusted for age, sex, calendar year, confounder risk score

Site	Sudden cardiac death	MI	Stroke	Combined
OptumInsight (Ingenix)	0.89 (0.49-1.62)	0.93 (0.71-1.23)	0.60 (0.36-0.98)	0.85 (0.68-1.07)
Kaiser California	1.03 (0.45-2.36)	0.87 (0.57-1.34)	0.73 (0.40-1.33)	0.86 (0.62-1.18)
TN Medicaid	0.62 (0.30-1.29)	0.63 (0.41-0.97)	1.23 (0.77-1.98)	0.77 (0.58-1.04)
HMORN	0.63 (0.14-2.82)	1.05 (0.75-1.46)	0.59 (0.32-1.11)	0.85 (0.62-1.17)

The Medicaid sample had the lowest rate ratios for MI, sudden death, and the combined outcome, but the highest rate ratio for stroke. As Dr. McEvoy noted in the Biometrics review, these rates suggest that the Medicaid population differed with respect to cardiovascular risk, and that aggregating the Tennessee data with the private insurance data may have introduced heterogeneity.

On balance, the other new data presentations in the manuscript do not materially alter the conclusions in the previous review of the adult ADHD study reports.

4 CONCLUSIONS AND RECOMMENDATIONS

The adult study manuscript provides data that makes clearer the differences in cardiovascular risk between the Medicaid and private insurance patient samples. On balance, however, this reviewer found no new information in the revised child study reported dated 10-25-11 or the adult study manuscript received 11-4-11 that would materially affect the prior interpretation of these studies, as outlined in the 9-1-11 DEPI/OSE review. Accordingly, one should refer to that review for conclusions and recommendations regarding these studies.

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/s/

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11/28/2011

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