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 Report of the 2006 Update on Postmarketing Study of ORTHO EVRA® in Relation to Non-Fatal Venous Thromboembolism – January 16, 2007

Coordinating Investigator: not applicable

Publication (Reference):

Jick, S., J. A. Kaye, et al. (2007). "Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol." Contraception 76(1): 4-7.

Jick, S. S. and H. Jick (2007). "The contraceptive patch in relation to ischemic stroke and acute myocardial infarction." Pharmacotherapy 27(2): 218-20.

Jick, S. S., J. A. Kaye, et al. (2006). "Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol." Contraception 73(3): 223-8.

Study Period: 1 April 2002 to 31 August 2006

Phase of Development: Postmarketing, Phase 4

OBJECTIVES:

The primary objectives of this study update were: (1) to estimate the relative risk for nonfatal venous thromoembolism (VTE) in current users of ORTHO EVRA compared with current users of norgestimate-containing oral contraceptives (OCs) with 35 mcg of EE with special attention to duration of use employing an additional 16 months of data; (2) 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 from the update of the PharMetrics data in as much detail as available; and (3) 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 identified from the update of the PharMetrics data in as much detail as available.

METHODS:

Data Resource:

This study update 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 update includes all data that were collected by PharMetrics through August 2006. 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 184,082 women who had received either ORTHO EVRA or norgestimate containing oral contraceptive with 35 mcg of EE between April 1, 2002 and August 31, 2006.

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 August 31, 2006, 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 VTE, 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 update of an observational, longitudinal, case control and retrospective study. Two reports on this study have been submitted previously. The study outcome was restricted to non-fatal cases of VTE, 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) were not included in the first report; (3) enrolled in health plan for at least 6 months prior to the diagnosis date (index date); (4) 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:

VTE: a first-time recorded claim for an ICD-9 diagnosis of venous thrombosis or pulmonary embolism (PE) at any time during the study period, where long-term anticoagulation was started promptly; and no estrogen-containing contraceptive was initiated after the date of VTE diagnosis. Cases with prior use of an anticoagulant medication, major surgery (within the 90 days), trauma, epilepsy, or pregnancy were excluded.

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.

Controls for VTE Cases

Up to 4 controls were identified for each VTE case. Controls were women who were current users of ORTHO EVRA or norgestimate-containing oral contraceptives with 35 mcg of EE who did not have a recorded claim for VTE. Controls were matched to each case on year of birth and index date. As with cases, all controls were required to have at least 6 months of enrollment in their health plan prior to the index date (the event date of their matched case), and to have had the first recorded use of their study contraceptive use after April 1, 2002. The same exclusions were applied to the controls as to the cases.

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 effect of smoking was not reported in this update because there were too few subjects who had smoking information present in their records. Information on obesity was derived only from an ICD9 code for obesity.

STATISTICAL METHODS:

The relative risk of idiopathic VTE (deep vein thrombosis or pulmonary embolism) was estimated among current users of ORTHO EVRA compared with current users of norgestimate-containing oral contraceptives with 35 mcg of EE. Conditional logistic regression (conditional on the matching factors) was used to estimate odds ratios (OR's), which are equivalent to relative risks for the rare outcomes under study. Other covariates were included in the final model if they produced more than a 10% change in the relative risk estimate in a model containing the exposure and each covariate individually.

RESULTS:

VTE

- Fifty six new cases were identified as idiopathic VTE in the study population since the previous analysis and matched with 212 controls. The number of new cases by age group was: Age <30, 30 cases; age 30-39, 18 cases, age 40-44 8 cases.
- The unadjusted OR for developing VTE, controlling only for the matching factors, in users of ORTHO EVRA compared to users of a norgestimate-containing hormonal contraceptives with 35 mcg of EE was 1.1 (95% CI 0.6 – 2.1). The OR was 2.1 (95% CI 0.9– 5.0) for PE and 0.6 (95% CI 0.2 – 1.5) for DVT. Stratification by age yielded ORs of 1.3 (95% CI 0.6 – 3.2), 0.7 (95% CI 0.2 – 2.1), and 1.3 (95% CI 0.3 – 6.4) for age strata <30, 30 – 39, 40 – 44 respectively for ORTHO EVRA® users compared to norgestimate containing oral contraceptive with 35 ug of EE
- When the new data from this update were combined with those from previous reports of this study, there were 124 cases and 478 controls in all. The OR for VTE in all subjects comparing ORTHO EVRA users to users of a norgestimate-containing hormonal contraceptives with 35 mcg of EE was 1.0 (95% CI 0.7 – 1.5). Obesity, back problems and gynecological disorders were associated with an increased risk of VTE, but for none of these covariates did inclusion in the model materially change the main effect estimate.
- Crude incidence rates (not adjusted for age or calendar time) for VTE including cases in the updated study base population that had been identified in the first and second reports among users of ORTHO EVRA and users of norgestimate containing oral contraceptive with 35 mcg of EE were 68.0/100,000 woman years (95% CI 46.8 – 95.5), and 49.8/100,000 woman years (95% CI 36.9 – 65.9) respectively.
- The estimated IRR of VTE for current use of ORTHO EVRA compared to current use of norgestimate containing oral contraceptives with 35 mcg of EE, adjusted for age, but not calendar time, was 1.3 (95 % CI 0.8 – 2.0).

ISCHEMIC STROKE

- Five new cases were identified as ischemic stroke since the previous analysis.

- Four cases identified in previous report were also in this study population and included in the calculation of rates of stroke.
- The rates of stroke among users of ORTHO EVRA and the norgestimate-containing OCs with 35 mcg of EE were 2/48,504 or 4.1/100,000 woman years (95% CI 1.1 – 15.0), and 7/98,356 or 7.1/100,000 woman years (95% CI 3.0 – 14.7), respectively.

AMI

- Two new cases were identified as AMI in the study population since the previous analysis. One case had a complicated history of coronary artery atherosclerosis, coronary syndrome, hyperlipidemia, and hypertension. The second case had a diagnosis of obesity and hypertension recorded in the medical record prior to the index date.
- There was one additional case in the current study population who had been reported in the previous report.
- The accumulated rates of AMI in users of ORTHO EVRA and the norgestimate-containing OCs with 35 mcg of EE were 0/48,504 or 0.0/100,000 woman years (95% CI 0.0 – 7.9) and 3/98,356 or 3.1/100,000 woman years (95% CI 0.2 – 5.8).

CVST

- One new case was identified as idiopathic CVST in the study population since the previous analysis. The patient had a congenital anomaly of the circulatory system.
- There were no cases from the original report that were also in this updated data.
- The rates for CVST among current users of ORTHO EVRA and the norgestimate-containing OCs with 35 mcg of EE were 0/48,504 or 0.0/100,000 woman years (95% CI 0.0 – 7.9) and 1/98,356 or 1.0/100,000 woman years (95% CI 0.2 – 5.8).

STUDY LIMITATIONS:

For some analyses, the numbers of subjects in each group were small. Information on smoking and obesity was limited.. Using the limited information available in these data, obesity did not confound the relation between ORTHO EVRA, norgestimate-containing OCs with 35 mcg of EE, and VTE.

CONCLUSION:

The results from the updated PharMetrics data on ischemic stroke, AMI and CVST are entirely consistent with our previous reports and indicate that the risk of these thrombotic events is not increased among users of ORTHO EVRA compared to users of norgestimate-containing OCs with 35 mcg of EE.

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