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 Postmarketing Study of ORTHO EVRA® in Relation to Non-Fatal Venous Thromboembolism and Cerebral Sinus Thrombosis – September 21, 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 objective of this study update was to estimate the relative risk for nonfatal VTE in current users of ORTHO EVRA compared to current users of norgestimate-containing hormonal contraceptives with 35 ug of EE with special attention to the assessment of the effect of duration of use.

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 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 of an observational, longitudinal, case control and retrospective study. The study outcome was restricted to non-fatal cases 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:

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.

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 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.

RESULTS:

VTE

- Sixty eight cases were identified as idiopathic VTE in the study population and matched with 266 controls
- The unadjusted odds ratio (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 ug of EE was 0.9 (95% CI 0.5 – 1.6). This result was the same in hospitalized cases and all cases combined. No covariate was found to produce more than a 10% change in the relative risk estimate so no adjusted models were produced.
- Crude incidence rates (not adjusted for age or calendar time) for VTE among users of ORTHO EVRA and users of norgestimate containing oral contraceptive with 35 mcg of EE were rates were similar for users of norgestimate containing oral contraceptive with 35 ug of EE and users of ORTHO EVRA (41.77/100,000 PYs and 52.76/100,000

PYs respectively), and the incidence rates increased with increasing age for both drugs. The incidence rate ratio for current use of ORTHO EVRA™ compared to current use of norgestimate containing oral contraceptive with 35 ug of EE, adjusted for age, but not calendar time, was 1.1 (95 % CI 0.7 to 1.8).

STUDY LIMITATIONS:

For some analyses, the numbers of subjects in each group were small. Information on smoking and obesity was limited. There is no information on actual height or weight in the database. Among those subjects with a code for obesity there was no confounding by the diagnosis.

CONCLUSION:

We conclude from the data in this study that the the risk of VTE for ORTHO EVRA users in this population is closely similar to those of norgestimate-containing OCs with 35 ug of EE.

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