Clinical Study Report

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Boston Collaborative Drug Surveillance Program
Name of Finished Product	ORTHO EVRA®
Name of Active Ingredient(s)	Ethinyl Estradiol (EE) and 17-Deacetylnorgestimate (17d-NGM)

Protocol No.: BCDSP-01

Title of Study: Final Postmarketing Study of ORTHO EVRA® in Relation to Ischemic Stroke, Acute Myocardial Infarction and Cerebral Sinus Thrombosis – December 15, 2005

Coordinating Investigator: not applicable

Publication (Reference):

None

Study Period: 1 April 2002 to 31 March 2005

Phase of Development: Postmarketing, Phase 4

OBJECTIVES:

The primary objectives of this study were (1) to estimate incidence rates of the study endpoints, acute myocardial infarction (AMI) and ischemic (thrombotic or embolic) stroke separately and combined in current users of ORTHO EVRA and users of norgestimate-containing OCs with 35 mcg of EE, and to describe all new cases identified in as much detail as available; and (2) to estimate the incidence of cerebral venous sinus thrombosis (CVST) in users of ORTHO EVRA and users of norgestimate-containing OCs with 35 mcg of EE, and to describe all new cases in as much detail as available.

METHODS:

Data Resource:

This study used data from the PharMetrics database, which is a United States based, ongoing longitudinal database with information on around 55 million covered lives going back as far as 1995 (20 million current lives). It comprises data contributed by managed care plans throughout the United States and it contains information on paid claims for pharmaceuticals, medical diagnoses and procedures as well as demographic information on all subjects. This includes all data that were collected by PharMetrics through March 2005. Demographic information included the patient's year of birth, sex, and enrollment details such as date and length of enrollment. Prescription drug dispensings were coded using the National Drug Code (NDC) provided by the United States Food and Drug Administration (FDA). Each drug claim was entered as a separate event and it included information on the specific entity dispensed, the date of dispensing, the quantity dispensed and the length of the supply. Each medical event had an episode number so all medical services provided for one medical condition could be linked. This enabled in-hospital treatments and procedures to be attributed to a medical condition since the event code would be the same for each entry. All diagnoses were coded using the ICD – 9 coding system. Procedures were coded using the CPT-4 system. All events described above were coded with the date on which the initial service was delivered.

Number of Subjects (planned and analyzed):

Base population comprised women who had received either ORTHO EVRA or norgestimate containing oral contraceptive with 35 mcg of EE between April 1, 2002 and March 31, 2005.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

- All 15 to 44 year old women who were ORTHO EVRA users or who were first time users of norgestimate-containing oral contraceptives with 35 mcg EE between 1 April 2002 and March 31, 2005, and who were identified in the Pharmetrics database using the National Drug Code (NDC) assigned by the FDA and modified by Pharmetrics.

- 6 months of enrollment in their health plan prior to the index date (the date of the event for cases, the date of the corresponding case's event for the controls matched to that case).

- Start of study contraceptive use after January 1, 2002

- The study was restricted to non-fatal cases of ischemic stroke, AMI and CVST, i.e. to subjects who were seen by a health care provider for the outcome and were not diagnosed with the event at death. This restriction reflects the fact that the PharMetrics database does not capture deaths that occur outside a healthcare facility, and thus it was not possible to include people who died without first having had contact with the medical delivery system.

Exclusion Criteria

Patients with any code for cancer (except for non-melanoma skin cancer), renal failure, or chronic inflammatory disease

Test Product, Dose and Mode of Administration, Batch No.: ORTHO EVRA transdermal patch containing 6 mg NGM and 0.75 mg EE is worn for 1 week and replaced for 3 consecutive weeks; the fourth week is patch-free.

Reference Therapy, Dose and Mode of Administration, Batch No.: Norgestimate-containing oral contraceptives (OCs) with 35 mcg of EE pill is taken for 21 consecutive days followed by no pill or a drug-free pill for 7 days

Duration of Treatment: Not applicable.

CRITERIA FOR EVALUATION:

This is an observational, longitudinal, case control and retrospective study. The study outcome was restricted to non-fatal cases of ischemic stroke, AMI and CVST, because the PharMetrics database does not capture deaths that occur outside a healthcare facility.

Cases

New cases were defined as those with (1) a first-time recorded claim for an ICD-9 diagnosis of study endpoints at any time during the study period; (2) enrolled in health plan for at least 6 months prior to the diagnosis date (index date); (3) had the first recorded use of the study contraceptive after April 1, 2002.

In addition to the general criteria for new cases described above, specific criteria for cases of each study endpoint were:

Ischemic stroke: hospitalized with a first-time recorded claim for an ICD-9 diagnosis of ischemic stroke at any time during the study period. Risk factors for stroke such as treated hypertension, treated diabetes, angina, congestive heart failure, cardiac dysrhythmias, or other chronic heart disease were described for each new case. Cases with recent pregnancy, major trauma or major surgery (within 90 days), were excluded.

