The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared to Women Using Norgestimate-Containing Oral Contraceptives With 35 µg Ethinyl Estradiol

Nested Case-Control Study Extension

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EXECUTIVE SUMMARY

Ortho Evra is the first transdermal contraceptive system approved by the U.S. Food and Drug Administration. Open label trials have demonstrated efficacy comparable to that of oral contraceptives and superior compliance.

At the time of this study's inception, it was not known whether users of the transdermal contraceptive system faced the same risk of acute myocardial infarction (AMI), ischemic stroke and venous thromboembolism (VTE) as users of OCs. The 03 August 2006 Final Report (revised 22 January 2009) from i3 Drug Safety, of a nested case-control study of users of Ortho Evra and norgestimate-containing oral contraceptives with 35 μg of ethinyl estradiol (NGM-OC), found no increased risk of the primary endpoint of combined AMI and ischemic stroke in current Ortho Evra users compared with current NGM-OC users [odds ratio (OR) 0.69, 95% confidence interval (95% CI) 0.15-3.13].[1] There was an estimated doubling of risk of AMI alone among current Ortho Evra users compared with current NGM-OC users (OR 2.06, 95% CI 0.28-15.47), but the interpretation of this is inconclusive due to the width of the confidence intervals. Following exclusion of women with short-term risk factors, there was a greater than 2-fold higher risk of VTE in current Ortho Evra users compared with current NGM-OC users (OR 2.46, 95% CI 1.10-5.52). In contrast to these results, Jick et al reported no association between nonfatal VTE and current use of Ortho Evra compared to current use of a NGM-OC in both their initial study (OR=0.90, 95% CI 0.5-1.6) and in a subsequent analysis (OR 1.1, 95% CI 0.6-2.1).[2,3] In additional unadjusted analyses, Jick and Jick found no excess risk of ischemic stroke and AMI among users of Ortho Evra compared to the same NGM-containing OCs.[4]

Since the confidence interval surrounding the OR for AMI was compatible with a wide range of possible effects, questions remain around a more definitive risk estimate in association with Ortho Evra. Further, an association with VTE was observed, but there were too few events to further characterize the nature of the risk, such as with respect to duration of use. This report describes an extension of the prior case-control study, with data added from 01 January 2005 to 31 December 2006, to evaluate risk of the study outcomes among current Ortho Evra users compared with current users of an NGM-containing OC with 35μg EE.

This case-control study, nested within a cohort of hormonal contraceptive users, was conducted using data from the Ingenix Research Data Mart (RDM; now known as the Normative Health Informatics Database), containing insurance claims information from a large U.S. health plan affiliated with i3 Drug Safety. The RDM contains medical and pharmacy claims data from health plans and large employer groups located in the

Northeast, South/Southeast, Midwest, and Western United States. We identified outcomes of death using the National Death Index (NDI).

The endpoints of interest for this report were the following events confirmed through abstracted medical records and/or the NDI:

- AMI or ischemic stroke, combined (primary outcome)
- AMI
- Ischemic stroke
- VTE [pulmonary embolism (PE) or deep vein thrombosis (DVT)]
- AMI or ischemic stroke or PE, combined
- AMI or ischemic stroke or VTE, combined
- All deaths identified in the NDI
- NDI-identified deaths due to AMI, ischemic stroke, or VTE
- NDI-identified deaths due to sudden or unknown causes

This nested case-control study had the following objectives:

- Estimate relative risks of the study endpoints in current and recent users of Ortho Evra compared to current and recent users of norgestimate-containing hormonal contraceptives (HC) with 35 μg ethinyl estradiol, and according to duration of use of the last course of HC treatment before the event onset.
- Characterize cases and controls with respect to exposure to Ortho Evra and comparison oral contraceptives, along with risk factors identified through the medical and pharmacy claims data.

In this extension, we added cases and controls from 01 January 1 2005 to 31 December 2006 to data from prior analyses, which covered 01 April 2002 to 31 December 2004. This executive summary presents the combined data only.

