



JANSSEN-ORTHO

**IMPORTANT DRUG SAFETY INFORMATION**  
**EVRA\* (norelgestromin and ethinyl estradiol) Transdermal System**

November 21, 2006

**SUBJECT: New Safety Information about EVRA\* (norelgestromin and ethinyl estradiol) Transdermal System**

Dear Health Care Professional:

Following discussions with Health Canada, Janssen-Ortho Inc. would like to update you on important new safety information pertaining to EVRA\*. The EVRA\* transdermal system marketed in Canada contains 6.0 mg norelgestromin (NGMN) and 0.60 mg ethinyl estradiol (EE) and is indicated for contraception. ORTHO EVRA<sup>®</sup> is the formulation of EVRA marketed in the United States and contains 6.0 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE). EVRA\* was previously found to be bioequivalent to ORTHO EVRA<sup>®</sup>, and as such, post-marketing adverse event data for ORTHO EVRA<sup>®</sup> are considered to apply equally to the EVRA formulation marketed in Canada.

Health care professionals should be aware of the following new information which has been incorporated into the EVRA Product Monograph:

▪ **The risk of venous thromboembolism (VTE) in users of the ORTHO EVRA patch (the formulation of EVRA marketed in the United States) compared to users of oral contraceptives containing norgestimate and 35µg of EE was assessed in two epidemiological studies with a nested case-control design conducted in women aged 15 to 44 years. One of these studies found an increased risk of VTE for current users of ORTHO EVRA compared to current users of the oral contraceptives [odds ratio 2.42 (95% CI 1.07 – 5.46). <sup>1</sup>The other study did not find an increase in risk of VTE for current users of ORTHO EVRA [odds ratio 0.9 (95% CI 0.5 – 1.6)]<sup>2</sup>**

▪ **Prescribers are advised to carefully assess a patient's baseline and cumulative risk of thromboembolism before prescribing EVRA. Obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) has been identified as a risk factor for venous thromboembolism. Particular caution should be exercised when prescribing EVRA to women who are obese.**

▪ **The results of a recent pharmacokinetic study to evaluate the ethinyl estradiol (EE) and norelgestromin (NGMN) exposure with the EVRA contraceptive patch sold in Canada compared with an oral contraceptive containing norgestimate 250 µg / EE 35 µg indicated that C<sub>max</sub> values were 2-fold higher for NGMN and EE in subjects administered the oral contraceptive compared to EVRA, while overall exposure (AUC and C<sub>ss</sub>) was comparable in subjects treated with EVRA. Inter-subject variability (%CV) for the PK parameters following delivery from EVRA was higher relative to the variability determined from the oral contraceptive. The mean pharmacokinetic profiles are different between the two products and caution should be exercised when making a direct comparison of these**

**PK parameters. The clinical relevance of the difference in PK profile between transdermal and oral delivery is not known.**

In addition to incorporation of the above information in the Product Monograph, the Contraindications and Warnings and Precautions sections have also been updated to include general information pertaining to thromboembolism. New information has also been added to the Warnings and Precautions, Drug-Lifestyle Interactions and Pharmacology sections of the Product Monograph describing the theoretical risk of unintentional increase in estradiol exposure in patients with fever or in whom the patch application site is exposed to direct external heat sources such as sauna or whirlpool bath. The Adverse Reactions section of the Product Monograph has also been revised to include adverse reactions reported during clinical trials and during the post-market period.

Health care professionals should also be aware that an additional study to re-evaluate the average daily amount of hormones released from the EVRA transdermal contraceptive patch will be conducted. Once this information is submitted to and reviewed by Health Canada, Janssen-Ortho Inc. will communicate any new information to health care professionals and consumers.

#### **Previous Public Advisories**

Health Canada issued two previous Public Advisories pertaining to EVRA on November 28, 2005 and March 30, 2006. These can be found at [http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index\\_e.html](http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/index_e.html).

Janssen-Ortho Inc. continues to work closely with Health Canada to monitor ongoing clinical trials, and worldwide pharmacovigilance reports.

The current Prescribing Information is available on the Janssen-Ortho Inc. website at [www.janssen-ortho.com](http://www.janssen-ortho.com). Updates to the Prescribing Information will be posted on this website and will be provided for the next edition of *The Compendium of Pharmaceuticals and Specialties*.

The identification, characterization, and management of marketed health product-related adverse reactions are dependent on the active participation of health care professionals in adverse drug reaction reporting programmes. Any occurrences of serious and/or unexpected adverse reactions in patients receiving EVRA, including reports of fatality or thromboembolism, should be reported to Janssen-Ortho Inc. or the Marketed Health Products Directorate at the following addresses:

Janssen-Ortho Inc.  
19 Green Belt Drive  
Toronto, Ontario  
M3C 1L9  
Or call toll free at 1-800-567-3331  
Or email to [dsscan@joica.jnj.com](mailto:dsscan@joica.jnj.com)  
Or toll free Fax to 1-866-767-5865

#### **Any suspected adverse reaction can also be reported to:**

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)  
Marketed Health Products Directorate  
HEALTH CANADA  
Address Locator: 0701C  
OTTAWA, Ontario, K1A 0K9  
Tel: (613) 957-0337 or Fax: (613) 957-0335

To report an Adverse Reaction, consumers and health professionals may call toll free:

Tel: 866 234-2345

Fax: 866 678-6789

[cadmp@hc-sc.gc.ca](mailto:cadmp@hc-sc.gc.ca)

The [AR Reporting Form](#) and the [AR Guidelines](#) can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

**For other inquiries related to this communication, please contact Health Canada at:**

Bureau of Metabolism, Oncology and Reproductive Sciences (BMORS)

E-mail: [bmors\\_enquiries@hc-sc.gc.ca](mailto:bmors_enquiries@hc-sc.gc.ca)

Tel: (613) 941-3171

Fax: (613) 941-1365

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Should you have any questions or require additional information regarding the use of EVRA, please contact Janssen-Ortho Inc. Medical Information Department at 1-800-567-3331 from 9:00 am to 5:00 pm Monday to Friday Eastern Standard Time (EST) or by facsimile at 416-449-2658. A copy of this letter is also available on the Janssen-Ortho website at [www.janssen-ortho.com](http://www.janssen-ortho.com) and on the Health Canada website at [http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index_e.html)

Sincerely,



Cathy Lau, PhD.  
Vice President  
Regulatory and Quality

1. The Risk of Venous Thromboembolism, Myocardial Infarction, and Ischemic Stroke Among Women Using the Transdermal Contraceptive System Compared with Women Using Norgestimate-Containing Oral Contraceptives with 35 µg Ethinyl Estradiol”, Draft Final Report, Nested Case Control Study, prepared by i3 Drug Safety, For Johnson & Johnson Pharmaceutical Research and Development, June 30, 2006.

2. Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 micrograms of ethinyl estradiol. *Contraception*. 2006 Mar;73(3):223-8. Epub 2006 Jan 26.

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