AMI: hospitalized with a first-time recorded claim for an ICD-9 diagnosis of acute myocardial infarction or acute coronary revascularization at any time during the study period. Risk factors for AMI such as treated hypertension, treated diabetes, angina, congestive heart failure, cardiac dysrhythmias, or other chronic heart disease were described for each new case. Cases with a history of stroke or VTE, recent major trauma, pregnancy or major surgery (within 90 days) were excluded.

CVST: hospitalized with a first-time recorded claim for an ICD-9 diagnosis of CVST at any time during the study period. Risk factors for CVST such as gynecological disorders (menstrual disorders, endometriosis, uterine fibroids), cardiovascular disease (varicose veins, peripheral vascular disease, unstable angina, atherosclerosis, dysrhythmias, coagulation defects, and congestive heart failure), asthma, and thyroid disease were described for each new case. Cases with use of an anticoagulant medication, major surgery (within 90 days), trauma, epilepsy, or pregnancy were excluded.

Case assignments for each case category were made without knowledge of exposure. All data recorded in each subject's record prior to the index date was used to identify potential risk factors and exclusion factors.

Exposure

Current use of a hormonal contraceptive was defined as having a recorded claim for dispensing of a study contraceptive whose filled use extended to within 30 days before the index date or past the index date. Recent use was defined as having a recorded claim for dispensing of a study contraceptive that extended to within 90 days of the index date, but did not meet the criteria for current use. Additional exposure information included duration of use, i.e. the interval from the date of the first recorded claim for the study hormonal contraceptive to the index date, and switching among contraceptives (non-study contraceptives, or either of the study contraceptives).

Other covariates

The BCDSP evaluated the claims history of each case individually for diagnoses that indicate smoking status or the presence of obesity and noted them when possible.

STATISTICAL METHODS:

Cohort data for the two study contraceptives was used to estimate incidence rates and 95 percent confidence intervals for each of the three study outcomes, ischemic stroke, acute MI, and cerebral sinus thrombosis by exposure. We estimated incidence rate ratios (IRR) for the study outcomes comparing users of ORTHO EVRA to users of norgestimate-containing oral contraceptives with 35 ug of EE

RESULTS:

ISCHEMIC STROKE

- Eighteen cases were identified as ischemic stroke, 4 were identified as embolic stroke and 14 were thrombotic stroke.
- The rates of ischemic stroke among users of ORTHO EVRA and the norgestimate-containing OCs with 35 mcg of EE were 8/58,752 or 13.6 per 100,000 woman years (95% CI 5.9 – 26.8) and 10/88,571 or 11.3 per 100,000 woman years (95% CI 5.4 – 20.8) respectively. The crude incidence rate ratio (IRR) for ischemic stroke in ORTHO EVRAÔ users compared to users of norgestimate-containing oral contraceptives with 35 ug of EE was 1.2 (95% CI 0.41 – 3.4). There were not enough cases in either exposure group to adjust for any potential confounders.

AMI

- Eight cases were identified as AMI in the study population.
- The crude incidence rates of AMI in current ORTHO EVRAÔ users was 1/58,752 or 1.7 per 100,000 woman years (95% CI 0.04 – 9.5) and 7/88,571 or 7.9 per 100,000 woman years (95% CI 3.2 – 16.3) in users of norgestimate-containing oral contraceptives with 35 ug of EE. The IRR for ORTHO EVRA users compared to users of norgestimate-containing oral contraceptives with 35 ug of EE was 0.2 (95% CI 0.004 – 1.7).

ISCHEMIC STROKE AND ACUTE MYOCARDIAL INFARCTION COMBINED

The crude incidence rates for ischemic stroke and AMI combined were 15.3 per 100,000 woman years (95% CI 7.0 – 29.1) for users of ORTHO EVRA™ and 19.2 per 100,000 woman years (95% CI 11.2 – 30.7) for users of norgestimate-containing oral contraceptives with 35 ug of EE. The IRR for the two outcomes combined, comparing ORTHO EVRA™ users to users of norgestimate-containing oral contraceptives with 35 ug of EE, was 0.8 (95% CI 0.3 – 1.9).

CVST

- Three cases were identified as idiopathic CVST in the study population. All 3 cases were currently exposed to a norgestimate-containing OC with 35 ug EE.
- The incidence rate for ORTHO EVRAÔ users was 0/58,752 or 0 per 100,000 woman years (95% CI .0 – 6.3), and 3/88,571 or 3.4 per 100,000 woman years (95% CI 0.7 – 9.9) for users of norgestimate-containing oral contraceptives with 35 ug of EE. The IRR could not be calculated.

STUDY LIMITATIONS:

We are aware that samples of ORTHO EVRA™ were distributed in the years that ORTHO EVRA™ has been marketed. This would not have been the case for norgestimate-containing OCs. We cannot rule out some influence of this difference but the nature of the results as noted above were such that any effect is likely to be minimal.

CONCLUSION:

We conclude from the data in this study that the rates of ischemic stroke, AMI, and cerebral sinus thrombosis for ORTHO EVRAÔ users in this population are closely similar to those of norgestimate-containing OCs with 35 ug of EE and that these events are rare among young women who use hormonal contraceptives.

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