The base cohort consisted of all women between the ages of 15 and 44 in the Ingenix RDM who received at least one dispensing of Ortho Evra or a NGM-OC between 01 April 2002 and 31 December 2006. Women remained in the cohort from their first eligible dispensing through 183 days following the last day of use of hormonal contraception, as estimated from the days of contraceptive supplied. Women exited the cohort upon discontinuation of use, and re-entered with a new eligible dispensing.

Case events in this cohort were identified by review of insurance claims and the NDI. Cases identified in the claims review were confirmed by a physician using abstracted medical records. We sought a 4-fold larger random sample of women (controls) from the cohort. Controls were matched to cases according to year of birth, date of event, and initiator status, which categorized women as either new initiators of their most recent course of hormonal contraception or other users (switchers, or those with interrupted or

unknown prior use). For cases and controls, hormonal contraceptive usage status as of the event date was ascertained from pharmacy billing records, and relevant medical conditions were identified from diagnoses associated with medical insurance claims records.

The relative risks associated with exposure to Ortho Evra or NGM-OC were estimated using odds ratios (OR) from conditional logistic regression models. The regression models incorporated case-control matching on year of birth, date of event, and initiator status (new initiator, switcher, unknown, or interrupted). The ORs of study outcomes associated with use of Ortho Evra and NGM-OCs are presented for the full study population, and for the subgroups of new initiators of their most recent course of hormonal contraception, and other users (switchers,or those with interrupted or unknown prior use).

Controls represented the general population experience of users of Ortho Evra and NGM-OCs. Ortho Evra-exposed controls and NGM-OC-exposed controls resembled one another with respect to demographics, recent history of relevant medical conditions, and other conditions associated with increased risk of thrombotic events. There were more (8% vs. 3%) hospital visits in the 90 days prior to start of hormonal contraception among current Ortho Evra-exposed controls compared with current NGM-OC exposed controls.

Of 400 medical charts sought for confirmation of study outcomes, abstractions were completed for 290 (73%). The most common reason for non-completion was provider refusal. Following medical review of abstracted charts, 16 of 111 potential AMIs, 19 of 68 potential strokes and 108 of 221 potential VTEs identified through insurance claims were confirmed as study outcomes. The fraction of outcomes confirmed were as expected, reflecting the broad and sensitive, but nonspecific, list of insurance codes chosen to screen for possible outcomes. Following a search of the National Death Index, we identified 4 additional AMI cases and 5 additional VTE cases and included these events in the analysis. The search of the NDI yielded 81 deaths due to all causes, 8 due to AMI, stroke, or VTE (one death was attributed to VTE and AMI), and 9 due to sudden or unknown causes.

The primary endpoint analysis (AMI and stroke) yielded an OR close to one with a confidence interval including one (OR=0.92, 95% CI 0.34-2.51) comparing current Ortho Evra use to current use of NGM-OCs. Two strokes occurred among current Ortho Evra users compared with 15 among current NGM-OC users (OR 0.62, 95% CI 0.12-3.24). The outcome of AMI had an OR of 1.24 comparing current Ortho Evra users to current NGM-OC users, and this relativelyinfrequent outcome had somewhat wider confidence intervals (95% CI 0.33-4.69).

There was a 2-fold increased risk of VTE events in current Ortho Evra users, compared with current NGM-OC users (OR 1.98, 95% CI 1.18-3.33). The strength of the association was similar within strata of new initiators (OR=1.78, 95% CI 0.84-3.78) and women who were not new initiators (OR 2.21, 95% CI 1.07-4.54). Among cases and controls remaining after the exclusion of women with short-term risk factors (trauma, pregnancy, major surgery, postoperative complications, or anti-coagulant or anti-thrombolytic therapy) in the 90 days prior to the index date, current Ortho Evra use remained associated with an increased risk of VTE compared with current NGM-OC users (OR 2.19, 95% CI 1.20-3.99). Seven deaths occurred among current Ortho Evra users compared with 59 among current NGM-OC users.

The results of this analysis are consistent with prior analyses in showing an elevated risk of thromboembolic outcomes, in particular VTE, associated with use of Ortho Evra relative to NGM-OCs. Confidence intervals for the individual outcomes of AMI, ischemic stroke, and death are narrower with the additional cases and controls from this extension, but remain consistent with a fairly wide range of associations with Ortho Evra use.

REFERENCES

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