SYNOPSIS OF BCDSP-04

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Name of Finished Product	ORTHO EVRA	
Name of Active Ingredient(s)	norelgestromin/ethinyl estradiol	

Protocol No.: BCDSP-04

Title of Study: Postmarketing study of ORTHO EVRA and levonorgestrel oral contraceptives in relation to non-fatal venous thromboembolism, ischemic stroke and myocardial infarction.

Coordinating Investigator: Boston Collaborative Drug Surveillance Program, Lexington, MA; U.S.A.

Publication (Reference): None.

Study Period: April 1, 2002 to March 31, 2006	**Phase of Development:** 4

Objectives: Use the PharMetrics insurance claims database to estimate relative risks for non-fatal venous thromboembolism (including cerebral venous sinus thrombosis) (VTE), ischemic stroke (stroke due to blood clots), and acute myocardial infarction (heart attack) (MI), in current users of ORTHO EVRA compared to current users of levonorgestrel-containing oral contraceptives with 30 micrograms ethinyl estradiol (LNG-30 OC).

Methodology: Nested Case-Control Pharmacoepidemiology Study using a claims database to assess occurrence of VTE, ischemic stroke, and MI in current users of ORTHO EVRA compared to LNG-30 OC.

Diagnosis and Main Criteria for Inclusion: Users of ORTHO EVRA or first time users of LNG-30 OC during study period identified in the database using the National Drug Code assigned by the FDA and modified by PharMetrics; 6 months of enrollment in their health plan prior to the event date; ≥4 months of history in claims record before first use of contraceptive. Duration of contraceptive use varied.

Test Product, Dose and Mode of Administration: Transdermal patch containing 6 milligrams norelgestromin and 0.75-milligram ethinyl estradiol; each patch is worn for 1 week for 3 consecutive weeks; fourth week is patch-free.

Reference Therapy, Dose and Mode of Administration: LNG-30 OC is taken for 21 consecutive days followed by no or inert pill for 7 days.

Criteria for Evaluation: Three sets of cases with first-time recorded claim for an ICD-9 diagnosis during study period: (1) deep vein thrombosis, pulmonary embolism, or cerebral venous sinus thrombosis, venous thrombotic event with hospitalization, visit to the emergency room or positive indication of VTE from diagnostic test results. Requirement for multiple prescriptions for anticoagulation therapy provided evidence of original diagnosis of VTE; (2) ischemic stroke with hospitalization; or (3) MI or acute coronary revascularization with hospitalization. Controls were identified for VTE cases.

Statistical Methods: Relative risk of VTE estimated by odds ratios (ORs) obtained from logistic regression models, and for ischemic stroke or MI by incidence rate ratios (IRRs). Estimates of the OR were made separately for women with and without pre-existing strong risk factors for VTE, and also overall. Formal case-control analysis was not performed for stroke and MI due to insufficient cases.

SUMMARY - CONCLUSIONS:

VTE: ORs comparing risk in current users of the two contraceptives.

Exposure	Cases	Controls	OR (95% CI)	P value
Idiopathic VTE				
LNG-30 OC	16	98	1.0	-
ORTHO EVRA	30	109	2.0 (0.9 – 4.1)	0.07
With Risk Factors				
LNG-30 OC	10	8	1.0	-
ORTHO EVRA	19	20	1.6 (0.1 – 18.3)	0.7
All VTES				
LNG-30 OC	26	175	1.0	-
ORTHO EVRA	49	190	1.9 (1.1 – 3.3)	0.02

Stroke: Incidence rates were 5/42,787 or 11.7 per 100,000 woman years (95% CI 5.0 – 27.4) for ORTHO EVRA; 7/28,445 or 24.6 per 100,000 woman years (95% CI 11.0 – 50.8) for LNG-30 OC. The ratio (IRR) of these rates was 0.47 (95% CI 0.15-1.51).

MI: Incidence rates were 1/42,787 or 2.3 per 100,000 woman years (95% CI 0.4 – 13.2) for ORTHO EVRA; 3/28,445 or 10.5 per 100,000 woman years (95% CI 3.6 – 31.0) for LNG-30 OC. The ratio (IRR) of these rates was 0.22 (95% CI 0.3-1.64).

CONCLUSIONS: Risk of idiopathic (unknown cause) VTE for ORTHO EVRA users in the studied population may be slightly higher than for levonorgestrel-containing oral contraceptives with 30 micrograms ethinyl estradiol. Risk of stroke and heart attack for users of these 2 contraceptives in this population appears similar.

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